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CADTH Drug Reimbursement Review

Pharmacoeconomic Report

Ozanimod (Zeposia)

(Celgene Inc., a Bristol Myers Squibb Company)

Indication: Treatment of Adult Patients With Relapsing-Remitting Multiple Sclerosis

Service Line: Common Drug Review
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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

ARR	annualized relapse rates
BIA	business impact analysis
BSC	best supportive care
CDP6	confirmed disease progression at 6 months
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
ICER	incremental cost-effectiveness ratio
MS	multiple sclerosis
NMA	network meta-analysis
QALY	quality-adjusted life-years
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary progressive multiple sclerosis

Executive Summary

The executive summary is comprised of Table 1: Submitted for Review, Table 2: Summary of Economic Evaluation, and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Ozanimod (Zeposia)
Submitted price	Ozanimod (Zeposia), 0.23 mg, 0.46 mg, and 0.92 mg capsules (as ozanimod hydrochloride), oral administration, $68.4932
Indication	The treatment of patients with relapsing-remitting multiple sclerosis to decrease the frequency of clinical exacerbations
Health Canada approval status	Notice of Compliance
Health Canada review pathway	Standard review
Notice of Compliance date	October 2, 2020
Reimbursement request	As per indication
Sponsor	Celgene Inc., a Bristol Myers Squibb company
Submission history	Previously reviewed: No

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with relapsing-remitting multiple sclerosis
Treatment	Ozanimod
Comparators	• Interferon beta-1a (Avonex, Rebif) • Interferon beta-1b (Betaseron, Extavia) • Pegylated interferon beta-1a (Plegridy) • Glatiramer acetate • Fingolimod • Teriflunomide • Dimethyl fumarate • Natalizumab • Alemtuzumab • Ocrelizumab • Cladribine
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	25 years
Key data source	Sponsor-commissioned NMA
Submitted results for base case (and key scenario analyses as required)	• Ozanimod was dominated by (less effective and more costly than) alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate, and Rebif. • Ozanimod was more effective and more costly than Avonex at an incremental cost per QALY gained (ICER) of $68,833 and teriflunomide at an ICER of $2.2 million.

Component	Description
	• Ozanimod was less effective and less costly than ocrelizumab and natalizumab.
Key limitations	• The sponsor adopted a more favourable assumption regarding the treatment effectiveness for ozanimod than estimated by its NMA with respect to disease progression. CADTH used the NMA estimate for its reanalyses. • The sponsor adopted a 25-year time horizon to address uncertainty about the duration of treatment effect. However, applying a treatment-waning effect is a more appropriate way to account for the impact of treatment duration. CADTH adopted a lifetime horizon (50 years) as per CADTH guidelines and adopted the assumption of waning of treatment effect as suggested by the clinical expert consulted for the review. • The sponsor's analysis did not include BSC as a comparator. Based on recommendations within the CADTH guidelines, BSC should be considered when new technologies have not been fully adopted by the decision-makers, or newer technologies represent uncertain (or poor) value. This also aligns with previous CADTH reviews for MS therapies.
CADTH reanalysis results	In the CADTH base case, a treatment-waning effect was applied, effect estimates from the NMA were used, and BSC was included as a comparator. • Ozanimod was less effective (fewer QALYs) than all active therapies. • Ozanimod was dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, Avonex, dimethyl fumarate, Rebif, and teriflunomide. • Ozanimod was more effective and more costly than BSC at an ICER of $578,039 per QALY.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; MS = multiple sclerosis; NMA = network meta-analysis; QALY = quality-adjusted life-year.

Conclusions

Based on a CADTH reanalyses that added a treatment-waning effect, used effect estimates from the network meta-analysis (NMA), and added best supportive care (BSC) as a comparator, ozanimod was associated with lower health benefits (fewer quality-adjusted life-years [QALYs]) than all currently available active therapies.

Although ozanimod reduces annualized relapse rates (ARRs) relative to some available therapies, it appears to be less effective at reducing the rate of disease progression relative to all other therapies. As such, ozanimod results in fewer added QALYs than all other comparators, except for BSC. Even with substantial price reductions, ozanimod would not be considered a cost-effective therapy as any cost savings would not compensate for the reduction in QALYs at a willingness-to-pay threshold of $50,000 per QALY. If reimbursement is restricted to first-line use at a price reduction of 77%, only then may ozanimod represent a cost-effective alternative at a willingness-to-pay threshold of $50,000 per QALY.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process.

One patient group, the Multiple Sclerosis Society of Canada, provided input. The unpredictable and disabling nature of the disease was described, with the most common symptoms being fatigue, difficulty in walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. Patients reported that current treatments include ocrelizumab, glatiramer acetate, dimethyl fumarate, teriflunomide, and others, with the most common side effects being injection-site reactions, flushing, hair-thinning, rashes, and increased risk of infections. The society noted that Canadian reimbursement criteria often require clinical failure on a low-to-moderate efficacy treatment prior to initiating a high-efficacy agent. It emphasized that ozanimod does not require medical supervision for up to 6 hours for the first dose as is usually required for other sphingosine 1-phosphate receptor modulators, filling a significant gap in treatments for multiple sclerosis.

The sponsor's model reflected some elements of the patient input in that specific adverse events were explicitly modelled; however, only those events that required hospitalization were modelled.

Some aspects of patient input — costs incurred by patients receiving infusion therapy in particular — were not addressed in the sponsor's model and could not be addressed by CADTH owing to structural or data limitations.

Economic Review

The current review is for ozanimod (Zeposia) for adult patients with relapsing-remitting multiple sclerosis (RRMS).

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted an economic model that estimates outcomes in terms of long-term costs and QALYs in patients with RRMS.[1] Primary analysis was conducted on a patient population whose eligibility requirements mirrored those of the RADIANCE Part B and SUNBEAM trials[2,3] (adults with RRMS aged 18 to 55 years with a baseline EDSS [Expanded Disability Status Scale] score of less than 6).

Analysis was conducted from the perspective of a provincial ministry of health, with a time horizon of 25 years and an annual discount rate of 1.5%.

