CADTH

CADTH Drug Reimbursement Review

Pharmacoeconomic Report

OFATUMUMAB (KESIMPTA)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Multiple Sclerosis, Relapsing-Remitting

Service Line: CADTH Common Drug Review
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CADTH

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

3mCDP	3-month confirmed disease progression
6mCDP	6-month confirmed disease progression
ARR	annualized relapse rates
BIA	budget impact analysis
BSC	best supportive care
CDP	confirmed disease progression
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
ICER	incremental cost-effectiveness ratio
IFN	interferon
MS	multiple sclerosis
NMA	network meta-analysis
QALY	quality-adjusted life-years
RRMS	relapsing-remitting multiple sclerosis
SPMS	active secondary progressive multiple sclerosis

Executive Summary

The executive summary is comprised of 2 tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Ofatumumab (Kesimpta)
Submitted price	Ofatumumab 20 mg/0.4 mL subcutaneous injection: $2.333.33
Indication	Treatment of adult patients with relapsing-remitting multiple sclerosis with active disease
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	January 22, 2021
Reimbursement request	As per indication
Sponsor	Novartis Pharmaceuticals Canada Inc.
Submission history	Previously reviewed: No

NOC = Notice of Compliance.

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	Ofatumumab
Comparator(s)	• First-line therapy only (primary analysis): BSC that manages RMS symptoms, IFN beta-1a (Avonex, Rebif-22 and 44), IFN beta-1b (Betaseron, Extavia), glatiramer acetate, teriflunomide, dimethyl fumarate, and ocrelizumab. • First-, second-, and third-line therapy (scenario analysis): same comparators as first-line therapy only and also natalizumab, fingolimod, cladribine, and alemtuzumab.
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	65 years (lifetime)
Key data source	ASCLEPIOS I and II trials and a sponsor-conducted NMA
Submitted results for base case (and key scenario analyses as required)	• First-line therapy only (primary analysis): Ofatumumab was the most effective therapy (largest number of QALYs). The ICER for ofatumumab versus BSC was $27,009 per QALY gained. All other therapies were subject to dominance or extended dominance. • First, second-, and third-line therapy (secondary analysis): Ofatumumab was the most effective therapy. The ICER for alemtuzumab versus BSC was $12,907 per QALY, and the ICER for ofatumumab versus alemtuzumab was $95,289 per QALY.
Key limitations	• The sponsor assumed ARRs were dependent on a patient's EDSS state. Based on the input from the clinical expert consulted for the review, the CADTH base case assumed that ARRs were independent of EDSS as per the sponsor's scenario analysis. • The sponsor assumed the relative effectiveness from short-term clinical trials would be maintained for the full time horizon of the model (65 years). Based on feedback from the clinical expert consulted, the CADTH base case assumed a waning-treatment effect as per the sponsor's scenario analysis. • The sponsor's base case compared ofatumumab to other first-line therapies, although 59.2% of patients randomized to ofatumumab in the clinical trials had received previous DMTs. Therefore, the

Component	Description
	data are drawn from a mix of treatment-naive patients who would be eligible for first-line therapies and treatment-experienced patients who would be eligible for second- and third-line therapies. The CADTH base case adopted an analysis comparing ofatumumab to all therapies. CADTH notes that the effectiveness data incorporated into all analyses are for the full patient population (both treatment-experienced and treatment-naive) as no breakdown was provided. • The sponsor assumed that a significant proportion of patients would improve each year in terms of EDSS state, with a higher proportion of patients receiving ofatumumab improving. As per previous submissions and based on input from the clinical expert consulted for the review, CADTH assumed patients would not improve as per the sponsor's scenario analysis. • The sponsor outlined 2 definitions of CDP when analyzing treatment efficacy in its NMA. One was based on the predefined criteria from the ASCLEPIOS trials, and the other was a post hoc analysis. The sponsor used the post hoc definition while CADTH used the predefined definition as specified in the sponsor's protocol.
CADTH reanalysis results	• In the CADTH base case, ARRs were based on disease duration rather than EDSS score; a treatment-waning effect was applied; all first, second, and third lines of therapy were included; improvement in EDSS score was removed; and effect estimates based on predefined CDP definitions were used. • When compared to first-line therapies only, ofatumumab was extendedly dominated by ocrelizumab and glatiramer acetate — more QALYs would be generated at lower costs by a mix of ocrelizumab and glatiramer use. A 45.2% price reduction would make ofatumumab cost-effective at a threshold of $50,000 per QALY. • When compared to first-, second-, and third-line therapies, ofatumumab was dominated by alemtuzumab and cladribine. A 45.4% price reduction would make ofatumumab cost-effective at a threshold of $50,000 per QALY.

ARR = annualized relapse rate; BSC = best supportive care; CDP = confirmed disease progression; DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; ICER = incremental cost-effectiveness ratio; IFN = interferon; NMA = network meta-analysis; RMS = relapsing multiple sclerosis; QALY= quality-adjusted life-year.

Conclusions

The CADTH reanalysis, which based annualized relapse rates (ARRs) on multiple sclerosis (MS) disease duration rather than Expanded Disability Status Scale (EDSS) scores, applied a treatment-waning effect; considered all first, second, and third lines of therapies; removed EDSS improvement; and based effect estimates on predefined confirmed disease progression (CDP) definitions, found that ofatumumab was not cost-effective as a first-line therapy. The analysis found that ofatumumab was extendedly dominated by ocrelizumab and glatiramer acetate; that is, more QALYs would be generated at lower costs by a mix of ocrelizumab and glatiramer use. When considering ofatumumab as a second- or third-line therapy, it was not cost-effective as it produced fewer QALYs at a high cost, and was therefore dominated by alemtuzumab and cladribine.

These findings were driven largely by a sponsor-submitted network meta-analysis (NMA) that showed wide confidence intervals concerning the relative efficacy of ofatumumab versus other disease-modifying therapies (DMTs). Although point estimates showed ofatumumab was inferior or superior to some DMTs, these conclusions were highly uncertain. At minimum, ofatumumab should be priced no higher than the lowest-cost DMT with similar efficacy. Where it was found that ofatumumab was not as clinically effective as other DMTs, a price reduction of 45.2% would be required to ensure cost-effectiveness at a threshold of $50,000 per QALY when considering only first-line therapies. If second- and third-line therapies are considered relevant comparators, a 45.4% price reduction would be required.

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, including ocrelizumab, glatiramer acetate, dimethyl fumarate, teriflunomide, and others, were associated with a variety of side effects, the most common being injection-site reactions, flushing, hair-thinning, rashes, and increased risks 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 drug. It was highlighted that ofatumumab, being a subcutaneous formulation, had notable benefits for patients in that they would no longer be required to travel to a specialty infusion clinic for another treatment. This fills a significant gap in treatment for MS.

The sponsor's model reflected some elements of the patient input. For example, administration costs for infusion therapies were included in the sponsor's base case of the model. However, these were removed in the CADTH base case as they are funded by sponsor-supported clinics.

Two aspects were not addressed in the sponsor's model and could not be addressed by CADTH owing to structural or data limitations. First, because adverse events were broadly categorized and poorly implemented, the full impact of adverse events was not captured. Second, costs incurred by patients receiving infusion therapy were not considered.

