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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

CLADRIBINE (MAVENCLAD)

(EMD Serono)

Indication: As monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and delay the progression of disability. Cladribine is generally recommended in RRMS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for RRMS.

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Table of Contents

Abbreviations 5
Executive Summary 7
Background 7
Summary of Identified Limitations and Key Results 8
Conclusions 9
Information on the Pharmacoeconomic Submission 10
Summary of the Manufacturer's Pharmacoeconomic Submission 10
Manufacturer's Base Case 11
Summary of Manufacturer's Sensitivity Analyses 12
Limitations of Manufacturer's Submission 12
CADTH Common Drug Review Reanalyses 15
Issues for Consideration 17
Patient Input 17
Conclusions 18
Appendix 1: Cost Comparison 19
Appendix 2: Additional Information 21
Appendix 3: Summary of Other HTA Reviews of Drug 22
Appendix 4: Reviewer Worksheets 24
References 33

Tables

Table 1: Summary of the Manufacturer's Economic Submission 6
Table 2: Summary of Results of the Manufacturer's Base Case: Pre-Treated Population 11
Table 3: Summary of Results of the Manufacturer's Base Case: HDA Population 12
Table 4: CDR Base Case: Full Relapsing-Remitting Multiple Sclerosis Population 15
Table 5: CDR Base Case: Pre-Treated Population 16
Table 6: CDR Base Case: High Disease Activity Population 16
Table 7: CDR Reanalysis Based on Price-Reduction Scenarios for Cladribine 16
Table 8: CDR Cost Comparison for Relapsing-Remitting Multiple Sclerosis 19
Table 9: CDR Cost Comparison for Relapsing-Remitting Multiple Sclerosis – Interferons 20
Table 10: Submission Quality 21
Table 11: Authors Information 21

Table 12: Other Health Technology Assessment Findings 22
Table 13: Baseline Distribution of Patients by Expanded Disability Status Scale Level 24
Table 14: Transition Matrix for Best Supportive Care based on British Columbia Cohort 25
Table 15: Comparative Efficacy of DMT Versus Placebo for Annualized Relapse Rate 25
Table 16: Comparative Efficacy of DMT Versus Placebo for CDP at 3 Months 25
Table 17: Comparative Efficacy of DMT Versus Placebo for CDP at 6 Months 26
Table 18: Data Sources 26
Table 19: Manufacturer's Key Assumptions 27
Table 20: Steps in CDR Reanalysis 28
Table 21: Full RRMS population – Inclusion of All Comparators 28
Table 22: Full RRMS population – Inclusion of All Comparators; Use of London Natural History Data 28
Table 23: Full RRMS Population – Inclusion of All Comparators; Equal Discontinuation (10% in Years 1 and 2 Followed by Curtailment); Equal Treatment Waning 29
Table 24: HDA Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine) 29
Table 25: HDA Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine); Use of London Natural History Data 29
Table 26: HDA population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine); Equal Discontinuation (10% in Years 1 and 2 Followed by Curtailment); Equal Treatment Waning 30
Table 27: Pre-Treated Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine) 30
Table 28: Pre-Treated Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine); Use of London Natural History Data 30
Table 29: Pre-Treated Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine); Equal Discontinuation (10% in years 1 and 2 followed by Curtailment); Equal Treatment Waning 31

Figure

Figure 1: Manufacturer's Model Structure 24

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Abbreviations

BSC	best supportive care
CDP	confirmed disease progression
CDR	CADTH Common Drug Review
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
HDA	high disease activity
ICER	incremental cost-effectiveness ratio
MS	multiple sclerosis
QALY	quality-adjusted life-year
RRMS	relapsing-remitting multiple sclerosis

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Cladribine (Mavenclad) 10 mg tablet
Study Question	What is the incremental cost-effectiveness of cladribine for the second-line treatment of relapsing-remitting multiple sclerosis (RRMS) as compared with standard of care in Canada?
Type of Economic Evaluation	Cost-utility analysis (CUA)
Target Population	Adult patients with RRMS in Canada who either • Had prior treatment with any disease-modifying therapy (DMT) – pre-treated group • Had at least one relapse in the previous year while on DMT therapy and at least 1 T1 Gd+ lesion or 9 T3 lesions; or had two or more relapses in previous year whether or not on DMT treatment – high disease activity (HDA) group
Treatment	Cladribine
Outcome	Quality-adjusted life-years (QALYs)
Comparators	Pre-treated • Fingolimod HDA • Fingolimod • Natalizumab • Daclizumab (Note: daclizumab was voluntarily withdrawn from the market in March 2018) • Alemtuzumab
Perspective	Canadian public health care payer
Time Horizon	25 years
Results for Base Case	• Pre-treated patients: cladribine dominated fingolimod (cladribine is associated with lower total costs and greater QALYs) • For patients with HDA: cladribine dominated alemtuzumab, fingolimod, and natalizumab
Key Limitations	• Assumption of improving health status is an area of debate and, consistent with patient input, the clinical expert consulted by CADTH felt the assumption was inappropriate. • Data on comparative clinical effectiveness within the subpopulations was insufficient to model incremental effectiveness. • Assumption of differential treatment waning was not supported • Assumption relating to continued benefit of cladribine and alemtuzumab after treatment curtailment was inappropriate and biased in favour of these treatments.
CDR Estimate(s)	CDR reanalysis of the manufacturer's base case addressed the issues detailed above by altering parameters relating to relative clinical effectiveness, rates of treatment discontinuation, treatment waning, and natural history. • For all RRMS patients, cladribine was subject to extended dominance through fingolimod and alemtuzumab. The ICER for cladribine versus fingolimod was $131,055. • For pre-treated patients: cladribine was dominated by fingolimod (e.g., cladribine was associated with greater total costs and fewer QALYs). • For patients with HDA: cladribine was dominated by fingolimod.

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; DMT = disease-modifying therapy; Gd+ = gadolinium-enhanced; HDA = high disease activity; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

Drug	Cladribine (Mavenclad)
Indication	As monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and delay the progression of disability. Cladribine is generally recommended in RRMS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for RRMS.
Reimbursement Request	As per indication
Dosage Form(s)	10 mg tablet
NOC Date	November 29, 2017
Manufacturer	EMD Serono Inc.