Ozanimod is an oral treatment administered daily and comes in 3 capsule formulations: 0.23 mg, 0.46 mg, and 0.92 mg. The recommended dosage is 0.23 mg daily for days 1 through 4, followed by 0.46 mg daily for days 5 through 7, and 0.92 mg daily from then on. The annual cost of treatment with ozanimod is $25,017.

Ozanimod was compared to various disease-modifying therapies (DMTs): interferon beta-1a (Avonex, Rebif), interferon beta-1b (Betaseron, Extavia), peginterferon beta-1a (Plegridy), glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, natalizumab, alemtuzumab, ocrelizumab, and cladribine.

Model Structure

A cohort multi-state Markov model was developed in Microsoft Excel to simulate the disease course of RRMS patients receiving treatment with ozanimod and other DMTs. The model was based on patients transitioning across EDSS states 0 to 9, transitioning from RRMS to secondary progressive multiple sclerosis (SPMS) and death. The model consisted of 21 states (10 RRMS, 10 SPMS, and death). Patients with RRMS entered the model in an EDSS state between 0 and 5 based on the pooled patient population of the RADIANCE Part B and SUNBEAM trials.[2,3] The specific proportion in each EDSS level at baseline varied in a scenario analysis for treatment-naive patients. In each cycle, patients could transition between EDSS states and between RRMS and SPMS or enter the absorbing death state. Cycle length was 1 year, with half-cycle corrections applied to estimates of life-years and QALYs.

It was assumed that patients who either reached an EDSS score of 7 or greater or transitioned to SPMS while on treatment with DMTs would discontinue treatment. Following discontinuation, patients switched to BSC, with further transitions between EDSS states informed by natural history information. Treatment duration for alemtuzumab and cladribine was capped at 5 years, with treatment duration based on long-term observational data. The probability of death was assumed to be independent of EDSS level but higher than that of the general population.

Model Inputs

The patient cohort within the model represented the pooled clinical trial population from the RADIANCE Part B and SUNBEAM trials.[2,3]

For patients on BSC, transition probabilities between EDSS states were derived from natural history information relating to untreated RRMS and SPMS from a previously published study that used data from London, Ontario.[4] Both progression and conversion to SPMS was assumed to be irreversible; i.e., patients could not move to a lower EDSS level, and once patients transitioned to SPMS they could not revert to RRMS. This aligns with the CADTH RRMS therapeutic review.[5]

Annualized relapse rates were assumed to vary by EDSS level independent of the time in a level or time with disease.[6] Relapses were assumed not to affect progression rates. This is also consistent with the CADTH RRMS therapeutic review.[5]

For patients receiving DMTs, the natural history data were adjusted by a treatment effect derived from a sponsor-provided NMA.[7] The NMA provided estimates of relative effectiveness in the form of a hazard ratio with respect to time to confirmed disease progression at 6 months (CDP6) and rate ratios with respect to ARR. For ozanimod, the NMA result was not included. Instead, it was assumed that ozanimod had a hazard ratio for time to CDP6 equivalent to that of Avonex; the NMA estimated the hazard ratio was worse than that of Avonex. Waning of treatment effect with respect to time to disease progression was not included in the base case. A scenario analysis was provided in which treatment effects were reduced by 25% for years 3 to 5 and 50% in subsequent years.

All-cause mortality rates for the general population were derived from Statistics Canada life tables and weighted by a relative risk of mortality due to multiple sclerosis (MS) from Kingwell.[8,9] Adverse events probabilities were incorporated by collecting data from the clinical trials identified within the NMA for 24 specific adverse events.[7]

Discontinuations were a combination of loss of efficacy and tolerability. Loss of efficacy related to transition within the model to EDSS level 7 or to SPMS. In addition, an additional probability of discontinuation that was assumed to differ by DMT but be consistent across time was derived from the NMA and incorporated. For cladribine and alemtuzumab, the discontinuation rates were only applied for the first 2 years. Patient who discontinued treatment transferred to BSC. It is unclear if the discontinuation rates from the trials were adjusted to avoid double-counting discontinuations because of disease progression.

Utility weights for EDSS states (both RRMS and SPMS) without a relapse were derived from a previous analysis of data from the DEFINE and CONFIRM clinical trials using the EuroQol 5-Dimensions index score.[10] These values were also used in analysis conducted by the Institute for Clinical and Economic Review and were consistent with those from a study by Orme frequently used in CADTH pharmacoeconomic reviews.[11,12] The disutility associated with relapses was sourced form a study by Prosser et al. that is consistent with a previous CADTH MS therapeutic review.[5,13]

Disutilities for adverse events that required hospitalization were included. For those events, the proportion of patients requiring hospitalization was weighted by the duration of the event and the associated disutility to obtain the decrement.[12,14-20]

Costs for both patient management by EDSS state and relapses were derived from a previous Canadian study consistent with the CADTH RRMS therapeutic review.[5,21] Drug

costs were derived from list prices from the Ontario Drug Benefit Formulary or the Ontario Exceptional Access Program.[22] Administration and monitoring costs for each treatment were included based on product monographs, allowing for the exclusion of costs covered by sponsor patient-access schemes. Resources were costed based on appropriate Canadian-based unit costs. All costs were adjusted to 2020 Canadian dollars.

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted results based on a probabilistic analyses with 5,000 iterations. Probabilistic scenario analyses were also presented.

Base-Case Results

In the sponsor's base-case analysis, alemtuzumab was optimal as it dominated all other DMTs. Ozanimod was dominated by (it was less effective and more costly than) alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate, and Rebif. Ozanimod was more effective and more costly than Avonex at an incremental cost-effectiveness ratio (ICER) of $68,833 per QALY gained and teriflunomide at an ICER of $2.2 million. Ozanimod was less effective and less costly than ocrelizumab and natalizumab. The ICER for ocrelizumab versus ozanimod was $13,074 and the ICER for natalizumab versus ozanimod was $95,586. At a willingness-to-pay threshold of $50,000 per QALY, ozanimod could only be considered cost-effective compared to natalizumab. At a willingness-to-pay threshold of $100,000 per QALY, ozanimod could only be considered cost-effective compared to Avonex. The probability that ozanimod was optimal was 0% for all threshold values of a QALY from $0 to $500,000.

