CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

OCRELIZUMAB (OCREVUS)

(Hoffmann-La Roche Limited)

Indication: Treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features.

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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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Table of Contents

List of Tables

List of Figure

CADTH

Abbreviations

AE	adverse event
ARR	annualized relapse rate
CDP	confirmed disability progression
CDR	CADTH Common Drug Review
DMT	disease-modifying therapy
EDSS	Kurtzke Expanded Disability Status Scale
EQ-5D-3L	EuroQol 5-Dimensions 3-Level questionnaire
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
LY	life-year
MS	multiple sclerosis
NICE	National Institute for Health and Clinical Excellence
NMA	network-meta-analysis
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RMS	relapsing forms of multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary-progressive multiple sclerosis

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Ocrelizumab (Ocrevus) 300 mg vial
Study Question	What is the incremental cost-effectiveness of ocrelizumab for the treatment of RRMS as compared with available therapies in Canada?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with RRMS in Canada
Treatment	Ocrelizumab 600 mg IV every 6 months
Outcome(s)	LYs Quality-adjusted life-years (QALYs)
Comparator(s)	• Alemtuzumab 12 mg IV (initial: once daily for 5 days; second dosage (after 12 months): once daily for 3 days) • Daclizumab 150 mg SC once monthly • Dimethyl fumarate 120 mg twice daily (initial), then 240 mg twice daily • Fingolimod 0.5 mg once daily • Glatiramer acetate 20 mg SC once daily • Natalizumab 300 IV every 4 weeks • Pegylated interferon beta-1a SC (initial: 63 mcg; day 14: 94 mcg; day 28 onward: 125 mcg once every two weeks) • Interferon beta 1-a 44 mcg SC three times weekly • Teriflunomide 14 mg once daily
Perspective	Canadian public health care payer
Time Horizon	Lifetime (approximately 63 years)

Results for Base Case	• Ocrelizumab was less costly and more effective (i.e., more QALYs gained) when compared with daclizumab, fingolimod, and natalizumab.
	• Ocrelizumab was more costly, yet more effective, when compared with alemtuzumab, dimethyl fumarate, glatiramer acetate, interferon beta-1a, pegylated interferon beta-1a, and teriflunomide, resulting in ICERs ranging from $20,300 to $39,600 per QALY gained.
	• In a sequential analysis, considering all comparators:
	  ○ ocrelizumab was more costly and more effective than pegylated interferon beta-1a, resulting in an ICER of $46,121 per QALY gained
	  ○ all other treatments were either dominated or subject to extended dominance.
	• The probability that ocrelizumab was cost-effective, given a willingness-to-pay threshold of $50,000 per QALY was 36.2%.

Key Limitations	• Uncertainty with the estimates from the manufacturer-commissioned indirect treatment comparison owing to reliance on mixed treatment-naive and/or treatment-experienced trials for evidence synthesis, lack of assessment of the impact of clinical heterogeneity, and lack of statistical analysis for inconsistency. • Reliance on 12-week confirmed disability progression (CDP-12) estimates is problematic, as this may be a poor indicator of permanent disease worsening. • The approach to modelling duration of treatment and efficacy was biased against alemtuzumab and unsupported by evidence. • The submitted model lacked transparency and was unnecessarily complex. This was not addressed by the manufacturer despite CDR's requests. This made both the assessment of validity and the ability to conduct reanalysis challenging.
CDR Estimate(s)	The CDR reanalysis, accounting for identified limitations, found that ocrelizumab was not a cost-effective treatment for adult patients with RRMS when considering all available therapies, regardless of a decision-maker's willingness-to-pay threshold for a QALY gain; the probability that ocrelizumab was cost-effective at a willingness-to-pay threshold of $50,000 per QALY was 2.0%.

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; IV = intravenous; LY = life-year; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous.

Drug	Ocrelizumab (Ocrevus)
Indication	Treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features
Reimbursement Request	Monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis
Dosage Form(s)	300 mg vial
NOC Date	August 14, 2017
Manufacturer	Hoffmann-La Roche Limited

Executive Summary

Background

Ocrelizumab (Ocrevus) is a recombinant humanized monoclonal antibody that selectively targets and depletes B cells that express CD20, which are thought to contribute to the inflammatory and neurodegenerative pathogenesis of multiple sclerosis (MS).[1] Ocrelizumab is indicated for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS).[2] It is available in 300 mg single-use vials for infusion. It is recommended that an initial 600 mg dose be administered as two separate intravenous (IV) infusions (initial 300 mg infusion followed by a second 300 mg infusion two weeks later), with subsequent ocrelizumab doses administered as single 600 mg IV infusions every six months. At the manufacturer's submitted unit price of $8,150 per 300 mg vial, ocrelizumab costs $32,600 per patient per year.[1] The manufacturer's reimbursement request is per the Health Canada indication.[1]

The manufacturer submitted a cost-utility analysis based on a Markov state-transition model, comparing ocrelizumab with currently available treatments for adult patients with RRMS. Comparators included other infusion

therapies (alemtuzumab and natalizumab), as well as injectable therapies (interferon beta-1a, interferon beta-1b, pegylated interferon beta-1a, glatiramer acetate, daclizumab) and oral therapies (dimethyl fumarate, fingolimod, teriflunomide). In the model, patients transitioned between Kurtzke Expanded Disability Status Scale (EDSS) states 0 through 9 in RRMS and EDSS states 0 through 9 in secondary-progressive MS (SPMS), and could progress from RRMS to SPMS; at any point, patients could also transition to the absorbing death state. The analysis was run over a lifetime time horizon (approximately 63 years) using annual cycles and undertaken from the perspective of the Canadian public health care payer. Data on disease progression and relapses in the absence of treatment were derived from two natural-history information sources: the British Columbia MS database, as reported by Palace et al.,[3] and the London, Ontario, database.[1] The effects of treatment on disease progression and rate of relapse were derived from a manufacturer-commissioned unpublished network meta-analysis.[4]

The manufacturer reported that ocrelizumab dominated daclizumab, fingolimod, and natalizumab in the base-case analysis, as it was less costly and produced more quality-

adjusted life-years (QALYs) than these treatments. When compared with alemtuzumab, dimethyl fumarate, glatiramer acetate, interferon beta-1a, pegylated interferon beta-1a, and teriflunomide, ocrelizumab was more costly yet more effective than these comparators and resulted in incremental cost-utility ratios (ICURs) that ranged from $20,328 per QALY gained (versus dimethyl fumarate) and $39,626 per QALY gained (versus pegylated interferon beta-1a). No large survival differences were predicted between comparators in terms of life-years gained. Sequential ICUR analysis of the manufacturer's base-case results found that ocrelizumab was the optimal therapy at a willingness-to-pay threshold greater or equal to $46,121; if a decision-maker's willingness-to-pay for a QALY gain is less than $46,122, then pegylated interferon beta-1a is the optimal therapy. All other treatments were either dominated or subject to extended dominance based on findings from the manufacturer's probabilistic analysis.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified the following primary limitations relating to the manufacturer's economic model:

- **Reliance on a 12-week confirmation period for disability progression:** The economic model used efficacy inputs for permanent disease worsening from a manufacturer-commissioned network meta-analysis; specifically, it used estimates of confirmed disability progression (CDP) based on a 12-week confirmation period. However, use of data for CDP at 12 weeks is problematic, given the possibility of recovery from a relapse in the early stages of RRMS, making this a poor indicator of permanent disease worsening. Confirmed disability progression is a more robust measure when performed over a 24-week period, and estimates of 24-week CDP are likely to better reflect clinical outcomes over an annual cycle. A 24-week confirmation period for the change in EDSS score is therefore deemed to be a better indicator of permanent disability progression than a 12-week confirmation period. Nevertheless, relying on such relatively short-term clinical data for assessing the cost-effectiveness of the continued use of disease-modifying therapies (DMTs) over a longer time period is a significant limitation that may overestimate the effectiveness of treatments.
- **Duration of treatment and efficacy:** Full efficacy of treatment was applied in the model for the duration of treatment for all DMTs except alemtuzumab. Treatment was assumed to continue for the duration of the model time horizon (approximately 63 years) unless patients experienced treatment failure, transitioned to an SPMS health state, or reached a disease stage at which treatment was discontinued (EDSS level 7). However, the model assumed that treatment with alemtuzumab would be continued for no more than two years. Given the paucity of published evidence for disability progression for any DMT used in the treatment of RRMS beyond 24 weeks, this approach for modelling treatment duration and efficacy was unfounded and biased against alemtuzumab. It may therefore be more appropriate to base the durability of treatment response and accrual of treatment costs on the same assumptions for all modelled comparators.
- **Uncertainty with comparative clinical information:** Disability progression and rate of relapse were incorporated in the model based on estimates from an unpublished network meta-analysis conducted by the manufacturer. However, these estimates of relative efficacy may be limited owing to several factors, including reliance on a mixture of studies reporting on treatment-naive and/or treatment-experienced patients for indirect treatment comparison, leading to uncertainty regarding the response to treatment among patients who have previously failed DMT and are likely to receive ocrelizumab; insufficient assessment of the potential impact of clinical heterogeneity across included studies on the estimates of treatment effect; and lack of statistical analysis for inconsistency, which brings into question the reliability of the synthesized evidence.