Executive Summary

Background

Cladribine (Mavenclad) is indicated as monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and delay the progression of disability.[1] It is administered orally and is available as a 10 mg tablet at a price of $3,082.70 per tablet.[2] The recommended cumulative dose is 3.5 mg/kg over the course of two years, with one treatment course of 1.75 mg/kg per year.[1] The treatment course is spread over two weeks each year, one week at the beginning of the first month of that year, and the other at the beginning of the second month. During each week, patients receive one or two 10 mg tablets, based on body weight, over the course of four to five days. The average annual cost is $43,158 based on patient weight of 70 kg.[2]

The manufacturer submitted a cost-utility analysis based on a Markov state-transition model comparing cladribine with other available disease-modifying therapies (DMTs).[3] Analysis was conducted for two distinct patient populations: 1) adult patients with RRMS in Canada who had prior treatment with any DMT – pre-treated group; 2) adult patients with RRMS in Canada who had at least one relapse in the previous year while on DMT therapy and at least one T1 gadolinium-enhanced lesion or nine T3 lesions, or had two or more relapses in the previous year whether or not on treatment – high disease activity (HDA) group. Comparators were limited to those DMTs included in a network meta-analysis that formed part of the manufacturer's submitted Clinical Summary.[2] For the pretreated population this was limited to fingolimod, while for the HDA population this was limited to fingolimod, natalizumab, and alemtuzumab. In the model, patients transitioned between Expanded Disability Status Scale (EDSS) states 0 through 9. For alemtuzumab and cladribine it was assumed that patients would take a maximum of two years of therapy, although re-initiation was allowed. Treatment was assumed to stop once patients reached an EDSS score of 7. The analysis was run over a 25-year time horizon using an annual cycle length. The analysis adopted a Canadian public health care system perspective.

The manufacturer reported that for pre-treated patients, cladribine dominated fingolimod (i.e., cladribine was associated with lower total costs and greater qualify-adjusted life-years [QALYs]); and, for patients with HDA, cladribine dominated alemtuzumab, fingolimod, and natalizumab.

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified a number of key limitations with the manufacturer's economic model that had a direct effect on the results of the analysis.

The manufacturer's model allows for an improvement in EDSS state within a cycle — for some states the probability of improvement exceeded 10%. While there is some debate regarding this aspect of natural history in RRMS, the clinical expert consulted by CADTH for this review did not accept that the assumption relating to patients improving was justified. CDR adopted the transition matrix based on the London, Ontario, study, which did not allow improvement in EDSS.

The manufacturer's base results were contingent on accepting the results of unpublished network meta-analyses specific to the pre-treated and HDA populations. There were a number of limitations identified by CDR clinical reviewers with this data specifically relating to the use of post hoc subgroup analysis and the limited amount of similar data for other comparators. CDR adopted the approach of assuming equal efficacy with respect to annualized relapse rate and confirmed disability progression.

Further, the manufacturer assumed a waning of treatment effect with all therapies except cladribine after one year, with effect sizes reduced by 75%. In the absence of comparative clinical data to support this assumption, CDR adopted the same treatment-waning assumptions for all therapies.

Finally, the manufacturer assumed that cladribine and alemtuzumab will be used for no longer than two years, and beyond two years patients were assumed to still be subject to the transition probabilities adjusted by the effectiveness of the therapy. CDR adopted an approach whereby all patients would stop treatment at two years and would then experience the transition probabilities associated with best supportive care.

CDR reanalysis incorporated all of the above concerns: CDR adopted the London database for the best supportive care transition matrix; assumed equal treatment waning and withdrawal for all treatments; and assumed equal effectiveness for DMTs in the specific subpopulations. In addition, CDR conducted and reported analysis for the full RRMS population given the concerns with the subgroup analyses.

For all RRMS patients, cladribine was subject to extended dominance by fingolimod and alemtuzumab — that is, regardless of a decision-maker's willingness to pay for a QALY, cladribine would not be cost-effective. The incremental cost-effectiveness ratio for cladribine versus fingolimod was $131,055.

For pre-treated patients, cladribine was dominated (associated with greater total costs and fewer QALYs) by fingolimod.

For HDA patients, cladribine was dominated by fingolimod.

Conclusions

CDR found that, based on conventionally accepted thresholds, cladribine was not a cost-effective treatment for patients with RRMS either in the total population or in the specific subpopulations considered. When compared with other DMTs, a price reduction for cladribine of approximately 33% would be required for cladribine to be cost-effective in the specific subpopulations considered, given a willingness to pay $50,000 for a QALY.

CDR was unable to consider any negotiated prices for available DMTs. Thus, the true cost-effectiveness of cladribine is uncertain, and 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 quality-adjusted life-years (QALYs) gained.[3] The analytical time horizon was 25 years with one-year cycles. The analysis incorporated a discount rate of 1.5% per annum and it was conducted from the perspective of the Canadian publicly funded health care system. Analysis was conducted for two distinct patient populations: 1) adult patients with RRMS in Canada who had prior treatment with any disease-modifying therapy (DMT) – pre-treated group; 2) adult patients with RRMS in Canada who had at least one relapse in the previous year while on DMT therapy and at least one T1 gadolinium-enhanced lesion or nine T3 lesions, or had two or more relapses in the previous year whether or not on treatment – high disease activity (HDA) group. Comparators were limited to those DMTs included in a network meta-analysis that formed part of the manufacturer's submitted Clinical Summary.[2] For the pretreated population this was limited to fingolimod, while for the HDA population this was limited to fingolimod, natalizumab, and alemtuzumab.

Model Structure

A cohort multi-state Markov model was developed in Microsoft Excel to simulate the disease course of RRMS patients receiving treatment with cladribine, other DMTs, and best supportive care (BSC). The model was based on patients transitioning across Expanded Disability Status Scale (EDSS) states 0 to 9 and death.[5] Patients with RRMS entered the model in a state between EDSS 0 and 6 inclusive, based on the patient population within the CLARITY trial.[6] The specific proportion in each EDSS level at baseline varied by the population considered. In each cycle, patients could transition between EDSS states or enter the absorbing death state. It was assumed that patients who reached an EDSS score of 7 or greater while on treatment with DMTs would discontinue treatment. Following discontinuation, patients switched to BSC EDSS states, with transitions informed by natural history information. Treatment duration for alemtuzumab and cladribine was capped at two years, though a small proportion of patients was assumed to re-initiate treatment. The probability of death from multiple sclerosis (MS) was based on general population mortality weighted by an estimate of the excess mortality risk in patients with RRMS.[7,8]

Model Inputs

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.[9] For patients receiving DMTs, the natural history data were adjusted by a treatment effect derived from a network meta-analysis detailed in the manufacturer's submitted Clinical Summary.[2] For the HDA population, two separate analyses were conducted. For comparison with natalizumab and fingolimod, analysis was based on confirmed disease progression (CDP) at six months. For comparison with alemtuzumab, analysis was based on CDP at three months.