The submitted analysis is based on publicly available prices of the comparator treatments.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs versus alemtuzumab ($)	Total QALYs	Incremental QALYs versus alemtuzumab	Sequential ICER
Non-dominated therapies					
Alemtuzumab	$653,707		8.18		
Dominated therapies					
Fingolimod	$662,466	$8,759	6.97	−1.210	Dominated by alemtuzumab
Cladribine	$677,897	$24,190	7.27	−0.910	Dominated by alemtuzumab
Glatiramer acetate	$693,724	$40,017	6.81	−1.370	Dominated by alemtuzumab, fingolimod, cladribine
Plegridy	$720,220	$66,513	7.02	-1.160	Dominated by alemtuzumab, cladribine
Extavia	$731,315	$77,608	7.01	−1.170	Dominated by alemtuzumab, cladribine, Plegridy
Betaseron	$732,580	$78,873	6.95	−1.230	Dominated by alemtuzumab, fingolimod, cladribine, Plegridy, Extavia
Teriflunomide	$742,407	$88,700	6.72	−1.460	Dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron
Dimethyl fumarate	$747,660	$93,953	7.11	−1.070	Dominated by alemtuzumab, cladribine

Drug	Total costs ($)	Incremental costs versus alemtuzumab ($)	Total QALYs	Incremental QALYs versus alemtuzumab	Sequential ICER
Rebif	$751,106	$97,399	6.75	−1.430	Dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate
Avonex	$758,619	$104,912	6.64	−1.540	Dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, teriflunomide, dimethyl fumarate, Rebif
Ozanimod	$764,814	$111,107	6.730	−1.450	Dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate, Rebif
Ocrelizumab	$776,581	$122,874	7.6300	−0.5500	Dominated by alemtuzumab
Natalizumab	$851,797	$198,090	7.6400	−0.5400	Dominated by alemtuzumab

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[1]

Deterministic analysis reported similar estimates of costs, QALYs, and ICERs.

Sensitivity and Scenario Analysis Results

Probabilistic scenario analyses were conducted adopting different assumptions across the model. As concluded by the sponsor, the results of the scenario analysis did not alter those of the reference-case analysis with respect to the cost-effectiveness of ozanimod.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Indirect estimates of treatment effectiveness:** Direct clinical evidence of the relative effectiveness for ozanimod versus other DMTs is available only for Avonex. Estimates of the magnitude of the relative effect versus other DMTs is based on a sponsor-conducted NMA.[7] The clinical expert consulted by CADTH expressed concern over the lack of direct evidence comparing ozanimod to other DMTs.

  The sponsor did not use the estimated hazard ratio for ozanimod for time to CDP6 from the NMA. The sponsor's submitted analysis adopted a more favourable hazard ratio of 0.81 to make it equivalent to Avonex. This was based on the argument that the RADIANCE clinical trials found no statistically significant difference in time to CDP6 between ozanimod and Avonex. However, this is not an appropriate basis to exclude the use of estimates from the NMA in the cost-effectiveness analysis. The hazard ratio for time to CDP6 for ozanimod versus Avonex in the RADIANCE phase III study was 1.44 (95% confidence interval, 0.89 to 2.31).

  - CADTH adopted the actual hazard ratio from the NMA in the base case.

- **Extrapolation of treatment effect beyond trial time horizon:** The relative effectiveness of DMTs was assessed through a NMA for relatively short-term clinical trials (range 1 to 3 years). To counteract this issue, the sponsor adopted a short time horizon (20 years) but assumed that the relative effectiveness from short-term clinical trials would be maintained for the full 20 years. However, the sponsor provided a

scenario analysis that adopted assumptions similar to a previous CADTH drug review in RRMS: 75% of the effect size in years 3 to 5 and 50% in year 6 and onward.[23]

- As stated in the CADTH economic guidance, a longer time horizon would be appropriate. Based on input from the clinical expert, CADTH assumed a waning of treatment effect as per the sponsor's scenario analysis, but with a longer time horizon (50 years).

- **Exclusion of BSC as a comparator:** Based on recommendations within the CADTH guidelines, BSC should be considered when new technologies have not been fully adopted by decision-makers, or newer technologies represent uncertain (or poor) value. This also aligns with previous CADTH reviews for MS treatments.
  - Given the results for ozanimod versus other DMTs, the CADTH pharmacoeconomic reviewer suggested that assessing the cost-effectiveness of ozanimod versus BSC would be appropriate.

Further key assumptions made by the sponsor and appraised by CADTH are presented in Table 4.

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Use of utility values primarily from Mauskopf[10]	Probably appropriate In previous pharmacoeconomic reviews CADTH has tended to use utility values from a study by Orme but accepts that the use of values from the Mauskopf study is unlikely to greatly affect the study conclusions[10,11]
Costs for patient management by EDSS state were derived from Canadian sources [21,24]	Appropriate Consistent with the CADTH RRMS therapeutic review[5]
Constant mortality multiplier independent of EDSS	Appropriate

EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

The CADTH reanalysis addressed the limitations of the submitted model and report (Table 5).

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH base case		
1. Choice of relative effectiveness estimate for CDP6	Sponsor assumed the same effect size versus BSC for ozanimod as for Avonex	CADTH adopted the actual effect size versus BSC for ozanimod from the sponsor's NMA
2. Waning of treatment effect and time horizon	Sponsor assumed the relative treatment effect for DMTs would continue indefinitely but capped the model time horizon at 20 years	CADTH adopted a 50-year time horizon but introduced waning of treatment effect after 3 years
3. Inclusion of BSC as a comparator	Sponsor compared ozanimod to other DMTs	Given the results for ozanimod compared to DMTs, the CADTH pharmacoeconomic reviewer argues that BSc may be considered an appropriate comparator

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH base case		
CADTH base case		1 + 2 + 3

BSC = best supportive care; CDP6 = confirmed disability progression at 6 months; DMT = disease-modifying therapy; NMA = network meta-analysis.

The impact of addressing each of these assumptions on the results of the analysis are detailed in Table 6.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Result
Sponsor base case	Ozanimod is dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate, and Rebif
1. Choice of relative effectiveness estimate for CDP6	Ozanimod is dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, teriflunomide, dimethyl fumarate, Avonex, and Rebif
2. Waning of treatment effect and time horizon	Ozanimod is dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate, and Rebif
3. Inclusion of BSC as a comparator	Ozanimod is dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate, and Rebif ICER for ozanimod versus BSC = $164,540
CADTH base case	Ozanimod is dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, teriflunomide, dimethyl fumarate, Avonex, and Rebif ICER for ozanimod versus BSC = $578,039

BSC = best supportive care; CDP6 = confirmed disability progression at 6 months; ICER = incremental cost-effectiveness ratio.