CDR identified several other parameters of uncertainty, including health-state utility values, the treatment cost of daclizumab, and natural-history data. These parameters were considered in combination with key limitations relating to the use of data for CDP at 12 weeks and the assumption regarding treatment duration and efficacy in defining the CDR base case. CDR reanalysis, accounting for these limitations and considering all available RRMS treatments, suggested that ocrelizumab was not cost-effective, regardless of a decision-maker's willingness-to-pay threshold for a QALY gain. The probability that ocrelizumab was cost-effective at a willingness-to-pay threshold of $50,000 per QALY was 2.0%, and at a willingness-to-pay threshold of $100,000, it was 12.9%. Sequential ICUR analysis of the CDR base case found that pegylated interferon beta-1a was the optimal therapy at a willingness-to-pay threshold of less than $151,610 per QALY gained, while daclizumab is the optimal therapy if a decision-maker's willingness to pay for a QALY gain was greater than $151,610 but less than $258,857. If a decision-maker's willingness to pay for one QALY was greater than $258,857, alemtuzumab was the optimal therapy.

Conclusions

When considering all available therapies, CDR found that ocrelizumab was not a cost-effective treatment for adult patients with RRMS, regardless of a decision-maker's willingness to pay for a QALY gain, with a 2.0% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY, and a 12.9% probability of being cost-effective at a willingness-to-pay threshold of $100,000 per QALY. At a price reduction of 50% or greater (of the submitted price), the probability that ocrelizumab would be cost-effective at a willingness-to-pay threshold of $50,000 per QALY is above 80%.

Given the lack of transparency in the manufacturer-submitted model, which made both the assessment of validity and the ability to conduct reanalysis challenging, results may warrant careful interpretation.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted an economic model that captured health outcomes in terms of life-years (LYs) gained and quality-adjusted life-years (QALYs) gained. The model compared the cost-effectiveness of ocrelizumab and other therapies for relapsing-remitting multiple sclerosis (RRMS) reimbursed in Canada, including other infusion therapies (alemtuzumab, natalizumab), injectable therapies (interferon beta-1a, pegylated interferon beta1a, glatiramer acetate, daclizumab), and oral pharmacotherapies (dimethyl fumarate, fingolimod, teriflunomide).1 The target population was adult patients with RRMS, as in the OPERA-I and OPERA-II clinical trials.5,6 The modelled patients were on average assumed to be 37 years at the time of entry into the model; patients were also predominantly female (66%) and were distributed across different Kurtzke Expanded Disability Status Scale (EDSS) scores based on the baseline distribution observed in the OPERA trials. The model was run using annual cycles over a lifetime time horizon (approximately 63 years) in the base case. All costs and outcomes were discounted at an annual rate of 1.5%, and the analysis 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 patients with relapsing multiple sclerosis (RMS) receiving treatment with ocrelizumab and other relevant comparators based on a progression through EDSS scores. The model was based on EDSS scores 0 through 9 in RRMS (modelled as RRMS-treated and RRMS-untreated, separately), EDSS scores 0 through 9 in secondary-progressive multiple sclerosis (SPMS), and death. Patients with RRMS entered the model at one of the 10 EDSS scores under RRMS-treated (i.e., patients with RRMS treated with either ocrelizumab or another comparator), as illustrated in Figure 1 of Appendix 4. In each annual cycle, patients could then: (1) transition between EDSS states within RRMS-treated; (2) discontinue treatment and transition to RRMS-untreated; (3) progress to SPMS; or (4) transition to the absorbing death state. The transition from RRMS-treated to RRMS-untreated in EDSS scores 0 to 6 was based on treatment-specific all-cause discontinuation rates derived from the manufacturer-submitted network meta-analysis (NMA), while it was assumed that patients who reached an EDSS of score 7 or greater while receiving treatment would discontinue treatment. Following discontinuation, patients switched to RRMS-untreated and transitioned between EDSS states within this category, as informed by natural-history data.[3] The transitions from RRMS-treated and RRMS-untreated to SPMS and transitions within SPMS were also informed by natural-history data.[1,3] At any point, patients could transition to death, as informed by general population mortality, adjusted by EDSS state-specific mortality multipliers,[7] with no direct treatment effect assumed.

Model Inputs

For patients receiving treatment (i.e., RRMS-treated), transition probabilities between EDSS states were derived from natural-history information on untreated patients with RMS reported by Palace et al.,[3] adjusted by a treatment effect derived from the manufacturer's

NMA.[4] After discontinuing treatment (ocrelizumab or other therapy), patients were assumed to no longer be receiving a disease-modifying therapy (DMT) (i.e., RRMS-untreated), and that they transitioned between EDSS states within RRMS based on the Palace et al. data, which were derived from 898 untreated patients with RMS in the British Columbia Multiple Sclerosis (BCMS) database during the 1980 to 1995 period.[3] After entry into the model, patients with RRMS could progress to a higher or lower EDSS score or remain at the same EDSS score annually.

The probabilities of transition from RRMS to SPMS were based on natural-history data from the London, Ontario, data set, which captured at least 16 years of prospective follow-up data on patients from the London Multiple Sclerosis clinic in London, Ontario.[1] Transition from RRMS to SPMS is dependent on EDSS score and treatment. The treatment indirectly affects transition to SPMS, as conversion to SPMS increases with EDSS score.

The transition probabilities between EDSS states within SPMS were also based on the data reported by Palace et al.[3] The analyses in Palace et al. were based on a pooled population of patients with RRMS and SPMS who did not receive treatment. Similar to the application of Palace et al. data to RRMS, improvement in EDSS score was allowed when these data were applied to SPMS.

Natural-history annualized relapse rate (ARR) was informed by the United Kingdom (UK) multiple sclerosis (MS) survey and data from Patzold and Pocklington.[8] Treatment effects on disease progression and relapse rates were informed by the manufacturer's NMA[4] and assumed to remain constant over the time when patients were receiving treatment, without considering waning effects. For each treatment, the same relative effects on disability progression and relapse rates were assumed, regardless of EDSS score, due to limited data availability. It was assumed that relapses would not require hospitalization. The annual probability of adverse events (AEs) for ocrelizumab was derived from the OPERA-I and OPERA-II trial data,[5,6] while the annual AE rates for other comparators were obtained from the recent Biogen daclizumab submission to the UK National Institute for Health and Care Excellence (NICE).[9] Only those AEs with an annual risk of occurrence greater than or equal to 5% were included in the analysis. Mortality rates were estimated based on all-cause mortality data for the Canadian general population, adjusted by the female-to-male ratio of RRMS patients used in the model and by EDSS state-specific mortality multipliers sourced from Pokorski et al.[7]

Health-state utilities in the model were based on disease severity (as measured by EDSS) and disease phase (RRMS or SPMS). The utilities by EDSS in RRMS health states were elicited using the UK value set[10] for the EuroQol 5-Dimensions 3-Level questionnaire (EQ-5D-3L) values recorded from the OPERA trials; utility values for EDSS scores 8 and 9 were derived using utility weights from a cross-sectional study by Orme et al.,[11] as small sample sizes from the OPERA trials did not allow direct elicitation of these EDSS-specific utility values.[1] For patients who experienced a relapse without hospitalization or who transitioned from RRMS to SPMS, a further utility loss was applied in the model. Each relapse was assumed to last 46 days, as reported in a published University of Sheffield School of Health and Related Research report of beta interferons and glatiramer acetate.[12] Costs included were those for disease management (excluding costs of DMTs and relapses), administration and monitoring, and drug acquisition (excluding dispensing fees or mark-ups), as well as costs for non-hospitalized relapse and AEs; all costs were reported in 2017 Canadian dollars.

Manufacturer's Base Case

The manufacturer reported that ocrelizumab was associated with a cost of $770,304 and 13.76 QALYs over the model time horizon (Table 2). Ocrelizumab dominated daclizumab, fingolimod, and natalizumab in the base case, suggesting that ocrelizumab was associated with lower total costs and better outcomes (greater QALYs gained) when compared with these treatments. When compared with alemtuzumab, dimethyl fumarate, glatiramer acetate, interferon beta-1a, pegylated interferon beta-1a, and teriflunomide, the resulting incremental cost-utility ratios (ICURs) ranged from $20,328 per QALY gained (versus dimethyl fumarate) to $39,626 per QALY gained (versus pegylated interferon beta 1-a). There were no large survival differences predicted between comparators, with LY estimates ranging from 27.48 years (alemtuzumab) to 27.93 years (ocrelizumab) over a lifetime time horizon (approximately 63 years).