Economic Review

The current review is for ofatumumab (Kesimpta) 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 quality-adjusted life-years (QALYs) in patients with relapsing forms of MS.[1] Primary analysis was conducted for a patient population mirroring the eligibility criteria for the ASCLEPIOS clinical trials:[2] patients between the ages of 18 and 55 years with a relapsing form of MS (either RRMS or secondary progressive multiple sclerosis [SPMS] with disease activity), and with an EDSS score of less than 6. A subanalysis was provided that looked only at RRMS patients. Patients also had to meet at least 1 of the following criteria: 1 relapse in the previous year, 2 relapses in the previous 2 years, or a positive gadolinium-enhanced MRI scan during the year prior to randomization. The conclusions of this economic analysis are therefore specific to this patient population.

Analysis was conducted from the perspective of a provincial ministry of health with a lifetime horizon (65 years). A discount rate of 1.5% per annum was applied.

Ofatumumab is delivered as a 20 mg/0.4 mL subcutaneous injection. A 20 mg dose of ofatumumab is given at initiation and then again after 1 week, 2 weeks, and 4 weeks. Within the model it is assumed that it is subsequently given monthly, although in the ASCLEPIOS clinical trials it was given every 4 weeks.[2] The unit cost for ofatumumab is $2,333.33. Based on monthly dosing, the annual cost is between $32,667 and $35,000 in year 1, depending on when the first maintenance dose is taken, and $28,000 in subsequent years ($37,333 in year 1 and $30,333 in subsequent years if dosed every 4 weeks).

Ofatumumab is compared to no active therapy (best supportive care [BSC]) and various DMTs. The primary analysis compares ofatumumab as a first-line therapy to BSC, interferon (IFN) beta-1a (Avonex, Rebif 22 and 44), IFN beta-1b (Betaseron, Extavia), glatiramer acetate, teriflunomide, dimethyl fumarate, and ocrelizumab. In a scenario analysis, ofatumumab is compared to additional therapies to represent later lines of therapy — natalizumab, fingolimod, cladribine, and alemtuzumab. Within the ASCLEPIOS clinical trials, 59.2% of those randomized to ofatumumab had received previous DMTs, with a large but unreported proportion having received more than one DMT.[2]

Model Structure

A cohort multi-state Markov model was developed in Microsoft Excel to simulate the disease course of RRMS patients receiving treatment with ofatumumab, other DMTs, and BSC. The model was based on patients transitioning across EDSS states 0 to 9 and death. Patients with relapsing forms of MS entered the model in a state between EDSS 0 and 6 inclusive, based on the pooled patient population of the ASCLEPIOS I and II trials.[2] The specific proportion in each EDSS level at baseline varied for the analysis for patients with RRMS and active SPMS only. In each cycle, patients could transition between EDSS states or enter the absorbing death state. Cycle length was 1 year, with a half-cycle correction applied.

It was assumed that patients who achieved an EDSS score of 7 or greater while on 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 2 years, although a proportion of patients was assumed to re-initiate treatment. The probability of death was assumed to be independent of EDSS level but higher than that of the general population.

The model did not explicitly consider transition to SPMS. Rather, it was assumed that SPMS patients would continue to be treated and would be subject to the same natural-history EDSS transitions, costs, and utility values.

Model Inputs

As above, the patient cohort within the model represented the pooled clinical trial population from the ASCLEPIOS I and II trials.[2]

For patients on BSC, transition probabilities between EDSS states were derived from natural-history information relating to untreated RRMS from an analysis of a British Columbia database.[3] A complex approach to derive ARRs by EDSS levels was adopted.[1] Relapse rates by disease duration were obtained from a previous study.[4] Duration of disease was identified for each EDSS level. The ARR for each EDSS state was then calculated based on the disease duration for each EDSS states.[5] A scenario analysis was provided whereby ARRs were assumed to be dependent on disease duration, rather than EDSS level.[6]

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 6 months confirmed disease progression (6mCDP) and a relative risk with respect to ARR. The NMA provided analysis relating to 6mCDP based on definitions of CDP from each of the included clinical trials (predefined analysis) and a post hoc reanalysis of the ASCLEPIOS I and II trials. The sponsor adopted estimates from the post hoc analysis within the economic evaluation.

All-cause mortality rates for the general population were derived from Statistics Canada Life Tables and weighted by a relative risk of mortality with MS from Jick.[8,9] Within the submission, the number of patients experiencing an adverse event within each trial was summed for all types of adverse events to give an overall number of adverse events for each treatment. This value was then divided by the sample within the trial to produce an overall probability of having any adverse event. The analysis therefore did not incorporate an event-specific probability.[2,10-18] In addition, for alemtuzumab only, a chronic adverse event probability was included relating to the probability of developing thyroid disorder.[19]

The proportion of patients who discontinued treatment was calculated based on the drug discontinuation probability from the main clinical trials.[2,10-18] If a patient discontinued treatment, they were removed from a given therapy and transferred to BSC. In addition, patients were assumed to discontinue treatment after reaching EDSS level 7. It is unclear if the discontinuation rates in the trial also included those who progressed to EDSS 7; if so, this would overestimate the number of discontinuations occurring within the model.

Health-state utilities in the model were based on disease severity (as measured by EDSS) and were derived from a study by Tappenden that included Canadian MS patients.[20] The disutility associated with relapses was sourced from a study by Prosser and colleagues, the results of which are consistent with a previous CADTH MS Therapeutic Review.[21,22] A single

disutility value was applied within each category of adverse event — i.e., disutility did not vary by type of adverse event.[23]

Costs for patient management by EDSS state were derived from a previous Canadian study up to EDSS level 6 and adjusted to 2020 Canadian dollars.[24] Costs for health states greater than 6 were estimated based on a previous study that concluded the increase in health states by level of EDSS was qualitatively exponential.[25] Exact methods of this extrapolation were not provided. Drug costs were derived from list prices from the Ontario Drug Benefit Formulary or the Ontario Exceptional Access Program.[26] Re-treatment for alemtuzumab and cladribine was modelled assuming that 100% of patients experiencing a relapse were being re-treated. Administration and monitoring costs for each treatment were based on product monographs and appropriate Canadian-based costs.

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted results based on probabilistic analyses with 1,000 iterations. Several probabilistic scenario analyses were presented.

Base-Case Results

In the sponsor's base-case analysis, ofatumumab was found to dominate, was less costly, and produced more QALYs than teriflunomide, Rebif 44, Avonex, Extavia, Betaseron, dimethyl fumarate, and ocrelizumab. Ofatumumab was more effective and more costly than BSC, glatiramer acetate, and Rebif 22. The estimated ICER for ofatumumab was $27,009 versus BSC, $25,638 versus glatiramer acetate, and $9,288 versus Rebif 22. Both Rebif 22 and glatiramer acetate were therefore subject to extended dominance through BSC and ofatumumab.