When compared to all therapies in the CADTH base-case analysis, ozanimod is dominated (produces fewer QALYs at a larger cost) by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, teriflunomide, dimethyl fumarate, Avonex, and Rebif (Table 7). When including BSC, ozanimod is more effective and more costly than BSC; the ICER for ozanimod versus BSC is $578,039 per QALY. The probability that ozanimod is optimal is 0% for all threshold values of a QALY from $0 to $500,000.

Ocrelizumab and natalizumab produced higher QALY gains than ozanimod but generated higher costs to the health system. The ICER for ocrelizumab versus ozanimod was $4,418. At a willingness-to-pay threshold of $50,000 per QALY we would recommend the use of ocrelizumab over ozanimod as the additional health gains associated with ocrelizumab justify its increased cost relative to ozanimod. The ICER for natalizumab versus ozanimod was $73,436. At a willingness-to-pay threshold of $50,000 per QALY, ozanimod could be considered cost-effective, but only if natalizumab was the only available alternative as the additional health gains associated with natalizumab would not justify the additional cost.

If reimbursement of ozanimod was restricted to first-line use, then the appropriate comparators would be Avonex, Rebif, Betaseron, Extavia, Plegridy, glatiramer acetate, teriflunomide, and dimethyl fumarate. In this case, ozanimod would still not be cost-effective as it is dominated by all these alternatives.

It is worth noting that the clinical trial conducted by the sponsor showed that ozanimod was superior to interferon beta-1a (Avonex) at reducing the ARR in adult patients living with RRMS. However, the hazard ratio for time to CDP6 for ozanimod versus Avonex in the

RADIANCE phase III study was 1.44 (95% confidence interval, 0.89 to 2.31). Time to disease progression has a larger influence on QALYs within the sponsor's model, meaning that, although QALY are gained from reducing ARRs, they are counter-balanced by the increased rate of disease progression. Figure 2 and Figure 3 show the results from the sponsor's NMA for ARRs and time to disease progression. Although ozanimod reduces ARRs relative to some comparators, it has a negative impact on time to progression relative to all comparators; however, the effect is not statistically significant for some comparators. These data lead to ozanimod producing fewer QALYs than all other therapeutic options (Table 7).

The CADTH reanalysis is based on the publicly available prices of the comparator treatments.

Table 7: Summary of CADTH's Base-Case Results

Drug	Total costs ($)	Incremental costs versus fingolimod ($)	Total QALYs	Incremental QALYs versus fingolimod	ICER versus fingolimod ($)	Sequential ICER
Fingolimod	$1,098,952		6.29			
Alemtuzumab	$1,108,180	$9,228	7.24	0.950	$9,714	$ 9,714
Dominated therapies						
BSC	$1,104,350	$5,398	5.63	−0.660	Dominated by fingolimod	Dominated by fingolimod
Cladribine	$1,119,246	$20,294	6.54	0.250	$81,176	Dominated by alemtuzumab
Glatiramer acetate	$1,128,127	$29,175	6.16	−0.130	Dominated by fingolimod	Dominated by fingolimod, alemtuzumab, cladribine
Plegridy	$1,154,690	$55,738	6.35	0.060	$928,967	Dominated by alemtuzumab, cladribine
Extavia	$1,166,515	$67,563	6.33	0.040	$1,689,075	Dominated by alemtuzumab, cladribine, Plegridy
Betaseron	$1,167,069	$68,117	6.28	−0.010	Dominated by fingolimod	Dominated by fingolimod, alemtuzumab, cladribine, Plegridy, Extavia
Teriflunomide	$1,175,238	$76,286	6.09	−0.200	Dominated by fingolimod	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron
Dimethyl fumarate	$1,182,375	$83,423	6.42	0.130	$641,715	Dominated by alemtuzumab, cladribine
Rebif	$1,183,652	$84,700	6.13	−0.160	Dominated by fingolimod	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia,

Drug	Total costs ($)	Incremental costs versus fingolimod ($)	Total QALYs	Incremental QALYs versus fingolimod	ICER versus fingolimod ($)	Sequential ICER
						Betaseron, dimethyl fumarate
Avonex	$1,190,894	$91,942	6.020	−0.270	Dominated by fingolimod	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, teriflunomide, dimethyl fumarate, Rebif
Ozanimod	$1,208,397	$109,445	5.8100	−0.4800	Dominated by fingolimod	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, teriflunomide, dimethyl fumarate, Avonex, Rebif
Ocrelizumab	$1,212,948	$113,996	6.8400	0.5500	$ 207,265	Dominated by alemtuzumab
Natalizumab	$1,284,036	$185,084	6.8400	0.5500	$ 336,516	Dominated by alemtuzumab, 0crelizumab

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Scenario Analysis Results

Given the complexity of the sequential analysis, price-reduction analysis focused on the position of ozanimod on the cost-effectiveness frontier based on potential price reductions for the analysis. The analysis attempted to identify the necessary price reduction for ozanimod to be cost-effective given alternative ICER thresholds under both scenarios (Table 8).

Based on the sponsor's submitted analysis and the CADTH base-case analysis, ozanimod was not cost-effective with a 100% price reduction at a threshold of $50,000 per QALY. This was due to the fact that ozanimod produced fewer QALYs than alemtuzumab and even if the cost was $0 the cost savings would not compensate for the reduction in health.

If reimbursement was restricted to first-line use, then the appropriate comparators would be Avonex, Rebif, Betaseron, Extavia, Plegridy, glatiramer acetate, teriflunomide, and dimethyl fumarate. In this case the necessary price reduction would be 77%, at which point the ICER for glatiramer acetate versus ozanimod would exceed $50,000 per QALY.

Analysis is based on the list price of other comparators.

Issues for Consideration

Both the submitted analysis and the CADTH reanalysis are based on the publicly available prices of the comparator treatments. Conclusions must be considered in the context of any negotiated prices for DMTs.