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

	Total Costs ($)	Incr. Cost Vs. OCR ($)	Total QALYs	Incr. QALYs Vs. OCR	ICUR ($/QALY) for OCR Vs. Comparator	Total LYs	Incr. LYs Vs. OCR	ICER ($/LY) for OCR Vs. Comparator
Ocrelizumab	**770,304**	**–**	**13.757**	**–**	**–**	**27.927**	**–**	**–**
Alemtuzumab	704,668	65,636	11.746	2.010	32,651	27.480	0.447	146,694
Daclizumab	789,784	–19,480	12.370	1.387	Ocrelizumab dominant	27.622	0.305	Ocrelizumab dominant
Dimethyl fumarate	739,265	31,039	12.230	1.527	20,328	27.600	0.327	94,785
Fingolimod	784,183	–13,878	12.010	1.746	Ocrelizumab dominant	27.558	0.369	Ocrelizumab dominant
Glatiramer acetate	707,420	62,884	11.799	1.957	32,126	27.522	0.406	155,049
Interferon beta-1a SC	724,660	45,644	12.073	1.684	27,104	27.571	0.357	127,970
Natalizumab	919,671	–149,366	13.111	0.646	Ocrelizumab dominant	27.833	0.094	Ocrelizumab dominant
Pegylated interferon beta-1a	702,666	67,639	12.050	1.707	39,626	27.558	0.369	183,324
Teriflunomide	717,494	52,811	12.052	1.704	30,984	27.564	0.364	145,160

ICUR = incremental cost-utility ratio; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life-year; OCR = ocrelizumab; QALY = quality-adjusted life-year; SC = subcutaneous; vs. = versus.

Note: All costs are presented in 2017 Canadian dollars.

Source: Total costs, LYs, and QALYs are deterministic values, as reported in the manufacturer's submission report and based on the original economic model submitted to CDR.[1]

The manufacturer's submission was revised to reflect recent CADTH guidelines,[13] which indicate that the result of the manufacturer's base case should be presented sequentially through probabilistic analysis. This analysis involves comparing less costly comparators with the next most costly comparator and excluding all comparators that are either dominated or subject to extended dominance. In this analysis, ocrelizumab was found to be the optimal therapy at a willingness-to-pay threshold greater or equal to $46,121 per QALY. If a decision-maker's willingness to pay for a gain in QALY is less than $46,121, pegylated interferon beta-1a is the optimal therapy. All other treatments are either dominated or subject to extended dominance based on the manufacturer's probabilistic base-case results.

Table 3: Sequential Incremental Cost-Effectiveness Ratio Analysis Results of the Manufacturer's Base Case

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Peginterferon beta-1a	742,261	12.324		
Ocrelizumab	812,692	13.852	46,121	46,121
Dominated options				
Alemtuzumab	744,114	12.026	Dominated by pegylated interferon beta-1a	
Glatiramer acetate	744,737	12.108	Dominated by pegylated interferon beta-1a	
Fingolimod	820,261	12.279	Dominated by pegylated interferon beta-1a	
Interferon beta-1a SC	763,721	12.315	Dominated by pegylated interferon beta-1a	
Daclizumab	828,602	12.587	329,490	Dominated by ocrelizumab
Natalizumab	953,267	13.255	226,878	Dominated by ocrelizumab
Teriflunomide	755,720	12.326	11,639,362	Subject to extended dominance through ocrelizumab and pegylated interferon beta-1a
Dimethyl fumarate	776,755	12.501	194,892	Subject to extended dominance through ocrelizumab and pegylated interferon beta-1a

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

Note: All costs are presented in 2017 Canadian dollars.

Source: Total costs and total QALYs are probabilistic values sourced from the manufacturer's updated model submitted to CDR.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted both deterministic (DSAs) and probabilistic sensitivity analyses (PSAs).

DSAs were performed to determine the impact of individual model parameter inputs on the base-case results, where the manufacturer considered a number of parameters (e.g., time horizon, perspective, patient demographics, natural-history information, duration of treatment effect with alemtuzumab, utility values, discontinuation rates, and monitoring costs). The parameters that had the largest impact on the manufacturer's base case were: reducing the time horizon to two years, conducting the analysis from the societal perspective, varying the duration of alemtuzumab efficacy, and using the data for confirmation of disease progression (CDP) at 24 weeks. Specifically, if full alemtuzumab efficacy was assumed for the first nine years, followed by a 25% decrease in efficacy for year 10 and beyond, ocrelizumab was dominated by alemtuzumab. Conversely, if full alemtuzumab efficacy was assumed for the first five years, followed by a 25% decrease in efficacy from years 6 through 9 and a 50% decrease in efficacy for years 10 and beyond, ocrelizumab was more costly and more effective than alemtuzumab, resulting in an instrumental cost-effectiveness ratio (ICER) of $332,947 per QALY gained. In all other cases, ocrelizumab continued to dominate daclizumab, fingolimod, and natalizumab, and was more costly and more effective than other DMTs. Results of a one-way sensitivity analysis in which estimates of CDP at 24 weeks were used instead of CDP values at 12

weeks showed that ocrelizumab was dominant over daclizumab and fingolimod, but less costly and less effective than natalizumab. When compared with all other DMTs, ocrelizumab led to ICERs ranging from $25,100 per QALY gained (versus interferon beta-1a) to $109,900 per QALY gained (versus pegylated interferon beta-1a). In addition to a DSA, key variables used in the model were included as part of a PSA, and the inputs for these variables were drawn randomly and simultaneously, based on specified distributions, to calculate a corresponding ICER value. The process was repeated 1,000 times, and the results of the PSA were expressed by a cost-effectiveness acceptability curve. PSA results revealed that ocrelizumab continued to be less costly and more effective than daclizumab, fingolimod, and natalizumab, and resulted in expected ICERs of between $26,600 and $46,100 per QALY gained for the remaining DMTs. At a willingness-to-pay threshold of $50,000 per QALY gained, ocrelizumab had the highest probability of being cost-effective, at 36.2 %.[1]

Limitations of Manufacturer's Submission

CDR identified the following key limitations with the manufacturer's model:

Disability progression based on 12-week confirmation period: The effect of treatment on disability progression was handled in the model by applying 12-week CDP data related to permanent disease worsening from the manufacturer's NMA.[4] While the use of CDP data adequately accounts for patients moving between EDSS states in the model, a 12-week confirmation period for a change in EDSS score was deemed to be a poor indicator of permanent disability progression by the clinical expert consulted by CADTH for this review; instead, use of 24-week CDP estimates is recommended, as 24 weeks (i.e., six months of sustained accumulation of disability) is likely to better reflect clinical outcomes over a one-year cycle. In addition, because recovery from a relapse during the early stages of MS is likely (i.e., the possibility of recovery exists at 12 weeks), CDP is a more robust measure when performed over a 24-week interval.[14,15]

It should be noted that assuming the same relative effectiveness for the period beyond 24 weeks is a major assumption, and relying on such relatively short-term clinical data to assess the cost-effectiveness of continued use for a greater duration is a significant limitation that is likely to considerably overestimate the effectiveness of therapies.

Duration of treatment and efficacy: For all DMTs except alemtuzumab, it was assumed the full efficacy of treatment was obtained for a continuous duration of treatment of up to 63 years (i.e., lifetime time horizon), except when EDSS score increased to 7 (disease stage at which treatment is discontinued), due to all-cause discontinuation or upon conversion to SPMS. However, for alemtuzumab, the model assumed that treatment would be continued for no more than two years. As there is no published evidence for disability progression relating to any of the DMTs beyond 24 weeks, such a biased approach against alemtuzumab may be unwarranted. The clinical expert consulted by CADTH agreed that CDR should base the durability of treatment response and accrual of treatment costs on the same assumptions for all modelled comparators.

Uncertainty with comparative clinical information: Clinical efficacy inputs related to disability progression (CDP at 12 weeks and at 24 weeks) and ARR were based on an unpublished NMA conducted by the manufacturer.[4] However, CDP and ARR estimates derived from the manufacturer's NMA may be limited owing to several factors, which may render these estimates uncertain (see detailed summary and critical appraisal of the manufacturer-submitted indirect treatment comparison presented in the CDR Clinical

Review Report). In particular, the manufacturer's NMA synthesized evidence from a mixture of studies reporting on treatment-experienced and/or treatment-naive MS patients, and, as a result, effect estimates may not be reflective of response to treatment among patients who have previously failed DMT and are likely to receive ocrelizumab. In addition, the manufacturer's NMA did not adequately explore the potential impact of clinical heterogeneity across included studies on the estimates of treatment effect, and there was a lack of statistical analysis for inconsistency, which brings into question the reliability of the synthesized evidence.