After two years of treatment with alemtuzumab or cladribine, it was assumed that patients would discontinue treatment but would continue to benefit from the estimated treatment

effect. Patients receiving natalizumab, daclizumab, and fingolimod would discontinue treatment at a specific rate each year, and after discontinuing treatment, patients were assumed to experience the same transition probabilities as those on BSC.

The probability of death was based on adjusting all-cause mortality data for the Canadian general population by an MS excess risk ratio.[7,8]

Health-state utilities in the model were based on disease severity (as measured by EDSS) and were derived from a study by Tappenden.[10] Costs for patient management by EDSS state were derived from a previous Canadian study and adjusted to 2017 Canadian dollars.[11]

Manufacturer's Base Case

Pre-Treated Population

The manufacturer reported that, for patients in the pre-treated population, the costs associated with cladribine and fingolimod were $240,460 and $349,193, and total QALYs were 10.256 and 9.293, respectively. Thus, cladribine dominated fingolimod (Table 2) and the probability that cladribine was optimal at a threshold of $50,000 per QALY was 100%.

Table 2: Summary of Results of the Manufacturer's Base Case: Pre-Treated Population

	Total Costs ($)	Incremental Cost ($) of Cladribine	Total QALYs	Incremental QALYs Gained by Cladribine	Incremental Cost ($) per QALY Gained: Cladribine Versus DMT
Fingolimod	349,193	−108,733	9.293	0.963	Cladribine dominates fingolimod
Cladribine	240,460		10.256		

DMT = disease-modifying therapy; QALY = quality-adjusted life-year.

Note: All costs are presented in 2017 Canadian dollars.

Source: Total costs and QALYs are probabilistic values from the manufacturer's submitted report based on the economic model submitted to CADTH.[3]

HDA Population

The manufacturer reported that, for patients within the HDA population, when comparing cladribine and alemtuzumab, total costs were $240,591 and $277,620, and total QALYs were 11.298 and 9.95, respectively. Thus, cladribine dominated alemtuzumab (Table 3) and the probability that cladribine was optimal at a threshold of $50,000 per QALY was 98.4%.

The manufacturer reported that, for patients within the HDA population, when comparing cladribine, natalizumab, and fingolimod, total costs were $240,551, $494,062, and $344,120, and total QALYs were 10.662, 8.477, and 8.274, respectively. Thus, cladribine dominated both natalizumab and fingolimod (Table 3) and the probability that cladribine was optimal at a threshold of $50,000 per QALY was 100%.

Table 3: Summary of Results of the Manufacturer's Base Case: HDA Population

	Total Costs ($)	Incremental Cost ($) of Cladribine	Total QALYs	Incremental QALYs Gained by Cladribine	Incremental Cost ($) per QALY Gained: Cladribine Versus DMT
Comparison of cladribine and alemtuzumab					
Fingolimod	277,620	−37,030	9.950	1.345	Cladribine dominates alemtuzumab
Cladribine	240,591		11.298		
Comparison of cladribine, natalizumab, and fingolimod					
Fingolimod	344,120	−102,569	8.274	2.388	Cladribine dominates fingolimod
Natalizumab	494,062	−252,511	8.447	2.215	Cladribine dominates natalizumab
Cladribine	240,551		10.662		

DMT = disease-modifying therapy; QALY = quality-adjusted life-year.

Note: All costs are presented in 2017 Canadian dollars.

Source: Total costs and QALYs are probabilistic values from the manufacturer's submitted report based on the economic model submitted to CADTH.[3]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted an additional probabilistic analysis, focusing on all active RRMS patients (not the two subgroups).

Within this analysis, all DMTs were considered. Cladribine was found to have lower total costs than all DMTs but higher costs than BSC. Cladribine was found to be associated with higher QALYs than BSC and all DMTs except alemtuzumab. Thus, cladribine dominates natalizumab, daclizumab, and fingolimod. The incremental cost-effectiveness ratio (ICER) for cladribine versus BSC was $41,675. The ICER for alemtuzumab versus cladribine was $66,492. At a threshold of $50,000 per QALY gained, the probability that cladribine was optimal was greater than 50%.

Deterministic sensitivity analyses were conducted relating to the following:

- Effect of DMT on EDSS progression and relapse rates
- Discontinuation rates
- Mortality multiplier
- Baseline characteristics
- Discount rates.

Analyses reached the same conclusion as the manufacturer's base case analyses with respect to the cost-effectiveness of cladribine in the pre-treated and HDA populations.

Limitations of Manufacturer's Submission

CADTH Common Drug Review (CDR) identified the following limitations with the manufacturer's model:

- **Model allows for improvement in EDSS score**. Transition probabilities relating to natural history were derived from the Palace study.[4] The model allowed for an improvement in EDSS state within a cycle, and for some states the probability of improvement exceeded 10%. For example, for the cladribine model for all RRMS patients who start at EDSS level 4, within five years 39.6% will be at an EDSS level between 0 and 3 (62% of these would be at EDSS level between 0 and 2, representing a two-level improvement). By 20 years, 24.6% will still be in an EDSS level between 0 and 3.

This is an area of debate and, based on advice from a clinical expert consulted by CADTH and previous patient input received, CDR did not accept that the assumption relating to patients improving was justified. The degree of improvement in EDSS level suggested by the model lacks face validity. CADTH adopted the transition matrix based on the London, Ontario, study, which did not allow improvement in EDSS.