Overall Conclusions

The sponsor submitted a cost-utility analysis that compared ozanimod to various DMTs for RRMS. The sponsor reported that ozanimod was dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate, and Rebif. The model was similar in design to the model used in a previous CADTH MS therapeutic review; however, CADTH attempted to address a few deficiencies by adding BSC as a comparator, including a treatment-waning effect, and adopting effect sizes from the NMA. The CADTH reanalysis confirmed the sponsor's conclusion that ozanimod was dominated by the same DMTs, as well as teriflunomide and Avonex.

Based on list prices, CADTH concludes ozanimod is not cost-effective, even with significant price reductions. If reimbursement is restricted to first-line use and its price reduced by 77%, ozanimod may represent a cost-effective alternative at a $50,000 per QALY threshold. This conclusion is consistent with the sponsor's submitted analysis. Although ozanimod may reduce ARRs relative to a few therapeutic options, there is no evidence it has an influence on confirmed disease progression. As the influence on confirmed disease progression has a large influence on the cost-effectiveness of therapies targeted to treat MS, this severely reduces the cost-effectiveness of ozanimod, given it is considerably more expensive than many alternatives.

Appendix 1: Cost Comparison Table

Table 8: CADTH Cost Comparison Table for Relapsing-Remitting Multiple Sclerosis

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost ($)
Ozanimod (Zeposia)	1 mg	Capsule	68.4932[b]	1 mg daily	68.49	25,000
Injectable therapies						
Glatiramer acetate (Copaxone)	20 mg/1 mL	Pre-filled syringe	47.7000	20 mg daily	47.70	17,411
Glatiramer acetate (Glatect)	20 mg/1 mL	Pre-filled syringe	32.4000	20 mg daily	32.40	11,826
Interferon beta-1a (Avonex)	30 mcg/0.5 mL	Pre-filled syringe	463.0525	30 mcg weekly	66.15	24,145
Interferon beta-1b (Betaseron)	0.3 mg powder for injection	Single-use vial	110.0000	0.25 mg every 2 days	55.00	20,075
Interferon beta-1b (Extavia)	0.3 mg powder for injection	Single-use vial	103.8640	0.25 mg every 2 days	51.93	18,955
Interferon beta-1a (Rebif)	0.22 mcg/0.5 mL 44 mcg/0.5 mL	Pre-filled syringe, cartridge, or pen	146.4372 178.2722	22 mcg to 44 mcg 3 times weekly	62.76 to 76.40	22,907 to 27,887
Peginterferon beta-1a (Plegridy)	63 mcg/0.5 mL 94 mcg/0.5 mL 125 mcg/0.5 mL	Pre-filled syringe	1,771.6000	125 mcg every 2 weeks	126.54	46,188
Infusion therapies						
Alemtuzumab (Lemtrada)	12 mg/1.2 mL	Single-use vial	1,085.9258 per mg	12 mg/day for 5 days followed by 12 mg/day for 3 days after 12 months	Daily average, Year 1: 178.51 Year 2: 107.11	Year 1: 65,156 Year 2: 39,093
Natalizumab (Tysabri)	300 mg/15 mL	Single-use vial	3,491.4300	300 mg every 4 weeks	124.69	45,513
Ocrelizumab (Ocrevus)	300 mg/10 mL	Single-use vial	8,150.0000	600 mg every 6 months[c]	89.32	32,600
Oral therapies						
Cladribine (Mavenclad)	10 mg	Tablet	3,212.0000	3.5 mg/kg over 2 years[d]	107.80	39,347
Dimethyl fumarate (Tecfidera)	120 mg 240 mg	Capsule	17.8511 35.7023	240 mg twice daily	71.40	26,063
Fingolimod (Gilenya)	0.5 mg	Capsule	86.9525	0.5 mg daily	86.95	31,738
Fingolimod (generic)	0.5 mg	Capsule	73.9096	0.5 mg daily	73.91	26,977

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost ($)
Teriflunomide (Aubagio)	14 mg	Tablet	59.0710	14 mg daily	59.07	21,561

Note: All prices are from the Ontario Drug Benefit Formulary or the Ontario Exceptional Access Program Formulary (accessed November 2020),[22] unless otherwise indicated, and do not include dispensing fees. Annual costs based on 365 days per year.

[a] Recommended doses from the appropriate product monographs unless otherwise indicated.[25-38]

[b] Sponsor-submitted price.[1]

[c] The initial 600 mg dose of ocrelizumab is administered as 2 separate intravenous infusions: a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion. Subsequent doses are administered as single 600 mg intravenous infusions every 6 months.[38]

[d] Patient weight of 70.0 kg assumed based on the SUNBEAM trial of patients with MS.[2]

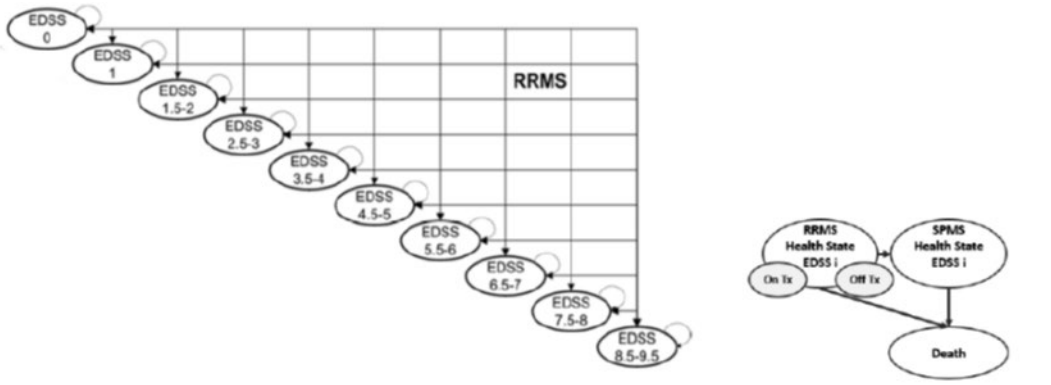
Appendix 2: Submission Quality

Table 9: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☒	☐	None
Model has been adequately programmed and has sufficient face validity	☐	☒	The model had a 1,597 IFERROR statements. These statements primarily related to cells reporting study results or defining probability distributions. IFERROR statements are problematic in that mask errors within programming and therefore should generally be unnecessary within a properly coded model. When included, these statements make the task of ensuring the validity of the model more difficult.
Model structure is adequate for decision problem	☒	☐	None
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	None
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☒	☐	The use of IFERROR statements in formulas relating to probability distributions may have led to the uncertainty around parameters being inappropriately considered.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☒	☐	None