Other limitations and parameters of uncertainty identified with the submitted evaluation include the following:

Health-state utility values for EDSS states 8 and 9 are uncertain: There is uncertainty in the methods used to elicit utility values for EDSS states 8 and 9 (derived using coefficients from Orme et al.[11]), and these values appear considerably lower than those used in other previous models for these health states, including the CADTH RRMS Therapeutic Review.[16] CDR undertook a reanalysis using utility values from a previously published cost-effectiveness analysis comparing pegylated interferon beta-1a with interferon beta-1a and glatiramer acetate.[17]

Cost of daclizumab may be overestimated: Given that daclizumab is not yet listed on any provincial formulary, the manufacturer estimated the annual cost of this treatment by averaging the annual costs of three second-line DMTs (alemtuzumab [year 2 costs], fingolimod, and natalizumab). However, the CDR submission for daclizumab was recently completed, and the CADTH Canadian Drug Expert Committee's (CDEC) recommendations were issued. Based on the CDR Pharmacoeconomic Review report for daclizumab,[18] the annual cost of this therapy was estimated at $27,700. CDR undertook a reanalysis using this value instead of the annual cost estimated by the manufacturer.

Natural-history data allowing for disability improvement may not be appropriate: Natural-history data were applied in the manufacturer's model using transition probabilities from Palace et al.,[3] which allowed for backward transitions (i.e., disability improvement). While it may be plausible for patients to experience improvement in their disability status and therefore transition to a lower EDSS score (i.e., lower level of disability), the clinical expert consulted by CADTH for this review noted that spontaneous improvement in disability is seldom observed in clinical practice. Therefore, it may be inappropriate to allow for backward transition probabilities in modelling the MS progression in the absence of treatment. CDR undertook a reanalysis using progression-only natural-history data from the London, Ontario, data set for transitions within RRMS (treated and untreated) and SPMS states.

Lack of transparency and functionality of the manufacturer's submitted model: The submitted model had several issues that made validation and evaluation challenging. In particular, the model did not allow for all comparators to be run simultaneously, and the coding used in modelling was overly complicated and lacked transparency. Thus, simple reanalyses adopting alternative assumptions were complicated to conduct and verify. Despite a number of requests made by CADTH for the manufacturer to provide the results for all comparators simultaneously, supplemented by separate Markov trace worksheets for each comparator, the manufacturer was unable to provide this information.

CADTH Common Drug Review Reanalyses

As noted in the limitations, CDR identified several important shortcomings related to the manufacturer's model. CDR presents a revised probabilistic analysis (CDR base case) in Table 4, with variations based on these limitations. The modifications made to the manufacturer-submitted model include the following:

- continuation of treatment effect and accrual of treatment costs was based on the same assumptions for all modelled comparators
- confirmation period for disability progression was modified to 24 weeks
- annual cost of daclizumab was updated to $27,700
- the London, Ontario, data set was used for modelling natural history within all model health states
- the utility values for EDSS states 8 and 9 was modified to those reported in Hernandez et al.[17]

Based on a sequential probabilistic analysis of the CDR base case (Table 4), CDR found that ocrelizumab was not a cost-effective treatment for patients with RRMS when considering all available treatments, regardless of a decision-maker's willingness-to-pay threshold for a QALY gain. Ocrelizumab had a 2.0% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained and a 12.9% probability of being cost-effective at a willingness-to-pay threshold of $100,000 per QALY gained. Sequential analysis further revealed that pegylated interferon beta-1a was the optimal therapy at a willingness-to-pay threshold less than $151,610 per QALY gained. If a decision-maker's willingness to pay for a gain in QALY was greater than $151,610 but less than $258,857, then daclizumab was the optimal therapy. If a decision-maker's willingness-to-pay threshold for one QALY was greater than $258,857, alemtuzumab was the optimal therapy.

Table 4: CADTH Common Drug Review Base Case

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Pegylated interferon beta-1a	923,642	12.424		
Daclizumab	958,850	12.657	151,610	151,610
Alemtuzumab	1,094,495	13.181	225,923	258,857
Dominated options				
Teriflunomide	954,592	11.993	Dominated by pegylated interferon beta-1a	
Interferon beta-1a SC	962,748	11.995	Dominated by pegylated interferon beta-1a	
Glatiramer acetate	934,738	12.090	Dominated by pegylated interferon beta-1a	
Dimethyl fumarate	971,372	12.189	Dominated by pegylated interferon beta-1a	
Fingolimod	1,007,689	12.241	Dominated by pegylated interferon beta-1a	
Natalizumab	1,127,130	12.986	362,444	Dominated by alemtuzumab
Ocrelizumab	1,001,296	12.787	214,504	Subject to extended dominance through alemtuzumab and daclizumab

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SC = subcutaneous; vs. = versus.

Results of CDR reanalyses focusing on individual parameters are presented in Appendix 4. The parameter that was the greatest driver of results was the use of 24-week CDP data for estimating disability progression. As a result, CDR undertook an exploratory analysis (Table 5) using clinical efficacy estimates from a published NMA conducted by the Institute for Clinical and Economic Review.[9] A detailed summary and critical appraisal of this NMA is presented in the CDR Clinical Review Report.

Table 5: CADTH Common Drug Review Multi-Way Exploratory Analysis Using Annualized Relapse Rate and Disability Progression Estimates From a Published Network Meta-Analysis

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Peginterferon beta-1a	913,611	12.39		
Daclizumab	948,834	12.62	152,600	152,600
Alemtuzumab	1,084,645	13.12	234,118	256,445
Dominated options				
Interferon beta-1a SC	952,406	11.95	Dominated by pegylated interferon beta-1a	
Teriflunomide	943,764	11.98	Dominated by pegylated interferon beta-1a	
Glatiramer acetate	924,568	12.05	Dominated by pegylated interferon beta-1a	
Dimethyl fumarate	959,643	12.18	Dominated by pegylated interferon beta-1a	
Fingolimod	997,073	12.23	Dominated by pegylated interferon beta-1a	
Natalizumab	1,116,329	12.92	377,142	Dominated by alemtuzumab
Ocrelizumab	991,091	12.75	211,847	Subject to extended dominance through alemtuzumab and daclizumab

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

Note: Published NMA was conducted by the Institute for Clinical and Economic Review.[9]

CDR undertook a price-reduction analysis based on the manufacturer-submitted and CDR base-case analyses, assuming proportional price reductions for ocrelizumab (Table 6). Using the manufacturer's base-case analysis, a price reduction for ocrelizumab of about 40% was required for ocrelizumab to become less costly and more effective (dominant) than pegylated interferon beta-1a.

Findings from the price-reduction analysis using the CDR base case showed that ocrelizumab would no longer be ruled out by extended dominance if the submitted price were reduced by approximately 10%; however, ocrelizumab would be the optimal therapy with a 10% price reduction if a decision-maker's willingness to pay for a QALY gain were greater than $200,563 but less than $282,941. If a price reduction of about 30% is achieved, ocrelizumab would be the optimal therapy if a decision-maker's willingness to pay were greater than $39,592 per QALY but less than $405,975. If a price reduction of at least 40% were achieved, ocrelizumab would be dominant over pegylated interferon beta-1a. The probability that ocrelizumab was cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained was 8.0% if a 10% price reduction was achieved, 48.7% if a 30% reduction was achieved, and 81.3% if a 50% reduction was achieved.