- **Comparative clinical effectiveness within subpopulations**. The manufacturer's base results are contingent on accepting the results of unpublished network meta-analyses specific to the two limited patient populations (pre-treated and HDA). These populations were not explored within specific clinical trials of cladribine; the evidence comes solely from post hoc subgroup analysis. The network meta-analyses specific to these populations are detailed within the manufacturer's Clinical Summary,[2] but there is insufficient data to assess the methodology adopted and the amount of data available for all relevant comparators — see *CDR Clinical Report*. As highlighted by the CDR clinical reviewers, "*the poor reporting of methods and results for this subgroup, as well as the apparent limited power (sparsely populated networks) and potential issues with subgroup definitions (in terms of the actual definitions and whether their formation in the individual trials maintained equal distribution of characteristics through randomization), there is a high degree of uncertainty as to the validity of the results for the high disease activity subgroup analyses. Moreover, the relevance of this subgroup is unclear in light of the Health Canada indication for cladribine.*"

  In addition, given that patients within the specific populations may been included in clinical trials of other comparators but similar post hoc analyses may not have been conducted, the network meta-analysis is unlikely to be based on the entirety of the evidence base. The network meta-analysis did not include all comparators for each specific population; natalizumab, fingolimod, daclizumab, and alemtuzumab are excluded for the pre-treated population; and daclizumab is excluded from the HDA population.

[redacted]

Given the following:

- The lack of detail of reporting of the network meta-analysis
- [redacted]
- The exclusion of relevant comparators from both populations
- [redacted]

CDR adopted the approach of assuming equal efficacy with respect to annualized relapse rate and confirmed disability progression. For both populations CDR assumed the hazard ratios and rate ratios for cladribine were applied to all therapies.

- **Differential treatment waning**. The manufacturer's submission assumes a waning of treatment effect with all therapies except cladribine, with effect sizes reduced by 75% for years two, three, and four. The manufacturer assumed no treatment waning for these years for cladribine. CDR took the position that without comparative clinical data to

support this assumption, it could not be supported. Therefore, CDR adopted the same treatment-waning assumptions for all therapies.

- **Continued effectiveness with alemtuzumab and cladribine post–treatment curtailment**. Within the model, it was assumed that cladribine and alemtuzumab typically will be given for no longer than two years, though a proportion of patients may require re-initiation. After two years, patients on cladribine and alemtuzumab were assumed to still be subject to the transition probabilities adjusted by the effectiveness of the therapies. This assumption is not justified, based on assuming continued patient benefit from treatment beyond curtailment. Continued patient benefit beyond treatment requires the assumption that the distribution of patients by EDSS at treatment curtailment will vary by treatment and lead to differences in estimated outcomes in the long term. The model assumes that, not only does the distribution of patients by EDSS at treatment discontinuation vary by patient at treatment withdrawal, but for alemtuzumab and cladribine, such benefits increase further the longer treatment has been withdrawn.

  Within the natalizumab, daclizumab, and fingolimod models, patients who remain on therapy after two years are subject to withdrawal and therefore will experience transition probabilities associated with BSC. Due to the assumption that there was continued treatment withdrawal with natalizumab, fingolimod, and daclizumab, and this was not applied to alemtuzumab or cladribine, the adopted approach compounds the problems identified above. Individuals within the cladribine and alemtuzumab treatment groups continue to benefit from treatment as the long-term transition probabilities continue to be weighted by the associated risk ratios, with few patients experiencing the cost of treatments.

  The impact of such assumptions can be illustrated by comparing the ranking of therapies in terms of QALYs gained in the all-RRMS patient population. Over a 25-year time horizon, alemtuzumab is associated with the greatest QALYs, followed by cladribine, natalizumab, daclizumab, and fingolimod. However, over a one-year time horizon, cladribine was estimated to have fewer QALYs than natalizumab and daclizumab.

  To ensure that the results of the model are not influenced by the assumptions related to continued effectiveness beyond treatment curtailment, CDR adopted an approach whereby all patients would stop treatment at two years and would then experience the transition probabilities associated with BSC. This would still allow a continuance of benefit from the initial treatment, as progression would be based on the distribution of patients by EDSS at two years and no assumption of loss of benefit from that period will be adopted.

  It is important to note that the manufacturer's submitted model assumes not just a continuance of benefit beyond two years but an increase in benefit. This can be illustrated by looking at the difference between average EDSS levels for cladribine and BSC at two and four years in the pre-treated population. In the manufacturer's model, the average EDSS level at two years is 0.27 lower with cladribine, representing improvement over baseline. However, the average EDSS level at four years is 0.47 lower with cladribine, representing not a continuance of benefit but an assumed increase in benefit. The difference in EDSS level increases up to 10 years post–treatment curtailment, suggesting benefits are exacerbated after treatment withdrawal for a period of at least five times longer than treatment itself. The CADTH reanalysis estimated a difference in EDSS levels at two years of 0.18, with continued benefit at four years and a difference of EDSS levels of 0.14. This approach more accurately reflects continued benefit rather than increasing benefit after treatment withdrawal.

- An alternative approach would have been to assume that only patients on alemtuzumab and cladribine would experience transition probabilities similar to BCS after two years. This would have led to cladribine being the least effective therapy within the all-RRMS patient population. CDR felt that the scenario assumption, which assumes the equivalent approach is adopted for all therapies and was more favourable to cladribine, was reasonable.

CADTH Common Drug Review Reanalyses

As noted in the limitations, CDR identified several important shortcomings relating to the manufacturer's model. CDR presents a revised probabilistic analysis (CDR base case) for three populations: all RRMS patients, the pre-treated population, and the HDA population (Tables 4, 5, and 6). The modifications made to the manufacturer-submitted model include:

- No assumption of improvements in EDSS state: use of the London, Ontario, data set for the BSC transition matrix
- Assumed equal treatment waning and withdrawal rates
- Included all DMTs for each population
- Assumed equal effectiveness for DMTs in the pre-treated and HDA subpopulations.

Full RRMS Population

Based on the above revisions, the CDR base case (Table 4) for the full RRMS population, found fingolimod was the least costly comparator. The ICER for alemtuzumab versus fingolimod was $110,715. Cladribine was subject to extended dominance through fingolimod and alemtuzumab. Thus, if a decision-maker is unwilling to pay $110,715 for each QALY gained, fingolimod is the optimal therapy. If a decision-maker is willing to pay at least $110,715 for each QALY gained, alemtuzumab is the optimal therapy.