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Sponsor's Submitted Model's Structure



Abbreviations: EDSS=Expanded Disability Status Scale; RRMS=Relapsing-remitting multiple sclerosis; SPMS=Secondary progressive multiple sclerosis; Tx: Treatment

Source: Sponsor's pharmacoeconomic submission.[1]

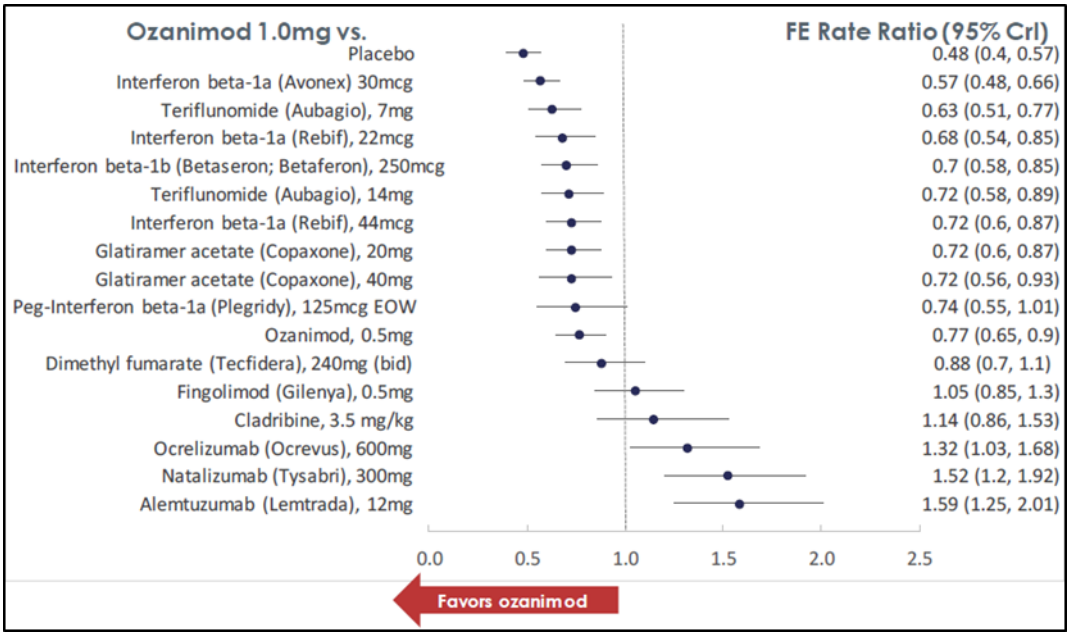
Detailed Results of the Sponsor's Base Case

Table 10 details the disaggregated results of the sponsor's base case.

Table 10: Disaggregated Summary of Sponsor's Base Case

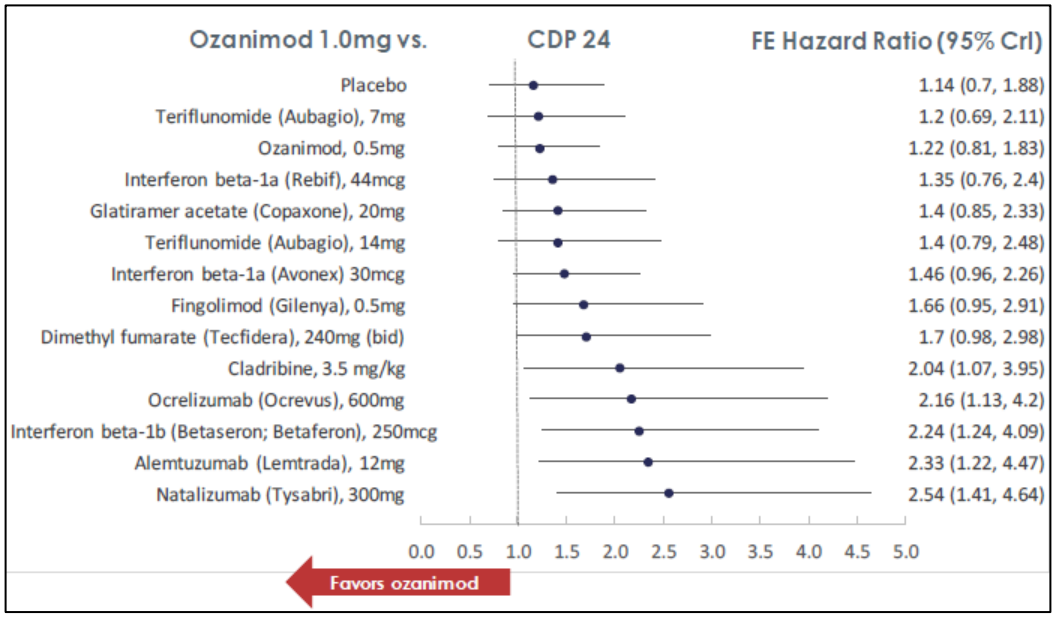
	Total costs ($)	Direct medical costs	Other direct costs	Relapse costs (not hospitalization)	Relapse costs (hospital-ization)	Acquisition costs	Administration costs	Monitoring costs	Adverse event costs	Total QALYs	Life-years
Ozanimod	$764,814	$483,704	$72,299	$43,457	$31,143	$133,885	$0	$154	$171	6.73	20.01
Avonex	$758,619	$486,348	$72,690	$50,688	$36,336	$111,662	$0	$211	$683	6.64	20.01
Rebif	$751,106	$481,196	$71,956	$48,333	$34,632	$114,203	$0	$191	$594	6.75	20.01
Glatiramer acetate	$693,724	$478,829	$71,598	$47,342	$33,932	$61,442	$0	$0	$580	6.81	20.01
Teriflunomide	$742,407	$483,096	$72,218	$47,654	$34,151	$104,725	$0	$186	$378	6.72	20.01
Fingolimod	$662,466	$472,026	$70,592	$42,444	$30,413	$46,427	$0	$153	$412	6.97	20.01
Dimethyl fumarate	$747,660	$464,001	$69,453	$45,503	$32,623	$135,614	$0	$138	$328	7.11	20.01
Alemtuzumab	$653,707	$412,927	$62,002	$37,737	$27,038	$112,171	$134	$1,000	$697	8.18	20.01
Natalizumab	$851,797	$439,325	$65,853	$39,588	$28,381	$277,002	$0	$1,569	$79	7.64	20.01
Ocrelizumab	$776,581	$439,035	$65,845	$42,313	$30,324	$198,550	$172	$0	$343	7.63	20.01
Betaseron	$732,580	$471,710	$70,564	$47,937	$34,343	$106,924	$0	$233	$870	6.95	20.01
Cladribine	$677,897	$457,060	$68,411	$41,597	$29,806	$80,729	$0	$32	$261	7.27	20.01
Extavia	$731,315	$468,414	$70,077	$47,531	$34,047	$110,098	$0	$253	$895	7.01	20.01
Plegridy	$720,220	$468,177	$70,085	$48,485	$34,751	$97,503	$0	$194	$1,025	7.02	20.01