Table 6: CADTH Common Drug Review Reanalysis Price-Reduction Scenarios

Sequential ICURs for Ocrelizumab Versus All Available RRMS Treatments		
Price	**Based on Manufacturer's Base Case**	**Based on CDR Base Case**
Submitted	If λ < $46,121, pegylated interferon beta-1a is optimal If λ > $46,121, ocrelizumab is optimal	If λ < $151,610, pegylated interferon beta-1a is optimal If $151,610 < λ < $258,757, daclizumab is optimal If λ > $258,757, alemtuzumab is optimal
10% reduction	If λ < $29,870, pegylated interferon beta-1a is optimal If λ > $29,870, ocrelizumab is optimal	If λ < $137,855, pegylated interferon beta-1a is optimal If $137,855 < λ < $200,563, daclizumab is optimal If $200,563 < λ < $282,941, ocrelizumab is optimal If λ > $282,941, alemtuzumab is optimal
15% reduction	If λ < $24,087, pegylated interferon beta-1a is optimal If λ > $24,087, ocrelizumab is optimal	If λ < $129,855, pegylated interferon beta-1a is optimal If $129,855 < λ < $322,248, ocrelizumab is optimal If λ > $322,248, alemtuzumab is optimal
20% reduction	If λ < $15,605, pegylated interferon beta-1a is optimal If λ > $15,605, ocrelizumab is optimal	If λ < $108,458, pegylated interferon beta-1a is optimal If $108,458 < λ < $326,409, ocrelizumab is optimal If λ > $326,409, alemtuzumab is optimal
25% reduction	If λ < $7,680, pegylated interferon beta-1a is optimal If λ > $7,680, ocrelizumab is optimal	If λ < $76,918, pegylated interferon beta-1a is optimal If $76,918 < λ < $351,838, ocrelizumab is optimal If λ > $351,838, alemtuzumab is optimal
30% reduction	If λ < $586, pegylated interferon beta-1a is optimal If λ > $586, ocrelizumab is optimal	If λ < $39,592, pegylated interferon beta-1a is optimal If $39,592 < λ < $405,975, ocrelizumab is optimal If λ > $405,975, alemtuzumab is optimal
40% reduction	Ocrelizumab dominant	If λ < $456,337, ocrelizumab is optimal If λ > $456,337, alemtuzumab is optimal
50% reduction	Ocrelizumab dominant	If λ < $495,322, ocrelizumab is optimal If λ > $495,322, alemtuzumab is optimal
60% reduction	Ocrelizumab dominant	If λ < $518,106, ocrelizumab is optimal If λ > $518,106, alemtuzumab is optimal
70% reduction	Ocrelizumab dominant	If λ < $631,401, ocrelizumab is optimal If λ > $631,401, alemtuzumab is optimal

λ = willingness to pay; ICUR = incremental cost-utility ratio; RRMS = relapsing-remitting multiple sclerosis.

Note: Treatments that were either dominated or subject to extended dominance and do not lie on the cost-effectiveness frontier are not mentioned in this table.

Issues for Consideration

- Potential for off-label use in patients with primary-progressive MS: Ocrelizumab has been approved by the US FDA and by the Australian Therapeutic Goods Administration (TGA) for the treatment of primary-progressive and relapsing forms of MS; it is the first agent approved for the treatment of primary-progressive MS. However, ocrelizumab has not received approval from Health Canada for this indication.
- Availability of biosimilar products: Glatect (subsequent-entry glatiramer acetate) recently received a positive recommendation by CADTH (July 2017) for use in patients with RRMS for whom glatiramer acetate is considered to be the most appropriate treatment option.[19] Teva-glatiramer is another glatiramer acetate biosimilar product that has received a Health Canada indication for the treatment of RRMS and may become available for reimbursement. The availability of less costly biosimilar products could reduce the relative attractiveness of other RRMS therapies, including ocrelizumab.

Patient Input

Input was received from the Multiple Sclerosis Society of Canada. Patients noted that MS is an unpredictable and frequently disabling condition that affects the central nervous system and presents with a wide range of symptoms. Given that the onset of disease usually occurs during peak years for education, career-building, and family-building, MS exerts a significant impact on all aspects of life including quality of life, psychosocial functioning, and the ability to maintain employment and undertake activities of daily living. This was accounted for in the manufacturer's economic evaluation by including progressively lower utilities with increasing EDSS level. Patients also noted there is a substantial burden on caregivers (emotional, physical, and financial support, and time commitment), but that demand for the caregiver's role may decrease with increased availability of therapeutic options that can better control disability progression and decrease the frequency of relapses among patients with relapsing forms of MS. Caregiver burden was not accounted for in the manufacturer's model.

Patients noted that a number of DMTs are available to treat relapsing forms of MS, in addition to symptomatic therapy and non-pharmacologic options. Adverse effects are generally well managed with over-the-counter medications and lifestyle changes (e.g., rest). Nevertheless, patients highlighted the importance of having access to multiple treatments to ensure their MS is controlled as effectively as possible, given that not all drugs work for all patients. The majority of patients (97%) providing input indicated they had no experience with ocrelizumab; however, 30 patients (28%) providing input indicated they would be willing to take the risk of experiencing adverse effects that may be associated with ocrelizumab in return for its perceived benefits. Despite the need to administer ocrelizumab by intravenous infusion at a specialized clinic, one anticipated benefit of this medication is its dosage schedule, as it requires only one infusion every six months, unlike other monoclonal antibodies.

Conclusions

Sequential analyses based on a CDR reanalysis of the manufacturer's base case found that ocrelizumab was not cost-effective when considering all available treatments for patients with RRMS, regardless of a decision-maker's willingness to pay for a QALY gain. Ocrelizumab had a 2.0% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY and a 12.9% probability of being cost-effective at a willingness-to-pay threshold of $100,000 per QALY. Pegylated interferon beta-1a was the optimal therapy if a decision-maker is unwilling to pay at least $151,610 per QALY gained. If a decision-maker's willingness to pay for a gain in QALY is greater than $151,610 but less than $258,857, then daclizumab is the optimal therapy. If a decision-maker is willing to pay at least $258,857 for a QALY, alemtuzumab is the optimal therapy.

Given a 30% reduction in its submitted price, ocrelizumab would be considered the optimal therapy if a decision-maker's willingness to pay is greater than $39,592 per QALY but less than $405,975 per QALY. With this reduction, the probability that ocrelizumab is cost-effective at a willingness-to-pay threshold of $50,000 per QALY is 48.7%.

It should be noted that the economic model submitted by the manufacturer was unnecessarily complex and lacked transparency, which made both the assessment of validity and the ability to conduct reanalysis challenging. Thus, interpretation of results is subject to the identified limitations.

Appendix 1: Cost Comparison

The comparators presented in the table below have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice, rather than actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer's list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as a result, the prices may not represent the actual costs to public drug plans.

Table 7: CADTH Common Drug Review Cost-Comparison Table for the Treatment of Relapsing-Remitting Multiple Sclerosis

Drug/ Comparator	Strength	Dosage Form	Price[a] ($)	Recommended Dosage	Average Weekly Drug Cost ($)	Average Annual Drug Cost ($)
Ocrelizumab (Ocrevus)	**300 mg/10 mL solution for infusion**	**Single-use vial**	**8,150.00[b]**	**600 mg IV every six months[c]**	**627**	**32,600**
Injectable therapies						
Daclizumab beta (Zinbryta)	150 mg/1 mL	Pre-filled syringe/pen	2,308[d]	150 mg SC once monthly	533	27,700
Glatiramer acetate (Copaxone)	20 mg/mL	Pre-filled syringe	45.2524	20 mg SC once daily	318	16,517
Glatiramer acetate (Glatect)	20 mg/mL	Pre-filled syringe	37.82[e]	20 mg SC once daily	265	13,804
Interferon beta-1a (Avonex)	30 mcg/0.5 mL (6 MIU)	Pre-filled syringe/pen	428.1300	30 mcg IM once weekly	428	22,263
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	386	20,075
Interferon beta-1b (Extavia)	0.3 mg (9.6 MIU) powder for injection	Single-use vial	102.3400	0.25 mg (8 MIU) SC every other day	359	18,677
Interferon beta-1a (Rebif)	22 mcg/0.5 mL (6 MIU) 44 mcg/0.5 mL (12 MIU)	Pre-filled syringe, cartridge or pen	134.0486 163.1902	22 mcg to 44 mcg SC three times weekly	402 480	20,912 25,458
Peginterferon beta-1a (Plegridy)	63 mcg/0.5 mL 94 mcg/0.5 mL 125 mcg/0.5 mL	Pre-filled syringe/pen	856.2600	SC injection every two weeks: Dose 1: 63 mcg Dose 2: 94 mcg Dose 3 and thereafter: 125 mcg	428	22,263
Infusion therapies						
Alemtuzumab (Lemtrada)	12 mg/1.2 mL solution for infusion	Single-use vial	1,045.8333 per mg	12 mg/day IV for five days followed by 12 mg/day IV for 3 days after 12 months	Weekly average, Year 1: 1,207 Year 2: 724	Year 1: 62,750 Year 2: 37,650
Natalizumab (Tysabri)	300 mg/15 mL solution for infusion	Single-use vial	3,295.8900	300 mg IV every four weeks	824	42,847

Drug/ Comparator	Strength	Dosage Form	Price[a] ($)	Recommended Dosage	Average Weekly Drug Cost ($)	Average Annual Drug Cost ($)
Oral therapies						
Dimethyl fumarate (Tecfidera)	120 mg 240 mg	Capsule	16.8464 33.6929	120 mg twice daily; after 7 days increase to 240 mg twice daily	Week 1: 236 Subsequent weeks: 472	Year 1: 24,360 Subsequent years: 24,596
Fingolimod (Gilenya)	0.5 mg	Capsule	85.1650	0.5 mg once daily	598	31,085
Teriflunomide (Aubagio)	14 mg	Tablet	55.6875	14 mg once daily	391	20,326

IM = intramuscular; IV = intravenous; SC = subcutaneous.

[a] Unit prices of medications are taken from the Ontario Formulary Exceptional Access Program[20] (accessed July 2017) unless otherwise indicated, and do not include prescription fees, costs of dose preparation or injection administration. Annual period assumes 52 weeks, or 13*4 weeks per year (365 days for all comparators).