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

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

Drug	Total costs ($)	Incremental costs vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	ICER vs. BSC ($/QALY)	Sequential ICER
BSC	763,965		7.68			
Ofatumumab	833,249	69,284	10.25	2.57	27,009	27,009
Dominated therapies						
Glatiramer acetate	789,193	25,228	8.53	0.85	29,792	Extendedly dominated through ofatumumab and BSC
Rebif 22	815,550	51,585	8.34	0.66	78,224	Dominated by glatiramer acetate
Teriflunomide	840,944	76,979	8.31	0.63	121,432	Dominated by glatiramer acetate, Rebif 22, ofatumumab
Rebif 44	841,479	77,514	8.27	0.59	131,494	Dominated by glatiramer acetate, Rebif 22, ofatumumab, teriflunomide
Avonex	842,472	78,507	8.55	0.87	90,101	Dominated by ofatumumab

Drug	Total costs ($)	Incremental costs vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	ICER vs. BSC ($/QALY)	Sequential ICER
Extavia	842,794	78,829	8.52	0.84	94,186	Dominated by glatiramer acetate, ofatumumab, Avonex
Betaseron	850,146	86,181	8.52	0.84	102,458	Dominated by glatiramer acetate, ofatumumab, Avonex
Dimethyl fumarate	850,197	86,232	8.84	1.16	74,358	Dominated by ofatumumab
Ocrelizumab	880,618	116,653	10.16	2.48	47,063	Dominated by ofatumumab

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[1]

Deterministic analysis reported similar estimates of costs, QALYs, and ICERs. The probability that ofatumumab is the optimal therapy based on a threshold of $50,000 per incremental QALY was 51.3%.

Sensitivity and Scenario Analysis Results

The results for scenario analyses comparing ofatumumab to only first-line therapies were generally consistent with the base-case analysis. Higher ICERs versus BSC were reported for analysis incorporating treatment-waning ($64,008) and ARRs independent of EDSS ($34,639) and assumed no improvements in EDSS levels ($39,388). For the scenario analysis including second- and third-line therapies, ofatumumab was found to be more effective and more costly than alemtuzumab and cladribine and dominant over fingolimod and natalizumab. The estimated ICERs for ofatumumab versus alemtuzumab and cladribine were $95,289 and $22,125 per QALY respectively.

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 evidence of the relative effectiveness for ofatumumab versus other DMTs is available only for teriflunomide. Direct evidence versus other DMTs that ofatumumab is expected to replace for many patients, such as ocrelizumab, was not available. Estimates of the magnitude of the relative effect versus other DMTs were therefore derived from a sponsor-conducted NMA.[7] The CADTH clinical review concluded that the network of trials within the NMA was sparse, which leads to uncertainty in the effect estimates due to heterogeneity and inconsistency of the network. The clinical expert consulted by CADTH expressed concern over the lack of direct evidence comparing ofatumumab to other DMTs, and highlighted the differences in the characteristics of patient populations in the early clinical trials of DMTs compared to current trials. The expert suggested that a more conservative approach should be taken to estimating the magnitude of benefit in terms of relative effects. CADTH did consider adjusting the relative effect sizes to be more conservative but the appropriate approach to adopt for such an analysis was unclear. As mentioned below, CADTH did introduce a treatment-waning effect into the base-case analysis for all DMTs. This leads to a reduced treatment effect for DMTs versus BSC in the long term but does not address the uncertainty with respect to the modelled superiority of ofatumumab compared to other DMTs.

- A further issue with respect to the NMA is that the sponsor adopted 2 approaches to analyzing data from the ASCLEPIOS trials with respect to CDP. One was an analysis based on the predefined criteria from the protocol and the other was a post hoc analysis.[2,7] Furthermore, the NMA presents results based on CDP for 3 months and 6 months. Thus, 4 analyses were presented: 3mCDP based on the predefined analysis, 6mCDP based on the predefined analysis, 3mCDP based on the post hoc analysis and 6mCDP based on the post hoc analysis. In 3 of these analyses ofatumumab was found to be clinically inferior to ocrelizumab in terms of CDP, although the results were not statically significant. The sponsor adopted the 1 criteria for which ofatumumab was favoured to ocrelizumab (6mCDP based on the post hoc analysis). The clinical expert consulted by CADTH concluded that the differences in the definitions for the predefined and post hoc analyses were not clinically meaningful for stakeholders or decision-makers.
    - The CADTH base case adopted results from the analysis of 6mCDP based on the predefined criteria**.** With a lack of direct head-to-head trial data there is considerable uncertainty regarding ofatumumab's efficacy relative to most DMTs that could not be captured within the CADTH base case.
- **Comparators used in the analysis**: In the ASCLEPIOS clinical trial 59.2% (560 of 946) of those randomized to ofatumumab had received a DMT. The most common previous DMTs were interferons (37.7% of all those randomized to ofatumumab) and glatiramer acetate (25.6% of all those randomized to ofatumumab). For the 946 patients randomized to ofatumumab, the total number of DMTs previously used was 943. For those with previous use of DMTs, the average number of DMTs used was 1.68. Therefore, a high proportion of patients within the ASCLEPIOS clinical trials was receiving ofatumumab as a second- or third-line therapy. Analysis of clinical outcomes stratified by line of therapy was not reported and therefore the sponsor's analysis used data for both treatment-naive and treatment-experienced patients.
    - Based on the above, the CADTH base case also compares ofatumumab to all therapies within the base case.
- **Assumed improvement in health status**: Transition probabilities relating to disease progression were derived from a British Columbia MS dataset.[3] This allowed for an improvement in EDSS state within a cycle. For example, for patients in EDSS state 2 (the most common baseline EDSS level), there is an annual probability of improvement in EDSS of 13.7% with BSC. Based on the transition probabilities employed in the model, within a cohort of patients starting at EDSS 6, by year 10, 21.2% of patients on BSC will be in a better EDSS state compared with their initial state. This is exacerbated by the sponsor's approach to incorporating the treatment effect of DMTs. Rather than assuming DMTs reduce the rate of progression, the sponsor assumes the treatment effect also increases the rate at which a patient's EDSS score improves. The CADTH clinical expert advised that such improvements in EDSS level were unjustified and analysis should assume that no patients would see an improvement in their EDSS levels over the long term.
    - The CADTH base case adopted the London MS dataset, which excluded the probability of health status improvement.[27] This was provided by the sponsor as a setting for scenario analysis.
- **Technical issues with the model**: The CADTH pharmacoeconomic reviewer suggested that the model lacks transparency. The model formulas are excessively complex and beyond what is necessary to program a relatively simple 11-state Markov model. The model relies heavily on IFERROR (20,065 instances) and ISBLANK (1,991 instances) statements. Both IFERROR and ISBLANK statements are problematic as they 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.

CADTH also noted that the characterization of uncertainty with respect to certain parameters was not reflective of the sample data from which they were obtained. For example, the method for assigning parameters to a beta distribution (assuming 20% uncertainty around the base value) is technically incorrect and leads to illogical values. Furthermore, the model assumes no uncertainty around the transition between EDSS levels for the natural-history model; only uncertainty in relative transitions across DMTs.

- CADTH suggests that the unnecessary complexity of the model makes review of the model problematic and, combined with further issues detailed in a subsequent section, suggests that the results presented in both the sponsor's submission and the subsequent CADTH reanalysis should be treated with a degree of caution.