Figure 2: Network Meta-Analysis Results Used in the Economic Model for the Annualized Relapse Rate (Rate Ratio)



Source: Sponsor-submitted indirect treatment comparison.[7]

Figure 3: Network Meta-Analysis Results Used in the Economic Model for Confirmed Disability Progression at 24 Weeks (Hazard Ratio)



Source: Sponsor-submitted indirect treatment comparison.[7]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Table 11 provides a detailed breakdown of CADTH's reanalysis.

Table 11: Disaggregated Summary of CADTH's Reanalysis

	Total costs ($)	Direct medical costs	Other direct costs	Relapse costs (not hospitalization)	Relapse costs (hospitalization)	Acquisition costs	Administration costs	Monitoring costs	Adverse event costs	Total QALYs	Life-years
Ozanimod	$1,208,397	$855,478	$125,879	$58,099	$41,628	$126,995	$0	$147	$170	5.81	28.09
BSC	$1,104,350	$862,015	$126,811	$67,302	$48,223	$0	$0	$0	$0	5.63	28.09
Avonex	$1,190,894	$843,422	$124,155	$65,415	$46,883	$110,127	$0	$208	$682	6.02	28.09
Rebif	$1,183,652	$838,826	$123,506	$63,085	$45,197	$112,258	$0	$188	$592	6.13	28.09
Glatiramer acetate	$1,128,127	$837,415	$123,298	$62,086	$44,491	$60,261	$0	$0	$576	6.16	28.09
Teriflunomide	$1,175,238	$840,728	$123,771	$62,414	$44,721	$103,043	$0	$184	$378	6.09	28.09
Fingolimod	$1,098,952	$832,219	$122,542	$57,278	$41,037	$45,314	$0	$149	$412	6.29	28.09
Dimethyl fumarate	$1,182,375	$825,361	$121,578	$60,261	$43,191	$131,522	$0	$134	$328	6.42	28.09
Alemtuzumab	$1,108,180	$787,192	$116,107	$52,979	$37,954	$112,123	$134	$993	$697	7.24	28.09
Natalizumab	$1,284,036	$806,441	$118,866	$54,610	$39,138	$263,409	$0	$1,492	$79	6.84	28.09
Ocrelizumab	$1,212,948	$805,633	$118,770	$57,208	$40,991	$189,838	$164	$0	$343	6.84	28.09
Betaseron	$1,167,069	$831,692	$122,479	$62,639	$44,871	$104,295	$0	$228	$865	6.28	28.09
Cladribine	$1,119,246	$820,443	$120,854	$56,474	$40,460	$80,722	$0	$32	$261	6.54	28.09
Extavia	$1,166,515	$829,322	$122,135	$62,221	$44,568	$107,134	$0	$246	$889	6.33	28.09
Plegridy	$1,154,690	$827,979	$121,970	$63,178	$45,273	$95,083	$0	$189	$1,018	6.35	28.09

Table 12 outlines the cost-effectiveness of ozanimod at varying price reductions.

Table 12: Price-Reduction Analysis

	Price-reduction analysis for ozanimod	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	Dominated by alemtuzumab, fingolimod, cladribine, Glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate, Rebif	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, teriflunomide, dimethyl fumarate, Avonex, Rebif
10%	Dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, dimethyl fumarate, Rebif	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, teriflunomide, dimethyl fumarate, Avonex, Rebif
20%	Dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron, teriflunomide, dimethyl fumarate
30%	Dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate, Plegridy	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy, Extavia, Betaseron
40%	Dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate, Plegridy
50%	Dominated by alemtuzumab, fingolimod, cladribine, glatiramer acetate	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate
60%	Dominated by alemtuzumab, fingolimod, cladribine	Dominated by fingolimod, alemtuzumab, cladribine, glatiramer acetate
70%	Dominated by alemtuzumab, fingolimod	Dominated by fingolimod, alemtuzumab, cladribine
80%	Dominated by alemtuzumab	Dominated by fingolimod
90%	$6,476 (ICER for alemtuzumab versus ozanimod)	$9,845 (ICER for alemtuzumab versus ozanimod)
100%	$15,709 (ICER for alemtuzumab versus ozanimod)	$18,726 (ICER for alemtuzumab versus ozanimod)

ICER = incremental cost-effectiveness ratio.

Appendix 5: Submitted Business Impact Analysis and CADTH Appraisal

Key take-aways of the business impact analysis

- CADTH identified the following key considerations for the sponsor's analysis
  - Some uncertainty around the compliance estimates for therapies due to a lack of empirical evidence.
- CADTH's budget impact analysis (BIA) base case did not differ from the sponsor's base case, which estimated a budget impact for funding ozanimod for RMS to be $42,507 in year 1, $1,312,776 in year 2, and $2,940,000 in year 3, for a total of $4,295,284 over the 3-year time horizon.
- CADTH found the BIA to be somewhat influenced by market share assumptions.