[b] Manufacturer's submitted price.[1]

[c] The initial 600 mg dose is administered as two separate IV infusions: a 300 mg infusion, followed two weeks later by a second 300 mg infusion. Subsequent doses thereafter are administered as single 600 mg IV infusions every six months.[2]

[d] CADTH Canadian Drug Expert Committee Recommendation report for daclizumab (Zinbryta).[21]

[e] CADTH Canadian Drug Expert Committee Recommendation report for glatiramer acetate (Glatect).[19]

Appendix 2: Additional Information

Table 8: 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”	As noted in the limitations section, there were concerns with the lack of transparency and cumbersome presentation of the model, with the inability to compare more than one treatment at a time.		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking “poor”	CADTH made several requests to the manufacturer to provide an updated model that allows all comparators to be run simultaneously, rather than single comparisons. The manufacturer was unable to provide separate Markov trace worksheets for each comparator to allow the reviewers to fully assess the model’s functioning.		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

Table 9: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ 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

CADTH

Appendix 3: Summary of Other Health Technology Assessment Reviews of Drug

Note there are no reviews for ocrelizumab conducted by health technology assessment organizations available at the time of this review. Ocrelizumab is currently undergoing review by the United Kingdom's National Institute for Health and Care Excellence and by the Australian Government's Pharmaceutical Benefits Advisory Committee.

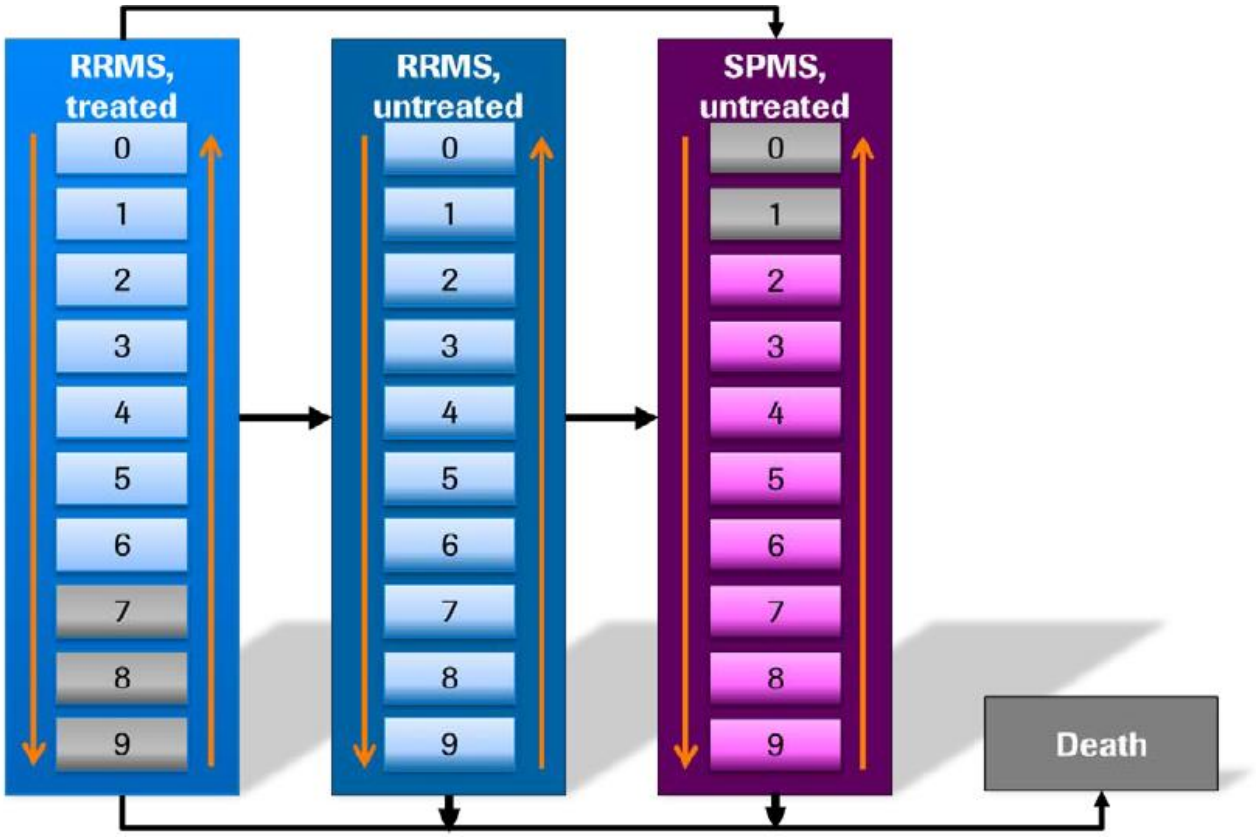
Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a cohort-based Markov health-state transition model that included 21 health states: 10 for each multiple sclerosis (MS) type (relapsing-remitting MS [RRMS] and secondary-progressive [SPMS]) and a death state. The MS-specific health states were grouped according to the Kurtzke Expanded Disability Status Scale (EDSS) levels, from 0 (normal neurological examination) to 9 (helpless bed patient).[22] The manufacturer's model structure is presented in Figure 1.

In the submitted model, all patients begin in the RRMS state, and the model prospectively predicts their movement through different health states based on several factors, including disability progression, relapses, adverse events, treatment discontinuation, and mortality. The distribution of patients by EDSS state was defined at the outset based on the proportion of patients in each EDSS state from the OPERA trials. After each annual cycle in the model, each patient in the modelled cohort can transition between EDSS states in RRMS, remain in the same state, or transition to the absorbing state of death. Patients may also transition to SPMS from RRMS and then move between EDSS states in SPMS. During each cycle, patients may also relapse or discontinue therapy, which is dependent on their RRMS or SPMS status and EDSS score. Patients may transition from any health state to the absorbing death state.

Figure 1: Manufacturer's Model Structure



Orange arrows = show the direction in which patients may move along the EDSS scale. Grey boxes = in 'RRMS treated' these indicate the stages at which treatment is discontinued (this can be adjusted on the 'Main Screen' tab in the model) and in 'SPMS, untreated' these indicate that the earliest stage a patient can be in SPMS is EDSS stage 2, as there were no transitions from RRMS EDSS 0 .

Source: Manufacturer's pharmacoeconomic submission.[1]

Table 10: Data Sources

Data Input	Description of Data Source	Comment
Efficacy, Safety, and Withdrawals		
Efficacy ARR Disability progression (CDP at 12 weeks and at 24 weeks)	Effects of treatment on the prevention of relapses (measured by ARR) and the avoidance of disability progression (measured by CDP at 12 weeks and at 24 weeks) were derived from the manufacturer's NMA.[4] The efficacy of ocrelizumab itself was assessed in two identical, active-controlled, phase III clinical trials (OPERA-I and OPERA-II) that compared the efficacy and safety of ocrelizumab with IFNB-1a SC in patients with RMS.	As noted in the CDR's Clinical Review Report, estimates derived from the manufacturer-commissioned NMA may be limited owing to (1) reliance on a mixture of studies reporting on treatment-naive and/or treatment-experienced trial populations for evidence synthesis, leading to uncertainty regarding the response to treatment among patients who have previously failed DMT and are likely to receive ocrelizumab; insufficient assessment of the potential impact of clinical heterogeneity across included studies on the estimates of treatment effect; and lack of statistical analysis for inconsistency, which brings

Data Input	Description of Data Source	Comment
		into question the reliability of the synthesized evidence.
AEs	The following AEs were considered: increased ALT, arthralgia, back pain, depression, dizziness, fatigue, headache, infusion-related reaction, nasopharyngitis, upper respiratory tract infection, and urinary tract infection. The set of AEs considered were those that occurred at an annualized risk of occurrence ≥ 5% for each comparator, according to data from the recent Biogen daclizumab submission to NICE[23]; if AEs occurred at ≥ 5% annualized risk for a given comparator, the 5 with the largest impact on costs were prioritized. The annual probability of AEs for ocrelizumab was obtained from the OPERA-I and OPERA-II trial data.	Appropriate
All-cause discontinuation	Each DMT in the model was associated with an annual probability of withdrawal. DMT-specific all-cause discontinuation rates were calculated using data from the manufacturer's NMA and applied equally to cost and efficacy parameters.	Appropriate
Natural History		
RRMS to RRMS EDSS transitions	Transition probabilities between EDSS states (disability progression) in the "RRMS, untreated" model were estimated based on natural-history data from the BCMS data set for patients not receiving therapy.[3] Transition probabilities between EDSS states in the "RRMS, treated" model were informed by the BCMS data set adjusted by a treatment effect.	The BCMS data set is a standard, widely used source that has been used in previous publications, including CADTH's therapeutic review.[16]
RRMS to SPMS EDSS transitions	Transitions from RRMS to SPMS were informed by natural-history data from the London, Ontario, data set. The probability of converting from RRMS to SPMS was calculated from hazard rates (Cox proportional hazards model from London, Ontario, data set) using a standard formula for conversion.	Data from the London, Ontario, data set are not publicly available, and it was therefore impossible to verify these calculations. It is also uncertain whether data for patients with primary progressive or "benign MS" were removed from the London, Ontario, data set before estimating the probability of progressing from RRMS to SPMS.
SPMS to SPMS EDSS transitions	Transition probabilities between EDSS states in SPMS were estimated based on natural-history data from the BCMS data set.	The BCMS data set is a standard, widely used source that has been used in previous publications, including CADTH's therapeutic review.[16]
Relapse rate	Natural-history relapse rates were derived from a study by Patzold and Pocklington[8] as well as from the UK MS Survey. The natural history of relapses was estimated by disease type and EDSS state.	The use of relapse rates from Patzold and Pocklington appears to be appropriate.
Duration of relapse	The mean duration of relapse (46 days) was derived from the University of Sheffield School of	Felt to be appropriate by the clinical expert consulted by CADTH for this review.