- **Extrapolation of treatment effect beyond trial time horizon**: The relative effectiveness of DMTs was assessed through an NMA for relatively short-term clinical trials (1 to 3 years) given the time horizon of the model (65 years). The sponsor's base case assumed the relative effectiveness from short-term clinical trials would be maintained for the full time horizon of the model. However, the sponsor provided a scenario analysis that adopted assumptions as per a previous CADTH review with respect to RRMS: 75% of the effect size in years 3 and 4, and 50% in year 5 and onward.[27]
  - Based on input from the clinical expert, CADTH assumed a waning of treatment effect as per the sponsor's scenario analysis; consistent with previous CADTH reviews on RRMS.[27]
- **Annualized relapse rates as a function of EDSS states**: The model assumed ARRs were a function of EDSS states. Combined with the relative effect of DMTs on ARR, as well as disease progression through EDSS, this may lead to double-counting of clinical benefits. The sponsor did supply a setting for scenario analysis whereby ARRs were independent of EDSS level.
  - Based on clinical input, CADTH assumed that ARRs were independent of EDSS as per the sponsor's scenario analysis. As a scenario analysis, CADTH assumed that ARRs were a function of EDSS state.
- **Costs of administration and monitoring**: The sponsor's analysis includes administration and monitoring costs for DMTs, although many such costs are covered by the sponsor's patient-access schemes and are therefore not applicable within a health care system perspective.
  - CADTH adopted an assumption whereby the costs of standard tests such as liver function tests and complete blood counts were included, but other costs relating to monitoring and administration (for both infusions and infections) were excluded.
- **Dosing of ofatumumab treatment**: The model assumed that after the first 3 doses, ofatumumab is given monthly, although in the ASCLEPIOS clinical trials it was given every 4 weeks.[2] The exact effectiveness of ofatumumab at monthly dosing is not established.
  - This limitation could not be addressed by CADTH.
- **Discontinuation**: The sponsor's submitted evaluation assumes that the discontinuation rate for cladribine and alemtuzumab is 16% after the second year, to be consistent with a previous CADTH pharmacoeconomic review.[27] Within the previous review, however, a 16% discontinuation rate was assumed for all DMTs.
  - Given the lack of long-term data on discontinuation rates for ofatumumab, and for consistency, the CADTH base-case analysis assumed a discontinuation rate after 2 years of 16% for all DMTs. A scenario analysis was conducted in which discontinuation rates were higher for cladribine and alemtuzumab.

- **Population**: The sponsor's submission included all relapsing forms of MS, which was aligned with the anticipated indication, whereas the CADTH base case aligns with the final approved Health Canada indication of just RRMS patients. CADTH notes this change is minor as RRMS patients provided more than 94% of the trial data used to inform the analysis.
  - CADTH used the RRMS dataset provided by the sponsor for the CADTH reanalysis.
- **Adverse events**: Incorporation of adverse events is poorly handled within the model, with data coming from studies of different design and different follow-ups. Furthermore, adverse events are grouped simply as adverse events or serious adverse events without consideration of the consistency with which events were covered in each study.
  - Given the very similar rates of adverse events for DMTs other than Extavia and Betaseron, for consistency and based on the advice of the clinical expert, the CADTH base case assumes the same rate for adverse events and serious adverse events for all DMTs with the exception of higher rates for Betaseron and Extavia.

Additionally, further key assumptions were made by the sponsor and have been appraised by CADTH (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 Tappenden[20]	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 Tappenden study is unlikely to greatly affect the study conclusions[5,20]
Costs for patient management by EDSS state up to level 6 and for relapses were derived from Canadian sources[24]	Appropriate Data sources are now dated but given the lack of other available Canadian data they are the best available
Costs for patient management by EDSS levels greater than 6 were based on exponential extrapolation of costs up to level 6[25]	Unclear Basis for this assumption is weak and the generation of more appropriate data would be preferred; likely to bias results in favour of DMTs which are assumed to be more effective
Constant mortality multiplier independent of EDSS	Appropriate
Severity of relapse the same for each comparator	Appropriate

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

The CADTH reanalysis (Table 5) addressed the limitations of the submitted model and report as outlined in Table 4.

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 CDP	Sponsor used a post hoc analysis based on CDP-6	CADTH adopted the estimates from the sponsor's NMA based on 6-month CDP based on the protocol definitions of CDP from the ASCLEPIOS trials
2. Transition between EDSS levels	Sponsor assumed a high proportion of patients would improve with respect to EDSS level and that the proportion improving would be higher for ofatumumab than for all other DMTs other than alemtuzumab	CADTH used the functionality in the sponsor-submitted model to use data from the London, Ontario, database, which does not allow for long-term improvement in EDSS level
3. Extrapolation of treatment effect beyond trial time horizon	Sponsor assumed the relative treatment effect for ofatumumab versus other DMTs would continue beyond the duration of clinical trial	CADTH used the functionality in the sponsor-submitted model to assume waning of relative treatment benefits after 3 years
4. Annualized relapse rates	The sponsor assumed the ARR was a function of EDSS state, thus leading to potential double-counting of clinical benefit	CADTH used the functionality in the sponsor submitted model to assume the ARR was independent of EDSS level
5. Costs of administration and monitoring	The sponsor includes administration and monitoring costs for DMTs	As these costs are typically covered by sponsor's patient-access schemes; CADTH included only the costs of standard tests
6. Discontinuation rates	The sponsor assumed higher discontinuation rates for cladribine and alemtuzumab after the second year	CADTH base-case analysis assumed the same discontinuation rate after 2 years for all DMTs
7. Adverse events	The sponsor assumed differential adverse event rates across the DMTs	Given problems with the reporting of adverse events in the sponsor's PE report, CADTH assumed the same adverse event rates for all DMTs, except higher rates for Extavia and Betaseron
8. Population	Sponsor analysis focused on RMS	The CADTH reanalysis focused on RRMS only
CADTH base case		1 + 2 + 3 + 4 + 5 + 6 + 7 + 8

ARR = annualized relapse rates; CDP = confirmed disability progression; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; NMA = network meta-analysis; PE = pharmacoeconomic report; RMS = relapsing forms of multiple sclerosis.

Given that 59.2% of those randomized to ofatumumab in the ASCLEPIOS clinical trials had received previous DMTs with a significant proportion having received more than 1 previous DMT, the CADTH base case compares ofatumumab to all therapies. (Table 6).

In the CADTH base-case analysis, ofatumumab was more costly than all comparators other than natalizumab and ocrelizumab. Ofatumumab was less effective and therefore dominated by cladribine and alemtuzumab. Ofatumumab was more effective than the following (with associated ICERs in parenthesis): ocrelizumab ($72,802), fingolimod ($2,059), teriflunomide ($23,158), dimethyl fumarate ($31,689), glatiramer acetate ($157,907), Avonex ($50,683), Rebif 22 ($85,559), Rebif 44 ($16,755), Betaseron ($48,576), Extavia ($60,556), and BSC ($138,088). Treatment with natalizumab was also estimated to have more QALYs than

ofatumumab but with a much higher ICER: $596,290. At a threshold of $50,000 per QALY the probability that ofatumumab was optimal was 0.1%.