Table 4: CDR Base Case: Full Relapsing-Remitting Multiple Sclerosis Population

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus FIN	Sequential Incremental Cost ($) per QALY Gained
Fingolimod	206,294	7.40		
Alemtuzumab	253,396	7.83	110,715	110,715
Dominated therapies				
Cladribine tablets	223,833	7.53	131,055	Subject to extended dominance through FIN and AL
Natalizumab	270,843	7.59	336,488	Dominated by AL

AL = alemtuzumab; CDR = CADTH Common Drug Review; CLAD = cladribine; FIN = fingolimod; QALY = quality-adjusted life-year.

Pre-Treated Population

The CDR base case (Table 5) for the pre-treated population found fingolimod dominated all other DMTs.

Table 5: CDR Base Case: Pre-Treated Population

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus FIN	Sequential Incremental Cost ($) per QALY Gained
Fingolimod	215,510	7.45		
Dominated therapies				
Alemtuzumab	263,333	7.43	Dominated by FIN	Dominated by CLAD and FIN
Cladribine tablets	232,835	7.44	Dominated by FIN	Dominated by FIN
Natalizumab	280,410	7.45	Dominated by FIN	Dominated by FIN

CDR = CADTH Common Drug Review; CLAD = cladribine; FIN = fingolimod; QALY = quality-adjusted life-year.

HDA Population

The CDR base case (Table 6) for the HDA population found fingolimod dominated all other DMTs.

Table 6: CDR Base Case: High Disease Activity Population

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus FIN	Sequential Incremental Cost ($) per QALY Gained
Fingolimod	220,939	6.71		
Dominated therapies				
Alemtuzumab	268,631	6.70	Dominated by FIN	Dominated by CLAD, FIN
Cladribine tablets	238,102	6.70	Dominated by FIN	Dominated by FIN
Natalizumab	286,334	6.71		Dominated by FIN

CDR = CADTH Common Drug Review; CLAD = cladribine; FIN = fingolimod; QALY = quality-adjusted life-year.

Price Reduction

CDR undertook a price-reduction analysis based on the CDR base case analyses, assuming a proportional price reduction for cladribine (Table 7).

For all RRMS patients, if a decision-maker was willing to pay $50,000 for a QALY, the price of cladribine would need to be reduced by 14.8% for cladribine to be cost-effective compared with fingolimod. If a decision-maker was willing to pay $100,000 per QALY, the price reduction would be 5.7%.

For pre-treated patients, if a decision-maker was willing to pay $50,000 for a QALY, the price of cladribine would need to be reduced by 32.7% for cladribine to be cost-effective compared with fingolimod. If a decision-maker was willing to pay $100,000 per QALY, the price reduction would be 33.4%.

For HDA patients, if a decision-maker was willing to pay $50,000 for a QALY, the price of cladribine would need to be reduced by 32.4% for cladribine to be cost-effective compared with fingolimod. If a decision-maker was willing to pay $100,000 per QALY, the price reduction would be 33.1%.

Table 7: CDR Reanalysis Based on Price-Reduction Scenarios for Cladribine

ICER for Cladribine Versus Comparator			
	RRMS Population	Pre-Treated Population	HDA Population
Comparator	FIN	FIN[a]	FIN[a]
Submitted price	$131,056	Dominated	Dominated
10% reduction	**$76,191**	Dominated	Dominated
20% reduction	Dominant	Dominated	Dominated
30% reduction	Dominant	Dominated	Dominated
40% reduction	Dominant	$577,082	$577,082
50% reduction	Dominant	$1.2 million	$1.3 million
60% reduction	Dominant	$1.8 million	$2.0 million
70% reduction	Dominant	$2.5 million	$2.7 million
80% reduction	Dominant	$3.2 million	$3.4 million

CDR = CADTH Common Drug Review; HDA = high disease activity; FIN = fingolimod; ICER = incremental cost-effectiveness ratio; RRMS = relapsing-remitting multiple sclerosis.

[a] Cladribine is less effective than the comparator, therefore the ICER is for comparator versus cladribine.

Issues for Consideration

- The confidential nature of the negotiated effective price for pharmaceuticals means that CDR was unable to assess the impact of potential lower prices of comparators on the results. Thus, should comparator prices be lower than current list prices, this would affect the results, requiring further price reductions for cladribine.
- Positive funding decisions have been made for current drugs for RRMS despite the lack of evidence that they are cost-effective. This makes interpretation of results for new drugs in this clinical area difficult, especially in this instance, where cladribine is estimated to be less effective in the total RRMS population (versus alemtuzumab) and in the specific populations (versus fingolimod).
- Daclizumab was voluntarily withdrawn from the market in March 2018, and as such, CADTH removed daclizumab as a comparator.
- Given that cladribine is "generally recommended in RRMS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for RRMS," BSC may be a relevant comparator. In a scenario analysis, cladribine would be less effective and more expensive than combinations of BSC and alemtuzumab (ruled out by extended dominance) for the full RRMS population and remains dominated by fingolimod (Tables 30, 31, and 32).

Patient Input

The Multiple Sclerosis Society of Canada provided patient input for this review. Input provided highlighted symptoms of fatigue, difficulty walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. The relapses, symptoms, medication side-effects, and disability progression of MS create barriers in a multitude of areas, including employment, education, physical activity, family commitments, interpersonal relationships, and social and recreational life. MS has a pronounced effect on caregivers, who play an instrumental role in the overall care management plan of people living with MS. The role of caregivers may include providing emotional support and assistance with medication administration, and helping with activities of daily living, such as personal care, feeding, and transportation to and from appointments. Symptoms of MS were captured by the manufacturer in its model using the EDSS as well as the application of utilities values to

EDSS-defined health states. The manufacturer did not consider a broader perspective to account for the burden on caregivers, nor was this information captured as part of clinical studies.

Conclusions

CDR found that cladribine was not a cost-effective treatment for patients with RRMS either in total population or in the specific subpopulations considered. When compared with other DMTs, a price reduction for cladribine of approximately 33% would be required for cladribine to be cost-effective, given a willingness to pay $50,000 for a QALY.

CDR was unable to consider any negotiated prices for available DMTs. The interpretation of results may warrant careful interpretation as the true cost-effectiveness of cladribine is uncertain.