Data Input	Description of Data Source	Comment
	Health and Related Research (ScHARR) assessment of beta interferons and glatiramer acetate for the treatment of MS.[12]	
Mortality	Transition to death was informed by a weighted mean of all-cause mortality rates for the Canadian general population based on female-to-male ratio of RRMS patients used in the model. Mortality multipliers by MS disease severity (EDSS state) were from Pokorski et al. and applied to the all-cause weighted mean mortality rates.	The values used by Pokorski et al. were derived from a study by Sandovnick et al. that presented mortality rates based on grouped EDSS categories. CDR notes that it would have been better to use actual data than interpolated values. The data are also quite outdated; more recent data on mortality by EDSS levels would be preferred.
Utilities		
Health-state utilities	Utilities were estimated from the OPERA-I and OPERA-II trial data using the EQ-5D-3L instrument and based on EDSS state (health states). The UK value set[10] for EQ-5D-3L was used to elicit utility values from the recorded EQ-5D-3L states. Utility values for EDSS states 8 and 9 were estimated based on published utility weights from a cross-sectional study by Orme et al,[11] which reported survey responses from MS patients and their caregivers using the EQ-5D utility scoring system. Regression analysis coefficients published by Orme et al. were applied to the OPERA-I and OPERA-II utilities to derive utilities for EDSS states 8 and 9.	Methods used to elicit utility values for EDSS states 8 and 9 are unclear.
Disutilities due to relapse	The utility loss for mild/moderate relapse was from the CADTH MS Therapeutic Review.[16]	The CADTH MS Therapeutic Review used values from Prosser et al. for disutility due to relapse. The disutility associated with severe relapse was not captured in the model.
Disutilities due to conversion to SPMS	The utility loss for transition to SPMS health state was derived from UK MS survey data by Orme et al.[11]	Appropriate
Disutilities due to AEs	Although not explicitly reported in the manufacturer's submission, it appears to be based on the Biogen submission to NICE.[23]	Appropriate
Disutilities for caregiver	The manufacturer's submission mentioned that each EDSS state was associated with caregiver disutilities, but the source of these data was not reported.	Not included in the base-cases analysis, which is appropriate
Resource Use and Costs		
Drug	The drug cost for ocrelizumab was provided by the manufacturer. Drug-acquisition costs for all other comparators (except daclizumab) were obtained from the Ontario Drug Benefit Exceptional Access Program.[20] The annual cost of daclizumab was	There were no major differences in calculations between the CDR cost-comparison table and the manufacturer's yearly drug-acquisition costs. One exception was daclizumab, the annual cost of which was overestimated by the manufacturer ($37,194 versus $27,700) according to the annual cost of daclizumab, reported in the CDEC

Data Input	Description of Data Source	Comment
	estimated by averaging the annual costs of second-line DMTs (alemtuzumab [year 2 cost], fingolimod, and natalizumab).	recommendation report for daclizumab.[21] Dispensing fees and mark-ups were not applied for any medications in the submitted model, which is appropriate.
Monitoring	Health care resources associated with treatment monitoring were estimated through clinical expert elicitation (i.e., three clinical advisors recruited by the manufacturer). Unit costs of monitoring resources were obtained from the Ontario Schedule of Benefits for Physician Services[24] and the Ontario Schedule of Benefits for Laboratory Services.[25]	Appropriate
Disease management Non-drug–related direct health care costs	Annual per-patient direct costs of RRMS management by EDSS scores were based on values reported in the CADTH MS Therapeutic Review,[16] inflated to 2016 values.	Appropriate
Relapse management	The cost per relapse not requiring hospitalization (mild/moderate relapses) was derived from the CADTH MS Therapeutic Review,[16] inflated to 2016 values.	Cost per relapse requiring hospitalization (severe relapse) was not included in the model. Indirect costs associated with relapses were also not considered.
AEs	Unit costs of physician services required to treat non-serious and serious AEs were obtained from the Ontario Schedule of Benefits.[24] The cost of an emergency department visit (physician fee and visit) was obtained from the Ontario Schedule of Benefits and a CIHI estimate published by Dawson and Zinck.[26] The cost of a hospital stay related to a serious AE was obtained from the CIHI patient cost estimator, and the costs of medications were obtained from the Ontario Drug Benefit Formulary.	Appropriate.

AE = adverse event; ALT = alanine aminotransferase; ARR = annualized relapse rate; BCMS = British Columbia multiple sclerosis; CDP = confirmed disease progression; CIHI = Canadian Institute for Health Information; DMT = disease-modifying therapy; EDSS = Kurtzke Expanded Disability Status Scale; EQ-5D-3L = EuroQol 5-Dimensions 3-Level questionnaire; IFNB = interferon beta; MS = multiple sclerosis; NMA = network meta-analysis; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; UK = United Kingdom.

Table 11: Manufacturer's Key Assumptions

Assumption	Comment
The model allowed patients to enter in EDSS state 0 (i.e., normal neurological examination). It was assumed that 3.08% of patients in the starting population distribution were in EDSS 0.	This was felt to be appropriate by the clinical expert consulted by CADTH for this review.
Patients either progress to a higher EDSS state, remain in the same state, regress to a lower severity EDSS state, or die.	The clinical expert 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 by more than one EDSS level while they are receiving treatment. Although it is possible for patients to experience improvement in EDSS score, the clinical expert felt that progression-only transitions in RRMS are a preferred, more conservative approach.
Model did not include transitions to EDSS state 10 (i.e., MS-related death).	Appropriate; patients experience an age-related risk of mortality adjusted for the probability of MS-related death.
Patients can transition to SPMS from RRMS, but not vice versa.	Appropriate
A half-cycle correction was applied to all comparators in the model, except alemtuzumab.	Appropriate; given that treatment costs and withdrawals are accrued at the start of the year (when patients are administered a dose), it is not appropriate to apply a half-cycle correction to alemtuzumab.
Progression of disability was measured using 12-week CDP estimates (i.e., 3-month sustained accumulation of disability) and assumed to be appropriate for a 1-year cycle.	Use of the 24-week CDP measure (6-month sustained accumulation of disability) is preferred, as it is likely to better reflect clinical outcomes over a 1-year cycle.[27] The clinical expert noted that using a longer confirmation period for disability progression is more clinically meaningful and preferred the 24-week measure over the 12-week estimates.
Full efficacy was assumed to be applied for the duration of treatment for all DMTs for RRMS patients.	Appropriate
The recommended treatment duration for alemtuzumab is 2 years. As a result, it was assumed that patients do not experience any clinical benefits associated with treatment after the first two years of therapy.	Not appropriate. The clinical indicated that, while treatment with alemtuzumab may last two years, it cannot be assumed that patients would not experience any clinical benefit following the end of the treatment course. In addition, some patients may require doses of alemtuzumab well beyond two years.[28] In addition, there is a paucity of published evidence relating to disability progression for any DMTs used in RRMS treatment beyond 24 weeks; thus, this approach to modelling treatment duration and efficacy is unsupported and biased against alemtuzumab.
Treatment waning was incorporated in a sensitivity analysis for the modelled comparators, although no waning effect was considered in the base case.	Likely appropriate. The clinical expert felt that treatment waning is not a common phenomenon in MS patients; rather, loss of efficacy is generally attributed to progression of illness.
Relative conversion to SPMS assumed that 50% of the CDP treatment effect was applicable.	Likely appropriate
No treatment effect was applied for patients with SPMS, as the patients were untreated once they reached SPMS.	Appropriate
Patients receive monotherapy and, upon discontinuation, receive no further treatment.	Patients would likely be administered a subsequent line of therapy following treatment failure in clinical practice. However, CDR acknowledges the paucity of data on treatment sequencing and its efficacy.