For an analysis limited to first-line therapies, ofatumumab would be subject to extended dominance through glatiramer acetate and ocrelizumab (i.e., more QALYs would be generated at lower costs by a mix of ocrelizumab and glatiramer use) and would therefore not be considered cost-effective.

Table 6: Summary of CADTH's Base Case Results

Drug	Total costs ($)	Incremental costs vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	ICER vs. BSC ($ per QALY)	Sequential ICER
BSC	873,811		5.42			
Alemtuzumab	923,728	49,917	6.51	1.09	45,888	$45,888
Dominated therapies						
Glatiramer acetate	911,911	38,100	5.76	0.34	112,761	Extendedly dominated by alemtuzumab
Cladribine	929,585	55,774	6.20	0.78	71,722	Dominated by alemtuzumab
Rebif 22	945,885	72,074	5.79	0.37	194,871	Dominated by alemtuzumab, cladribine
Extavia	951,883	78,072	5.73	0.30	256,952	Dominated by glatiramer acetate, alemtuzumab, cladribine, Rebif 22
Betaseron	957,585	83,773	5.73	0.31	273,485	Dominated by glatiramer acetate, alemtuzumab, cladribine, Rebif 22
Avonex	961,843	88,032	5.83	0.41	214,918	Dominated by alemtuzumab, cladribine
Teriflunomide	966,216	92,405	5.59	0.17	541,955	Dominated by glatiramer acetate, alemtuzumab, cladribine, Rebif 22, Extavia, Betaseron, Avonex
Dimethyl fumarate	971,132	97,321	5.91	0.49	199,870	Dominated by alemtuzumab, cladribine
Rebif 44	972,365	98,553	5.73	0.31	319,506	Dominated by glatiramer acetate, alemtuzumab, cladribine, Rebif 22, Avonex, dimethyl fumarate
Fingolimod	979,580	105,769	5.94	0.52	202,970	Dominated by alemtuzumab, cladribine
Ofatumumab	980,092	106,281	6.19	0.77	138,088	Dominated by alemtuzumab, cladribine
Ocrelizumab	990,218	116,407	6.33	0.91	128,096	Dominated by alemtuzumab
Natalizumab	1,051,190	177,379	6.31	0.89	199,550	Dominated by alemtuzumab, ocrelizumab

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Scenario Analysis Results

CADTH conducted 2 scenario analyses that explored the impact of discontinuation rates and assumed relapse rates were dependent on EDSS level. Neither influenced the conclusion that ofatumumab is not cost-effective at a threshold of $50,000 per QALY as either first- or second-line treatment.

Given the complexity of the sequential analysis, a price reduction analysis focused on the position of ofatumumab on the cost-effectiveness frontier based on potential price reductions for the analysis with all comparators and the analysis restricted to first-line therapies (Table 7).

In the CADTH base-case analysis, ofatumumab was less effective and more costly than alemtuzumab. This is driven by the indirect comparison used to inform the economic analysis, which found that ofatumumab was associated with smaller, albeit non-significant, health gains relative to some DMTs. Based on the results of the indirect comparison, compared with some DMTs, the comparative clinical effects of ofatumumab may be similar. As such, the price of ofatumumab should be no more than the least-expensive DMTs. However, based on this indirect evidence, further price reductions would be justified where ofatumumab may lead to smaller QALY gains relative to other DMTs. Based on the CADTH base case, which uses the estimates derived from the sponsor's indirect comparison, ofatumumab would be cost-effective at a threshold of $50,000 per QALY with a 45.4% price reduction.

If only first-line therapies are considered, ofatumumab would be cost-effective at a threshold of $50,000 per QALY with a 45.2% price reduction.

All estimated necessary price reductions are based on the list price of other comparators.

Table 7: Price Reduction Analysis

		Price reduction analysis for ofatumumab	
Price reduction	**Sponsor base case**	**CADTH reanalysis (all comparators)**	**CADTH reanalysis (first-line therapies only)**
No price reduction	$27,009 (ICER for ofatumumab vs. BSC)	Dominated by alemtuzumab, cladribine	Subject to extended dominance through glatiramer acetate and ocrelizumab
10%	$19,068 (ICER for ofatumumab vs. BSC)	Dominated by alemtuzumab, cladribine	$125,351 (ICER for ofatumumab vs. glatiramer acetate)
20%	$11,126 (ICER for ofatumumab vs. BSC)	Dominated by alemtuzumab, cladribine	$102,190 (ICER for ofatumumab vs. BSC)
30%	$3,184 (ICER for ofatumumab vs. BSC)	Dominated by alemtuzumab, cladribine	$81,428 (ICER for ofatumumab vs. BSC)
40%	Dominant over all comparators	$21,873 (ICER for alemtuzumab vs. ofatumumab)	$60,666 (ICER for ofatumumab vs. BSC)
50%	Dominant over all comparators	$73,799 (ICER for alemtuzumab vs. ofatumumab)	$39,904 (ICER for ofatumumab vs. BSC)
60%	Dominant over all comparators	$125,725 (ICER for alemtuzumab vs. ofatumumab)	$19,142 (ICER for ofatumumab vs. BSC)
70%	Dominant over all comparators	$177,651 (ICER for alemtuzumab vs. ofatumumab)	Dominant over all comparators

		Price reduction analysis for ofatumumab	
Price reduction	**Sponsor base case**	**CADTH reanalysis (all comparators)**	**CADTH reanalysis (first-line therapies only)**
80%	Dominant over all comparators	$229,576 (ICER for alemtuzumab vs. ofatumumab)	Dominant over all comparators
90%	Dominant over all comparators	$281,502 (ICER for Alemtuzumab vs. ofatumumab)	Dominant over all comparators
100%	Dominant over all comparators	$333,428 (ICER for Alemtuzumab vs. ofatumumab)	Dominant over all comparators

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; vs. = versus.

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

CADTH reported a number of concerns with the submitted model that were addressed in a reanalysis, which compared ofatumumab to a range of DMTs for first-, second-, and third-line treatment. These changes included adding a treatment-waning effect, using a different estimate from the indirect comparison, and removing the ability for a patient's EDSS score to improve. The CADTH base case found that ofatumumab was dominated by cladribine and alemtuzumab, and therefore would not be cost-effective at any threshold without price reductions. When compared only to therapies indicated for first-line treatment, ofatumumab was subject to extended dominance by ocrelizumab (i.e., more QALYs would be generated at lower costs by a mix of ocrelizumab and glatiramer use) and ofatumumab would therefore not be considered cost-effective.

The results and interpretation of the pharmacoeconomic evaluation are driven by the sponsor's NMA, which produced uncertain results with very wide confidence intervals. If it is considered likely that ofatumumab will provide similar health gains as other DMTs, then it should be priced no higher than the lowest-cost option available. If it is considered likely that ofatumumab would provide smaller health gains than other available DMTs, larger price reductions of at least 45% may be required to achieve cost-effectiveness at a threshold of $50,000 per QALY.