Appendix 1: Cost Comparison

The comparators presented in Table 8 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

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

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Weekly Drug Cost ($)	Average Annual Drug Cost ($)
Cladribine (Mavenclad)	**10 mg**	**tablet**	**3,082.7000[a]**	**1.75 mg/kg body weight per year taken over 2 weeks, for two years[b]**	**830**	**43,158**
Injectable therapies						
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[c]	20 mg SC once daily	265	13,804
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	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
Ocrelizumab (Ocrevus)	300 mg/10 mL solution for infusion	single-use vial	8,150.00[d]	600 mg IV every six months[e]	627	32,600
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

CDR = CADTH Common Drug Review; IV = intravenous; SC = subcutaneous.

[a] Manufacturer-submitted price,[2] based on a patient weight of 70 kg

[b] The total dose per patient annual is divided into two treatment courses, one at the beginning of the first month and the next at the beginning of the second month of the respective year. Each treatment week consists of 10 to 20 mg as a single daily dose.[1] For example, a patient weighing 70 kg would take seven tablets in treatment weeks 1 and 2 for both year 1 and 2 of the treatment course (14 tablets annually).

[c] CADTH Canadian Drug Expert Committee Recommendation report for glatiramer acetate.[14]

[d] CADTH Canadian Drug Expert Committee Recommendation report for ocrelizumab.[15]

[e] The initial 600 mg dose is administered as two separate IV infusions: first as 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.[15]

Note: Daclizumab was voluntarily withdrawn from the market in March 2018.

Source: Unit prices of medications are taken from the Ontario Formulary Exceptional Access Program[12] (accessed January 2018) 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).

Table 9: CDR Cost Comparison for Relapsing-Remitting Multiple Sclerosis – Interferons

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Weekly Drug Cost ($)	Average Annual Drug Cost ($)
Cladribine (Mavenclad)	**10 mg**	**tablet**	**3,082.7000[a]**	**1.75 mg/kg body weight per year taken over 2 weeks, for two years[b]**	**830**	**43,158**
Inteferons						
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) 66 mcg/1.5 mL (3 pack of 22 mcg/0.5 mL) 132 mcg/1.5mL (3 pack of 44 mcg/0.5 mL)	pre-filled syringe, cartridge or pen	134.0486 163.1902 402.1381 489.5602	22 mcg to 44 mcg SC three times weekly	402 to 480	20,912 to 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

CDR = CADTH Common Drug Review; IM = intramuscular; MIU = million international units; SC = subcutaneous.

[a] Manufacturer-submitted price,[2] based on a patient weight of 70 kg.

[b] The total dose per patient annual is divided into 2 treatment courses, one at the beginning of the first month and the next at the beginning of the second month of the respective year. For example, a patient weighing 70 kg would take seven tablets in treatment weeks 1 and 2 for both year 1 and 2 of the treatment course (14 tablets annually) — as detailed in the Dosing and Administration details in the product monograph.[1]

Source: Unit prices of medications are taken from the Ontario Formulary Exceptional Access Program[12] (accessed January 2018) 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).

Appendix 2: Additional Information

Table 10: 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”	The model structure in Excel was complex, with simple formulas often needing multiple cells before getting from the initial data to their use within the model.		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking “poor”	The description of the NMA used in the economic analysis was insufficient.		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”			

NMA = network meta-analysis.

Table 11: 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

CDR = CADTH Common Drug Review.

Appendix 3: Summary of Other HTA Reviews of Drug

The cost-effectiveness of cladribine for the treatment of relapsing-remitting multiple sclerosis has been assessed by three other international health technology assessment organizations: the Pharmaceutical Benefits Advisory Committee in Australia,[16] the National Institute for Health and Care Excellence in the UK,[17] and the Scottish Medicines Consortium.[18] It is also under review with Quebec's Institut national d'excellence en santé et en services sociaux.

Table 12: Other Health Technology Assessment Findings

	NICE (December 2017)	PBAC (March 2011)	SMC (February 2018)
Treatment	Cladribine (1.75 mg/kg per year for 2 years)		
Price	£2,047.24 per 10 mg tablet (C$3,641.63[a])	Confidential	£2,047.24 per 10 mg tablet (C$3,641.63[a])
Similarities with CDR submission	• Markov-cohort model structure using EDSS progression as health states • Clinical data sources • Patient population and subgroups • Perspective	• Patient population • Perspective	• Markov-cohort model structure using EDSS progression as health states • Clinical data sources • Patient population and subgroups
Differences with CDR submission	None apparent	• Comparators • Model structure • Sources of clinical data • No mention of severity of RRMS and pre-treatment populations	• Time horizon 50 years (versus 25 years) • Base case included costs and utilities beyond third-party payer perspective
Manufacturer's results	Cladribine dominated all comparators	• Cladribine dominated natalizumab • A$105,000 to A$200,000/QALY versus interferon 1a	Cladribine dominated all comparators
Issues noted by the review group	• Calculation of different rates of disability progression in subgroups may be inaccurate • Waning effect of treatment should be same for all comparators • Treatment stopping rates likely to be overestimated when based on annualized rates from clinical trials • Restarting cladribine should not be included in model • No evidence of any additional benefits of cladribine versus comparators	• Inappropriate main comparator • Uncertainty around trials and clinical benefit • Issues with indirect comparison • Claim of non-inferiority versus natalizumab not accepted, thus economic evaluation not deemed appropriate • Concerns with London, Ontario, data set for disease progression	• No evidence to confirm cladribine superior to comparators • Base case included caregiver utilities and non-medical costs • Difficult to determine sensitivity of model to individual parameters due to inappropriate base case • Differential re-initiation of cladribine versus alemtuzumab inappropriate
Results of reanalyses by the review group (if any)	• Cladribine dominated all treatments • In combined reanalysis, cladribine dominated all comparators except alemtuzumab; cladribine less effective and less costly (£219,549 gained per QALY lost in rapidly evolving severe subgroup [C$390,534] and £372,802 gained per QALY lost in suboptimal treatment subgroup [C$663,14])	None reported	None reported
Recommendation	Recommended as an option for highly active MS in adults, if: • RES RRMS • RRMS responded inadequately to treatment with DMT, defined as 1 relapse in previous year and MRI evidence of	Rejected due to use of an inappropriate comparator, uncertain clinical benefit and uncertain/ unacceptable cost-effectiveness in comparison with appropriate comparator	Recommended for restricted use, with conditions: • RES RRMS: patients with two or more relapses in prior year with/out treatment, and at least one T1 gadolinium-enhancing lesion