Assumption	Comment
Discontinuation from treatment was applied in the model once a modelled patient with RRMS reached an EDSS level 7 health state (stopping rule) or transitioned to any SPMS health state.	Alternative stopping rules have been used in previous submissions (e.g., stopping at EDSS level 5 in the daclizumab submission to CADTH). The impact of a lower EDSS level stopping rule was assessed and found to have no impact on the results.
Patients who discontinue treatment experience relapses at the natural-history rate.	Uncertain
Proportion of relapses requiring hospitalization was not accounted for in the model.	Based on feedback from the clinical expert, the majority of RMS patients are not hospitalized following a relapse event. However, a relapse leads to hospitalization in about 20% of patients, and severe relapses increase the likelihood of hospitalization. This was tested in the model and did not have an impact on the results.

Manufacturer's Results

Table 12: Sequential Incremental Cost-Effectiveness Ratio Analysis Results of the Manufacturer's Base Case (Probabilistic)

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Peginterferon beta-1a	747,973	12.336		
Ocrelizumab	818,166	13.865	45,906	45,906
Dominated options				
Alemtuzumab	750,726	12.038	Dominated by pegylated interferon beta-1a	
Glatiramer acetate	751,041	12.110	Dominated by pegylated interferon beta-1a	
Fingolimod	826,909	12.309	Dominated by pegylated interferon beta-1a	
Teriflunomide	762,358	12.312	Dominated by pegylated interferon beta-1a	
Daclizumab	834,993	12.599	330,040	Dominated by ocrelizumab
Natalizumab	958,261	13.257	228,152	Dominated by ocrelizumab
Interferon beta-1a SC	769,817	12.343	3,026,612	Subject to extended dominance through ocrelizumab and pegylated interferon beta-1a
Dimethyl fumarate	783,756	12.512	202,557	Subject to extended dominance through ocrelizumab and pegylated interferon beta-1a

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

Note: Total costs and total QALYs are probabilistic values obtained from the manufacturer's original model submitted to CADTH.[1]

Note: All costs are presented in 2017 Canadian dollars.

CADTH Common Drug Review Reanalyses

Table 13: CADTH Common Drug Review Probabilistic Analysis Results Assuming 24-Week Confirmation Period for Disability Progression

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Peginterferon beta-1a	732,712	12.776		
Ocrelizumab	817,543	13.485	119,712	119,712
Natalizumab	966,900	14.041	185,114	268,400
Dominated options				
Interferon beta-1a SC	772,769	11.977	Dominated by pegylated interferon beta-1a	
Teriflunomide	764,104	12.008	Dominated by pegylated interferon beta-1a	

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Alemtuzumab	746,116	12.033	Dominated by pegylated interferon beta-1a	
Glatiramer acetate	745,548	12.166	Dominated by pegylated interferon beta-1a	
Dimethyl fumarate	780,677	12.408	Dominated by pegylated interferon beta-1a	
Fingolimod	820,482	12.523	Dominated by pegylated interferon beta-1a	
Daclizumab	823,199	13.197	214,959	Dominated by ocrelizumab

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

Table 14: CADTH Common Drug Review Probabilistic Analysis Results Assuming Continuation of Treatment Effect and Accrual of Treatment Costs Based on Same Assumptions for All Comparators

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Peginterferon beta-1a	743,393	12.343		
Ocrelizumab	813,672	13.880	45,732	45,732
Alemtuzumab	926,626	14.264	95,393	294,095
Dominated options				
Glatiramer acetate	745,494	12.162	Dominated by pegylated interferon beta-1a	
Fingolimod	822,358	12.327	Dominated by pegylated interferon beta-1a	
Interferon beta-1a SC	764,967	12.353	2,153,884	Dominated by teriflunomide
Daclizumab	829,949	12.627	305,110	Dominated by ocrelizumab
Natalizumab	954,992	13.278	226,320	Dominated by ocrelizumab
Teriflunomide	757,271	12.361	758,989	Subject to extended dominance through ocrelizumab and pegylated interferon beta-1a
Dimethyl fumarate	779,128	12.505	220,376	Subject to extended dominance through ocrelizumab and pegylated interferon beta-1a

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SC = subcutaneous; vs. = versus.

Table 15: CADTH Common Drug Review Probabilistic Analysis Results Assuming Annual Cost of $27,700 for Daclizumab

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Peginterferon beta-1a	743,559	12.328		
Ocrelizumab	813,044	13.864	45,222	45,222
Dominated options				
Alemtuzumab	745,086	12.054	Dominated by pegylated interferon beta-1a	
Glatiramer acetate	746,231	12.094	Dominated by pegylated interferon beta-1a	
Fingolimod	820,797	12.304	Dominated by pegylated interferon beta-1a	
Interferon beta-1a SC	764,898	12.334	3,779,720	Dominated by teriflunomide
Natalizumab	954,004	13.258	226,149	Dominated by ocrelizumab
Teriflunomide	756,415	12.343	833,386	Subject to extended dominance through ocrelizumab and pegylated interferon beta 1-a
Dimethyl fumarate	778,834	12.481	229,988	Subject to extended dominance through ocrelizumab and pegylated interferon beta 1-a
Daclizumab	779,224	12.616	123,623	Subject to extended dominance through ocrelizumab and pegylated interferon beta 1-a

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

Table 16: CADTH Common Drug Review Probabilistic Analysis Results Assuming London, Ontario, Natural-History Data for All Health-State Transitions

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Peginterferon beta-1a	930,551	6.327		
Ocrelizumab	992,345	7.733	43,954	43,954
Dominated options				
Alemtuzumab	934,579	6.068	Dominated by pegylated interferon beta-1a	
Glatiramer acetate	932,375	6.094	Dominated by pegylated interferon beta-1a	
Fingolimod	1,004,276	6.276	Dominated by pegylated interferon beta-1a	
Teriflunomide	943,542	6.313	Dominated by pegylated interferon beta-1a	
Interferon beta-1a SC	951,539	6.317	Dominated by pegylated interferon beta-1a	
Daclizumab	1,013,134	6.586	317,988	Dominated by ocrelizumab
Natalizumab	1,117,877	7.133	232,417	Dominated by ocrelizumab

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Dimethyl fumarate	963,651	6.471	230,164	Subject to extended dominance through ocrelizumab and pegylated interferon beta 1-a

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

Table 17: CADTH Common Drug Review Probabilistic Analysis Results Assuming Hernandez et al.[17] Utilities for EDSS States 8 and 9

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Peginterferon beta-1a	745,166	15.246		
Ocrelizumab	814,680	16.355	62,652	62,652
Dominated options				
Alemtuzumab	746,684	15.080	Dominated by pegylated interferon beta-1a	
Glatiramer acetate	747,251	15.117	Dominated by pegylated interferon beta-1a	
Interferon beta-1a SC	766,645	15.257	1,889,961	Dominated by teriflunomide
Fingolimod	823,084	15.259	5,826,333	Dominated by teriflunomide
Daclizumab	830,230	15.467	383, 724	Dominated by ocrelizumab
Natalizumab	955,658	15.907	318,502	Dominated by ocrelizumab
Teriflunomide	757,522	15.284	322,709	Subject to extended dominance through ocrelizumab and pegylated interferon beta 1-a
Dimethyl fumarate	779,669	15.388	243,255	Subject to extended dominance through ocrelizumab and pegylated interferon beta 1-a

EDSS = Kurtzke Expanded Disability Status Scale; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SC = subcutaneous.

CADTH Common Drug Review
Exploratory Analyses

Table 18: Results of CADTH Common Drug Review One-Way Exploratory Analysis of the Manufacturer's Base Case Assuming Estimates for ARR and Disability Progression from Published NMA

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus Pegylated Interferon Beta-1a ($/QALY)	Sequential ICUR ($/QALY)
Non-dominated options				
Peginterferon beta-1a	733,784	12.796		
Ocrelizumab	819,006	13.543	114,130	114,130
Natalizumab	967,271	14.065	184,021	283,980
Dominated options				
Teriflunomide	766,616	12.005	Dominated by pegylated interferon-1a	
Interferon beta-1a SC	773,925	12.031	Dominated by pegylated interferon-1a	
Alemtuzumab	747,613	12.057	Dominated by pegylated interferon-1a	
Glatiramer acetate	746,697	12.191	Dominated by pegylated interferon-1a	
Dimethyl fumarate	783,261	12.404	Dominated by pegylated interferon-1a	
Fingolimod	821,537	12.517	Dominated by pegylated interferon-1a	
Daclizumab	826,972	13.234	212,676	Dominated by ocrelizumab

ARR = annualized relapse rate; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year; SC = subcutaneous.

Note: Published NMA was conducted by the Institute for Clinical and Economic Review.[9]

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