Given the uncertainty over the magnitude of effect sizes estimated from the sponsor's NMA and the unknown actual price for all comparators, the CADTH pharmacoeconomic reviewer suggests caution should be taken when interpreting the above results.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing product listing agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

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

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost ($)
Ofatumumab (Kesimpta)	20 mg/0.4 mL	Pre-filled syringe	2,333.3300[b]	20 mg at weeks 0, 1, 2, 4, and monthly thereafter[c]	Daily average, Year 1: 95.89 Year 2: 76.71	Year 1: 35,000[d] Year 2: 28,000
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[e]	89.32	32,600
Oral therapies						
Cladribine (Mavenclad)	10 mg	Tablet	3,212.0000	3.5 mg/kg over 2 years[f]	107.80	39,347

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost ($)
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
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), unless otherwise indicated, and do not include dispensing fees.[26,28] Annual costs based on 365 days per year.

[a] Recommended doses from the appropriate product monographs unless otherwise indicated.[29-42]

[b] Sponsor-submitted price.[43]

[c] The recommended dose according to the product monograph is 20 mg at weeks 0, 1, 2, and 4 and monthly thereafter.[44]

[d] CADTH notes this cost may be $32,667 in the first year for some patients if the first maintenance dose is taken on day 3 of week 4 or later.

[e] 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]

[f] Patient weight of 70.0 kg assumed based on the SUNBEAM trial.[45]

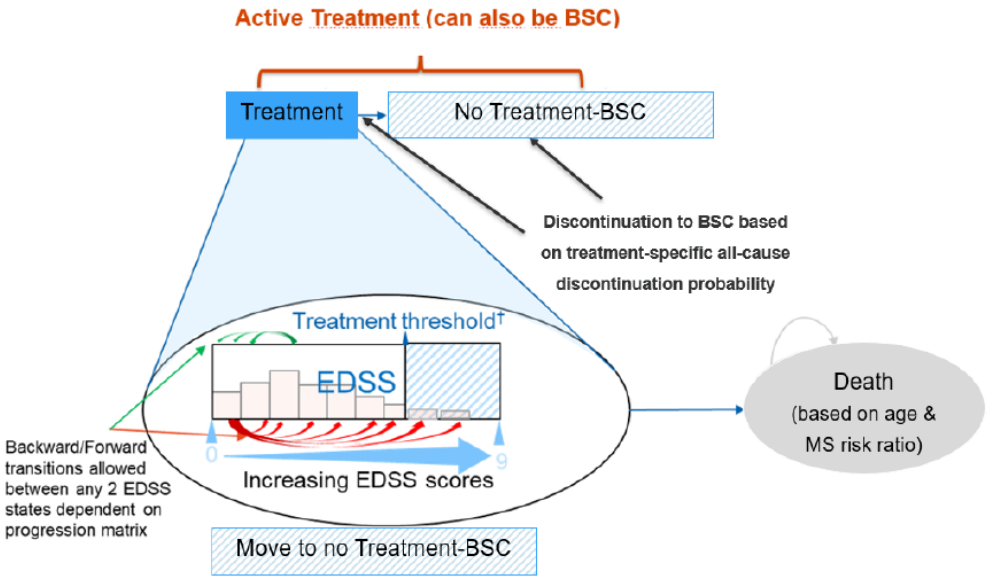
Appendix 2: Submission Quality

Table 9: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☒	☐	
Model has been adequately programmed and has sufficient face validity	☐	☒	There were concerns with the lack of transparency with both the model and its reporting
Model structure is adequate for decision problem	☒	☐	
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☐	☒	Parameterization of probability distributions did not always follow best practices
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☐	☒	An analysis based on the predefined criteria for CDP would have been appropriate
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☐	☒	There was a lack of transparency with respect to the assumptions, which led to greater improvements in EDSS levels with ofatumumab

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Sponsor's Submitted Model's Structure



BSC = best supportive care; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.
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

	Undiscounted		Discounted						
Intervention	Life-years	QALYs	Drug Costs (including re-treatment)	Administration and monitoring costs	Health-state costs	Adverse event costs	Relapse costs	Total cost	QALYs
Ofatumumab	30.22	11.76	$203,722	$1,301	$514,247	$406	$113,573	$833,249	10.25
Ocrelizumab	30.22	11.68	$233,822	$12,977	$518,985	$428	$114,406	$880,618	10.16
Teriflunomide	30.22	10.00	$112,694	$1,264	$600,137	$402	$126,447	$840,944	8.31
Dimethyl fumarate	30.22	10.47	$151,211	$1,427	$575,604	$502	$121,454	$850,197	8.84
Glatiramer acetate	30.22	10.20	$73,168	$1,248	$589,412	$463	$124,903	$789,193	8.53
Avonex	30.22	10.28	$125,102	$1,531	$585,071	$316	$130,452	$842,472	8.55
Rebif 22	30.22	10.05	$87,458	$1,386	$597,205	$307	$129,194	$815,550	8.34
Rebif 44	30.22	9.96	$110,474	$1,405	$602,039	$318	$127,244	$841,479	8.27
Betaseron	30.22	10.20	$133,411	$1,925	$588,990	$678	$125,142	$850,146	8.52
Extavia	30.22	10.20	$125,513	$1,923	$589,433	$676	$125,250	$842,794	8.52
BSC	30.22	9.43	$0	$0	$629,894	$0	$134,071	$763,965	7.68

QALY = quality-adjusted life-year.
Source: Sponsor's pharmacoeconomic submission.[1]

Appendix 4: Additional Details on the CADTH Reanalysis

Table 11: Disaggregated Summary of CADTH's Base Case

	Undiscounted	Discounted						
Intervention	Life-years	Drug costs (including re-treatment)	Administration and monitoring costs	Health- state costs	Adverse event costs	Relapse costs	Total cost	QALYs
Ofatumumab	30.75	$155,326	$791	$798,433	$303	$25,239	$980,092	6.19
Ocrelizumab	30.75	$173,629	$839	$790,006	$305	$25,440	$990,218	6.33
Alemtuzumab	30.75	$101,084	$1,521	$779,501	$334	$24,705	$907,145	6.51
Cladribine	30.75	$84,881	$937	$797,400	$311	$25,888	$909,418	6.20
Natalizumab	30.75	$233,251	$1,261	$791,043	$303	$25,331	$1,051,190	6.31
Fingolimod	30.75	$138,829	$996	$813,176	$294	$26,286	$979,580	5.94
Teriflunomide	30.75	$103,387	$868	$834,105	$274	$27,583	$966,216	5.59
Dimethyl fumarate	30.75	$128,455	$970	$814,834	$288	$26,585	$971,132	5.91
Glatiramer acetate	30.75	$59,965	$777	$823,460	$290	$27,420	$911,911	5.76
Avonex	30.75	$113,917	$1,073	$818,279	$278	$28,297	$961,843	5.83
Rebif 22	30.75	$95,482	$1,024	$821,243	$251	$27,885	$945,885	5.79
Rebif 44	30.75	$118,299	$1,033	$825,287	$255	$27,491	$972,365	5.73
Betaseron	30.75	$103,777	$1,389	$824,329	$527	$27,563	$957,585	5.73
Extavia	30.75	$97,882	$1,389	$824,509	$527	$27,577	$951,883	5.73
BSC	30.75	$0	$0	$844,344	$0	$29,467	$873,811	5.42

QALY = quality-adjusted life-year.