	NICE (December 2017)	PBAC (March 2011)	SMC (February 2018)
	disease activity		• Patients with suboptimal therapy RRMS: one or more relapses in previous year while on DMT, and at least one T1 gadolinium-enhancing lesion or nine T2 lesions

CDR = CADTH Common Drug Review; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; RES = rapidly evolving severe; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

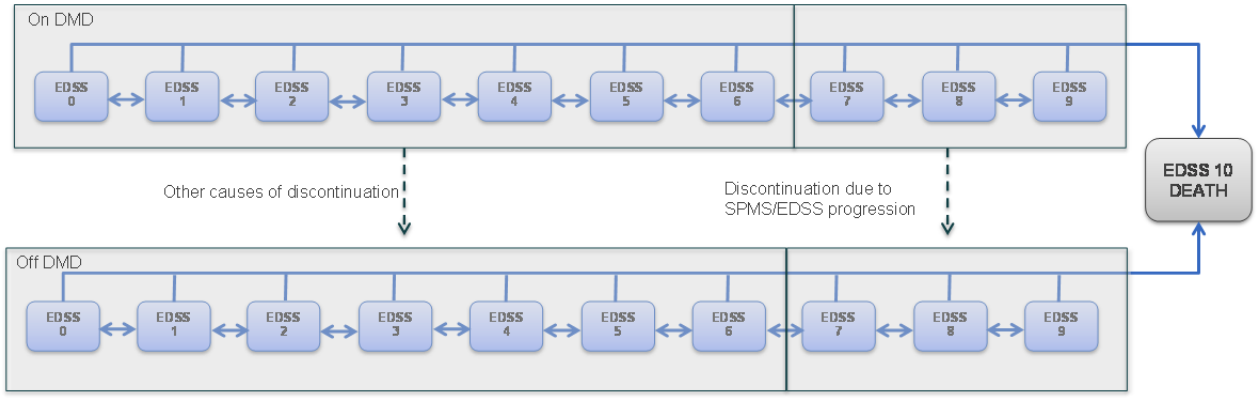
[a] Exchange rates to C$ obtained from Bank of Canada. C$1 = £1.7788; C$1 = A$1.0062 (https://www.bankofcanada.ca/rates/exchange/daily-exchange-rates/); accessed March 9, 2018.[19]

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a cohort-based Markov health-state transition model that included 11 health states: 10 Expanded Disability Status Scale states and a death state. The multiple sclerosis–specific health states were grouped according to the Kurtzke Expanded Disability Status Scale levels, from 0 (normal neurological examination) to 9 (helpless bed patient). The manufacturer's model structure is presented in Figure 1.

Figure 1: Manufacturer's Model Structure



DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; SPMS = secondary progressive multiple sclerosis.
Source: Manufacturer's pharmacoeconomic submission.[2]

In the submitted model, all patients begin in a relapsing-remitting multiple sclerosis state characterized by EDSS (beginning in level 0-6) — the proportions in each level varied by the population considered and were based on the placebo arm of the CLARITY trial (Table 13). The submitted model allows transitions between EDSS states based on data from the British Columbia cohort (Table 14), adjustment for disease-modifying therapy effectiveness (Table 15, 16 and 17) and risk of death.

Table 13: Baseline Distribution of Patients by Expanded Disability Status Scale Level

	Active RRMS (ITT)	Pre-Treated RRMS	HDA
EDSS 0	2.9%	5.0%	2.8%
EDSS 1.0	3.0%	3.3%	2.8%
EDSS 2.0	31.4%	28.1%	32.5%
EDSS 3.0	24.3%	24.0%	21.5%
EDSS 4.0	23.7%	21.5%	23.5%
EDSS 5.0	9.8%	13.2%	11.1%
EDSS 6.0	5.1%	5.0%	5.9%
Sample (placebo), N	870	242	289

EDSS: Expanded Disability Status Scale; HDA: high disease activity; ITT: Intention-to-treat; RRMS: relapsing-remitting multiple sclerosis.
Source: Manufacturer's pharmacoeconomic submission.[2]

Table 14: Transition Matrix for Best Supportive Care based on British Columbia Cohort

From/To EDSS	0	1 to 1.5	2 to 2.5	3 to 3.5	4 to 4.5	5 to 5.5	6 to 6.5	7 to 7.5	8 to 8.5	9 to 9.5	N
0	0.69537	0.20294	0.07251	0.02170	0.00422	0.00137	0.00175	0.00011	0.00003	0.00000	326
1 to 1.5	0.05826	0.69501	0.15783	0.06088	0.01638	0.00458	0.00643	0.00048	0.00013	0.00001	317
2 to 2.5	0.01586	0.12133	0.60789	0.16796	0.04458	0.01849	0.02159	0.00174	0.00052	0.00004	317
3 to 3.5	0.00594	0.04960	0.12006	0.54422	0.09109	0.05845	0.11649	0.01030	0.00355	0.00030	317
4 to 4.5	0.00165	0.2214	0.06660	0.11519	0.48935	0.10388	0.16811	0.02580	0.00671	0.00056	317
5 to 5.5	0.00052	0.00533	0.02942	0.05866	0.08736	0.48695	0.27310	0.03880	0.01883	0.00102	317
6 to 6.5	0.00012	0.00133	0.00444	0.02497	0.03069	0.04080	0.74069	0.10897	0.04377	0.00423	317
7 to 7.5	0.00001	0.00015	0.00052	0.00247	0.00727	0.00385	0.11684	0.69269	0.16061	0.01559	317
8 to 8.5	0.00000	0.00001	0.00004	0.00029	0.00055	0.00050	0.01881	0.05574	0.90340	0.02066	317
9 to 9.5	0.00000	0.00000	0.00000	0.00002	0.00004	0.00003	0.00176	0.00568	0.17414	0.81832	317

EDSS = Expanded Disability Status Scale.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 15: Comparative Efficacy of DMT Versus Placebo for Annualized Relapse Rate