Summary of Sponsor's Business Impact Analysis

The submitted BIA assessed the introduction of ozanimod as a treatment for adult patients with RRMS. The analysis was undertaken from a drug plan perspective using a claims-based approach and included drug acquisition costs, mark-up, and dispensing fees. Patient adherence was also considered in the base case, with estimates of 77%, 65%, and 92% for oral, injectable, and infusion therapies, respectively. A 3-year time horizon was used, from October 2021 to September 2024, with October 2020 to September 2021 as a base year. Market size was estimated based on historical drug dispensing data for RRMS patients and was assumed to grow at the same rate as the overall Canadian population.

The relevant comparators for this analysis included alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, natalizumab, peginterferon beta-1a, ocrelizumab, and teriflunomide. Market shares for each comparator were estimated using historical trends from 2017 to 2019 to make forward-looking projections. In the reference scenario ozanimod was assumed to not be available, and in the new scenario ozanimod was assumed to capture 0.1%, 3.0%, and 6.5% of the total market for RRMS in years 1, 2, and 3, respectively. This uptake was modelled after that of teriflunomide, a recently approved oral therapy indicated for the treatment of RRMS. Key inputs to the BIA are documented in Table 13.

Table 13: Summary of Key Model Parameters

Parameter	Sponsor's estimate (Year 1 / Year 2 / Year 3)
Target population	
Growth rate of Canadian population	1.3%
Number of patients eligible for drug under review	9,328 / 9,448 / 9,570
Number of patients treated with ozanimod	9 / 283 / 621
Market uptake for Ontario (3 years)	
Uptake (reference scenario)	
Ozanimod	0% / 0% / 0%
Fingolimod	5.2% / 4.6% / 4.1%
Teriflunomide	21.9% / 24.1% / 26.3%
Dimethyl fumarate	19.2% / 18.7% / 18.1%
Interferon β-1a	16.5% / 14.1% / 11.7%
Interferon β-1b	4.0% / 3.4% / 2.9%
Peginterferon β-1a	0.9% / 0.8% / 0.7%
Glatiramer acetate	22.4% / 21.7% / 21.0%
Alemtuzumab	0.7% / 0.6% / 0.6%
Ocrelizumab	5.3% / 7.9% / 10.5%
Natalizumab	2.1% / 1.7% / 1.2%
Cladribine	1.6% / 2.3% / 3.1%
Uptake (new drug scenario)	
Ozanimod	0.1% / 3.0% / 6.5%

Parameter	Sponsor's estimate (Year 1 / Year 2 / Year 3)
Fingolimod	5.2% / 3.6% / 1.8%
Teriflunomide	21.9% / 23.8% / 25.7%
Dimethyl fumarate	19.2% / 18.0% / 16.6%
Interferon beta-1a	16.5% / 13.9% / 11.3%
Interferon beta-1b	4.0% / 3.2% / 2.5%
Peginterferon beta-1a	0.9% / 0.7% / 0.5%
Glatiramer acetate	22.4% / 21.1% / 19.8%
Alemtuzumab	0.7% / 0.6% / 0.6%
Ocrelizumab	5.3% / 7.9% / 10.5%
Natalizumab	2.1% / 1.7% / 1.2%
Cladribine	1.6% / 2.3% / 3.1%
Cost of treatment (per patient)	
Cost of annual treatment (drug acquisition)	
Ozanimod	$25,017
Fingolimod	$26,996
Teriflunomide	$21,576
Dimethyl fumarate	$25,329
Interferon beta-1a	$24,966
Interferon beta-1b	$19,528
Peginterferon beta-1a	$22,339
Glatiramer acetate	$14,460
Alemtuzumab	$65,156
Ocrelizumab	$32,600
Natalizumab	$44,026
Cladribine	$44,968

Note: Market shares vary by jurisdiction. Ontario shares may not be representative of pan-Canadian market shares.

Summary of the Sponsor's Business Impact Analysis Results

The estimated budget impact of funding ozanimod for the treatment of RRMS was expected to be $42,507 in year 1, $1,312,776 in year 2, and $2,940,000 in year 3, for a total of $4,295,284 over the 3-year time horizon.

CADTH Appraisal of the Sponsor's Business Impact Analysis

CADTH identified several key limitations to the sponsor's analysis.

- **Drug compliance:** The sponsor assumed there would be compliance issues for all drugs. Specifically, it was estimated that 77% of oral, 65% of injectable, and 92% of infusion therapies would be claimed, based on feedback from the sponsor's clinical advisors. The clinical expert consulted by CADTH suggested that compliance would be most important for those drugs given less frequently.
  - CADTH conducted scenario analyses around the compliance estimates, increasing the estimates to 100% for all drugs and then for ozanimod specifically.

CADTH Reanalyses of the Business Impact Analysis

CADTH did not undertake reanalysis of the sponsor's BIA. The base-case analysis remained unchanged from the sponsor's base case and is presented in Table 14. Based on the BIA base case, the expected budget impact for funding ozanimod for RRMS is expected to be $42,507 in year 1, $1,312,776 in year 2, and $2,940,000 in year 3, for a total of $4,295,284 over the 3-year time horizon.

Table 14: Detailed Breakdown of the CADTH Scenario Analyses of the BIA

Stepped analysis	Scenario	Year 1	Year 2	Year 3	Three-year total
BIA base case (unchanged)	Reference	$178,099,000	$183,197,630	$188,454,374	$549,751,003
	New drug	$178,141,507	$184,510,406	$191,394,374	$554,046,287
	Budget impact	**$42,507**	**$1,312,776**	**$2,940,000**	**$4,295,284**
CADTH scenario analysis 1a: compliance is assumed to be 100% for all drugs	Reference	$236,180,624	$240,304,374	$244,574,223	$721,059,221
	New drug	$236,225,927	$241,713,901	$247,746,318	$725,686,147
	Budget impact	**$45,303**	**$1,409,528**	**$3,172,095**	**$4,626,926**
CADTH scenario analysis 1b: compliance is assumed to be 100% for ozanimod	Reference	$178,099,000	$183,197,630	$188,454,374	$549,751,003
	New drug	$178,199,326	$186,253,388	$195,213,667	$559,666,381
	Budget impact	**$100,326**	**$3,055,759**	**$6,759,293**	**$9,915,377**

BIA = budget impact analysis.

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