Table 12: Summary of CADTH's Scenario Analysis: Base-Case Results with ARRs Dependent on EDSS Levels: Based on Deterministic Analysis

Drug	Total costs ($)	Incremental costs vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	ICER vs. BSC ($ per QALY)	Sequential ICER
Non-dominated therapies						
BSC	972,348		4.12			
Alemtuzumab	1,057,914	85,566	5.27	1.16	73,793	$73,793
Dominated therapies						
Glatiramer acetate	1,007,405	35,056	4.49	0.37	93,673	Extendedly dominated by alemtuzumab and BSC
Rebif 22	1,042,000	69,651	4.51	0.40	174,642	Extendedly dominated by alemtuzumab and BSC
Extavia	1,047,162	74,814	4.46	0.34	217,327	Dominated by glatiramer acetate, Rebif 22
Betaseron	1,052,943	80,594	4.46	0.34	234,117	Dominated by glatiramer acetate, Rebif 22, Extavia
Avonex	1,059,144	86,795	4.54	0.42	204,855	Dominated by alemtuzumab
Teriflunomide	1,060,913	88,564	4.33	0.22	407,160	Dominated by glatiramer acetate, Rebif 22, Extavia, Betaseron, alemtuzumab, Avonex
Dimethyl fumarate	1,064,634	92,285	4.67	0.55	166,993	Dominated by alemtuzumab
Rebif 44	1,067,882	95,534	4.46	0.35	275,673	Dominated by glatiramer acetate, Rebif 22, alemtuzumab, Avonex, dimethyl fumarate
Ofatumumab	1,071,957	99,609	4.97	0.85	117,007	Dominated by alemtuzumab
Fingolimod	1,072,458	100,110	4.70	0.59	169,972	Dominated by alemtuzumab
Cladribine	1,073,111	100,763	4.96	0.84	119,589	Dominated by alemtuzumab
Ocrelizumab	1,083,725	111,377	5.07	0.96	116,356	Dominated by alemtuzumab
Natalizumab	1,142,725	170,377	5.09	0.97	175,022	Dominated by alemtuzumab

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Table 13: Summary of CADTH's Scenario Analysis: Base-Case Results With 16% Discontinuation Rates for Alemtuzumab and Cladribine and 10% for Other DMTs: Based on Deterministic Analysis

Drug	Total costs ($)	Incremental costs vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	ICER vs. BSC ($ per QALY)	Sequential ICER
Non-dominated therapies						
BSC	871,241		5.43			
Alemtuzumab	923,170	51,929	6.48	1.05	49,586	$49,586
Dominated therapies						
Glatiramer acetate	921,562	50,321	5.81	0.38	132,590	Extendedly dominated by alemtuzumab and BSC
Cladribine	928,015	56,773	6.19	0.76	74,820	Dominated by alemtuzumab
Rebif 22	963,469	92,228	5.86	0.43	216,833	Dominated by alemtuzumab, cladribine
Extavia	971,140	99,898	5.78	0.35	287,389	Dominated by glatiramer acetate, alemtuzumab, cladribine, Rebif 22
Betaseron	978,423	107,182	5.78	0.35	308,343	Dominated by glatiramer acetate, alemtuzumab, cladribine, Rebif 22, Extavia
Avonex	984,582	113,340	5.91	0.47	240,608	Dominated by alemtuzumab, cladribine
Teriflunomide	987,321	116,080	5.63	0.19	597,343	Dominated by glatiramer acetate, alemtuzumab, cladribine, Rebif 22, Extavia, Betaseron, Avonex
Rebif 44	996,707	125,465	5.78	0.35	361,027	Dominated by glatiramer acetate, alemtuzumab, cladribine, Rebif 22, Avonex
Dimethyl fumarate	997,155	125,913	6.00	0.57	222,285	Dominated by alemtuzumab, cladribine
Fingolimod	1,008,112	136,871	6.04	0.60	227,883	Dominated by alemtuzumab, cladribine
Ofatumumab	1,010,530	139,288	6.32	0.89	157,280	Dominated by alemtuzumab
Ocrelizumab	1,027,930	156,689	6.46	1.02	153,013	Dominated by alemtuzumab
Natalizumab	1,104,146	232,905	6.48	1.04	223,862	Dominated by alemtuzumab

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key take-aways of the Budget Impact Analysis

- CADTH identified the following key limitations with the sponsor's analysis:
  - The sponsor's model assumed monthly dosing of ofatumumab as per the final approved Health Canada product monograph but omitted a dose in the first year of treatment for patients.
  - It is unclear how many patients currently being managed on other therapies would switch to ofatumumab if it were available, leading to some uncertainty with market size.
- Based on CADTH reanalyses, the budget impact from the introduction of ofatumumab is expected to be $4,139,015 in year 1, $6,910,568 in year 2, and $8,054,716 in year 3, for a total of $19,104,299 over 3 years.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis (BIA)[43] assessed the introduction of ofatumumab as a treatment for adult patients with relapsing forms of MS. The analysis was undertaken from a drug-plan perspective using a claims-based approach, with only drug acquisition costs included in the base case. A 3-year time horizon was used, from April 2021 to March 2024, with a base year of April 2020 to March 2021. Market size was assumed to grow at the same rate as the overall Canadian population and the total number of patients was estimated by dividing the total costs by the annual costs of each comparator.

The relevant comparators for this analysis included dimethyl fumarate, glatiramer acetate, IFN beta-1a, IFN beta-1b, pegylated IFN beta-1a, teriflunomide, and ocrelizumab. The sponsor also considered the effect of ofatumumab on the second-line therapies alemtuzumab, natalizumab, fingolimod, and cladribine. Market shares for each comparator were estimated using historical trends from April 2019 to March 2020 to make forward-looking projections. In the reference scenario, ofatumumab was assumed to be unavailable, and in the new scenario ofatumumab was assumed to take up market from the other comparators. This uptake was modelled after that of ocrelizumab and varied by jurisdiction and the various therapies available. Key inputs to the BIA are documented in Table 14.

Table 14: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1/2/3)
Target population	
Growth rate of Canadian population, %	1.4
Number of patients eligible for drug under review	8,395/8,513/8,632
Market uptake for Ontario (3 years)	
Uptake (reference scenario), %	
First-line treatment	
Ofatumumab	0/0/0
Dimethyl fumarate	20.5/18.9/17.2
Glatiramer acetate (Copaxone)	19.7/18.1/16.5
Glatiramer acetate (Glatect)	3.5/3.3/3.0
Interferon beta-1a (Avonex)	9.8/9.0/8.2
Interferon beta-1a (Rebif 22)	2.1/2.0/1.8
Interferon beta-1a (Rebif 44)	6.7/6.1/5.6
Interferon beta-1b (Betaseron)	4.2/3.8/3.5
Interferon beta-1b (Extavia)	0.3/0.3/0.3

Parameter	Sponsor's estimate (reported as year 1/2/3)
Pegylated interferon beta-1a	1.2/1.1/1.0
Teriflunomide	26.7/24.6/22.4
Ocrelizumab	5.2/12.8/20.6
Subsequent lines of treatment	
Ofatumumab	0/0/0
Alemtuzumab	5.8/5.5/5.4
Natalizumab	26.3/25.1/24.5
Fingolimod	56.0/53.4/52.1
Cladribine	12.0/16.0/18.0
Uptake (new drug scenario), %	
First-line treatment	
Ofatumumab	4.4/11.1/18.3
Dimethyl fumarate	19.7/17.3/15.0
Glatiramer acetate (Copaxone)	18.9/16.6/14.4
Glatiramer acetate (Glatect)	3.4/3.0/2.6
Interferon beta-1a (Avonex)	9.4/8.3/7.2
Interferon beta-1a (Rebif 22)	2.1/1.8/1.6
Interferon beta-1a (Rebif 44)	6.4/5.6/4.9
Interferon beta-1b (Betaseron)	4.0/3.5/3.1
Interferon beta-1b (Extavia)	0.3/0.3/0.3
Pegylated interferon beta-1a	1.2/1.0/0.9
Teriflunomide	25.7/22.5/19.6
Ocrelizumab	4.5/8.8/12.1
Subsequent lines of treatment	
Ofatumumab	2.1/4.6/7.1
Alemtuzumab	5.6/5.3/5.0
Natalizumab	25.7/23.9/22.7
Fingolimod	54.8/51.0/48.4
Cladribine	11.7/15.3/16.7
Cost of treatment (per patient)	
Cost of annual treatment	
First-line treatment	
Ofatumumab first year (subsequent years)	$32,667 ($28,000)
Dimethyl fumarate	$25,557
Glatiramer acetate	$11,834 to $17,087
Interferon beta-1a	$21,831 to $26,577
Interferon beta-1b	$18,968 to $20,089
Pegylated interferon beta-1a	$22,339
Teriflunomide	$21,576
Ocrelizumab	$32,600
Subsequent lines of treatment	
Alemtuzumab	$39,093
Natalizumab	$44,026
Fingolimod (Gilenya)	$26,996
Cladribine	$44,968

Summary of the Sponsor's Budget Impact Analysis Results

The estimated budget impact of funding ofatumumab for the treatment of relapsing forms of MS was expected to be $3,245,064 in year 1, $5,484,409 in year 2, and $6,589,590 in year 3, for a total of $15,319,063 over the 3-year time horizon.

CADTH Appraisal of the Sponsor's Budget Impact Analysis

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

- **Dosing of ofatumumab treatment:** The sponsor assumed that ofatumumab would be administered monthly after the loading doses at weeks 0, 1, and 2, although within the ASCLEPIOS clinical trials it was given every 4 weeks.[2] This led to the assumption by the sponsor that in first and subsequent years of ofatumumab treatment, patients would receive 14 and 12 doses, respectively. CADTH notes that in some cases the sponsor has omitted a dose of ofatumumab in the first year, as the product monograph recommends 3 loading doses (at weeks 0, 1, and 2) followed by 12 regular doses administered monthly.
    - CADTH assumed that patients would receive 15 and 12 units of ofatumumab in the first and subsequent years of the model as part of the base case.
- **Overestimation of the number of patients who might switch from ocrelizumab to ofatumumab**: The sponsor assumed in its model that some proportion of patients currently taking ocrelizumab would switch to ofatumumab. This proportion varied by jurisdiction but ranged from 41.1% to 54.4% in year 3 in the jurisdictions that reimburse ocrelizumab. The clinical expert consulted by CADTH thought it unlikely that patients being managed well on ocrelizumab would switch to ofatumumab, given the 2 drugs have similar efficacy and mechanisms of action. It was suggested that only in the case of unfavourable side effects would a patient switch from ocrelizumab to ofatumumab.
    - CADTH's scenario analysis assumed no patient would switch from ocrelizumab to ofatumumab.
- **Population specifies relapsing forms of MS**: The sponsor-submitted BIA is specified for relapsing forms of MS whereas the final Health Canada approval is for RRMS. Given the sponsor's claim-based approach and the majority of drugs are indicated for RRMS, CADTH does not anticipate this to have a substantial impact on the BIA.

CADTH Reanalyses of the BIA

CADTH conducted 1 revision as part of the base case by increasing the expected number of units of ofatumumab that would be received by patients in the first and subsequent years of treatment.

Table 15: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None		
Changes to derive the CADTH base case		
1. Changed expected dosing of ofatumumab	14 units of ofatumumab in the first year and 12 units in subsequent years	15 units of ofatumumab in the first year and 12 units in subsequent years
CADTH base case		Reanalysis 1

The results of the CADTH step-wise reanalysis are presented in summary format in Table 16 and a more detailed breakdown is presented in Table 17.

Based on the CADTH base case, the expected budget impact of funding ofatumumab for the treatment of patients with relapsing forms of MS is expected to be $4,139,015 in year 1, $6,910,568 in year 2, and $8,054,716 in year 3, for a total of $19,104,299 over 3 years.

Scenario analyses were conducted using the CADTH base case, which found that the assumption of patients switching from ocrelizumab to ofatumumab slightly increased the 3-year budget impact to a total of $19,592,148. If price reductions of 45.4% and 45.2% from the pharmacoeconomic model appraisal were applied to the BIA, the budget impact estimated a cost savings of $24,183,364 and $23,992,669 over the 3-year horizon.

Table 16: Summary of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	3-year total
Submitted base case	$15,319,063
CADTH reanalysis 1 – dosing of ofatumumab	$19,104,299
CADTH base case	$19,104,299

Table 17: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 1	Year 2	Year 3	3-year total
Submitted base case	Reference	$190,146,829	$196,132,668	$203,736,685	$590,016,182
	New drug	$193,391,893	$201,617,078	$210,326,274	$605,335,245
	Budget impact	***$3,245,064***	***$5,484,409***	***$6,589,580***	***$15,319,063***
CADTH base case	Reference	$190,146,829	$196,132,668	$203,736,685	$590,016,182
	New drug	$194,285,844	$203,043,237	$211,791,400	$609,120,481
	Budget impact	***$4,139,015***	***$6,910,568***	***$8,054,716***	***$19,104,299***
CADTH scenario analysis 1: no patients switching from ocrelizumab	Reference	$190,146,829	$196,132,668	$203,736,685	$590,016,182
	New drug	$194,078,584	$202,861,818	$212,667,928	$609,608,330
	Budget impact	***$3,931,756***	***$6,729,149***	***$8,931,243***	***$19,592,148***
CADTH scenario analysis 2a: price reduction of 45.4%	Reference	$190,146,829	$196,132,668	$203,736,685	$590,016,182
	New drug	$188,198,037	$188,460,850	$189,173,931	$565,832,818
	Budget impact	***−$1,948,792***	***−$7,671,819***	***−$14,562,753***	***−$24,183,364***
CADTH scenario analysis 2a: price reduction of 45.2%	Reference	$190,146,829	$196,132,668	$203,736,685	$590,016,182
	New drug	$188,224,856	$188,525,089	$189,273,568	$566,023,513
	Budget impact	***−$1,921,973***	***−$7,607,579***	***−$14,463,117***	***−$23,992,669***

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