From /To EDSS	Mean Ratio of Annualized Relapse Rates Comparing Treatment Versus Placebo (Lower 95% Credible to Upper 95% Credible Value)		
	Active RRMS	Pre-Treated	HDA
Cladribine	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]	[redacted]

DMT = disease-modifying therapy; HDA = high activity disease; RRMS = relapsing-remitting multiple sclerosis.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 16: Comparative Efficacy of DMT Versus Placebo for CDP at 3 Months

From/To EDSS	Mean Hazard Ratio Comparing Treatment Versus Placebo (Lower 95% Credible to Upper 95% Credible Value)		
	Active RRMS	Pre-Treated	HDA
Cladribine	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]	[redacted]

CDP = confirmed disease progression; DMT = disease-modifying therapy; HDA = high activity disease; RRMS = relapsing-remitting multiple sclerosis.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 17: Comparative Efficacy of DMT Versus Placebo for CDP at 6 Months

From/To EDSS	Mean Hazard Ratio Comparing Treatment Versus Placebo (Lower 95% Credible to Upper 95% Credible Value)		
	Active RRMS	Pre-Treated	HDA
Cladribine	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]	[redacted]

CDP = confirmed disease progression; DMT = disease-modifying therapy; HDA = high activity disease; RRMS = relapsing-remitting multiple sclerosis.
Source: Manufacturer's pharmacoeconomic submission.[2]

Data Sources and Assumptions

Table 18: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Manufacturer submitted unpublished NMA.[2]	Insufficient detail in the reporting of the network meta-analysis. [redacted] The exclusion of relevant comparators from both populations [redacted]
Natural history	Analysis of British Columbia cohort data by Palace et al.[9]	The data from Palace et al. suggest the possibility of an improvement in EDSS state within a cycle — for some states the probability of improvement exceeded 10%. For example, for the cladribine model for all RRMS patients who start at EDSS level 4, within five years 39.6% will be at an EDSS level between 0 and 3 (62% of these would be at EDSS level between 0 and 2 representing a two-level improvement). By 20 years, 24.6% will still be in an EDSS level between 0 and 3. This lacks face validity. CDR adopted data from the London, Ontario, cohort.
Utilities	Published data by Tappenden.[10]	Limited data for EDSS level 9, which may introduce bias.
Adverse events	Rates of adverse events and disutility associated with them come from literature. Model includes: infusion site reaction; injection site reaction; PML; macular edema; malignancy; hypersensitivity reaction; gastrointestinal disorder; thyroid-related events; immune thrombocytopenic purpura; serious infection; influenza-like illness.	Little impact on results.
Mortality	General population data weighted by MS multiplier.	Appropriate.
Resource Use and Costs		
Drug	ODB formulary, previous CADTH recommendations.	Appropriate.
Administration	ODB formulary, Ontario Schedule of Benefits, Karampampa study.[11]	Appropriate.

Data Input	Description of Data Source	Comment
AEs	Published literature and expert opinion.	Little impact on results.
Health state	Karampampa study.[11]	Appropriate.

CDR = CADTH Common Drug Review; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NMA = network meta-analysis; ODB = Ontario Drug Benefit Program; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting multiple sclerosis.

Table 19: Manufacturer's Key Assumptions

Assumption	Comment
Patients can improve in EDSS level on an annual basis	• The model allowed for an improvement in EDSS state within a cycle — for some states the probability of improvement exceeded 10%. • For the cladribine model for all RRMS patients who start at EDSS level 4, within five years 39.6% will be at an EDSS level between 0 and 3 (62% of these would be at EDSS level between 0 and 2 representing a two-level improvement). By 20 years, 24.6% will still be in an EDSS level between 0 and 3. • A clinical expert consulted by CADTH did not accept that the assumption relating to patients improving was justified. CDR adopted the transition matrix based on the London, Ontario, study, which did not allow improvement in EDSS.
Differential treatment waning favourable to cladribine	• Analysis assumed better continued treatment effect for cladribine than other comparators. This was not justified and CDR assumed equal treatment waning.
Use of the results of unpublished network meta-analyses specific to the two limited patient populations (pre-treated and HDA).	• These populations were not explored within specific clinical trials of cladribine; the evidence comes solely from post hoc subgroup analysis. • The network meta-analysis is unlikely to be based on the entirety of the evidence base. [redacted] • For the specific subpopulations, CDR adopted the approach of assuming equal efficacy with respect to annualized relapse rate and confirmed disability progression.
Continued effectiveness with alemtuzumab and cladribine post–treatment curtailment	• It is assumed that cladribine and alemtuzumab will be given typically for no longer than two years, although a proportion of patients may require re-initiation, and that after two years patients on cladribine and alemtuzumab are still assumed to be subject to the transition probabilities adjusted by the therapies' effectiveness. • CDR felt this was an overly optimistic assumption. The model assumes that not only does the distribution of patients by EDSS at treatment discontinuation vary by patient at treatment withdrawal but for alemtuzumab and cladribine such benefits increase further the longer treatment has been withdrawn. • To ensure that the results of the model are not influenced by the assumptions related to continued effectiveness beyond treatment curtailment, CDR adopted an approach whereby all patients would stop treatment at two years and would then experience the transition probabilities associated with BSC.

BSC = best supportive care; CDR = CADTH Common Drug Review; EDSS = Expanded Disability Status Scale; HDA = high disease activity.

Table 20: Steps in CDR Reanalysis

Revised Assumption	Comment
Patients cannot improve in EDSS level on an annual basis	Changed CDREF_RRMS_Select to LOwithBC
Differential treatment waning favourable to cladribine	Adopted equal treatment waning relating to the proportion of treatment effects received Year 0 to 2 — 100% Year 2 to 5 — 75% After year 5 — 50%
Use of the results of unpublished network meta-analyses specific to the two limited patient populations (pre-treated and HDA).	For RRMS patients, used network meta-analysis results For the specific subpopulations, CDR used the efficacy for cladribine with respect to annualized relapse rate and confirmed disability progression for all other DMTs
Continued effectiveness with alemtuzumab and cladribine post–treatment curtailment	CDR assumed 100% withdrawal at two years for all treatments and would then experience the transition probabilities associated with BSC

BSC = best supportive care; CDR = CADTH Common Drug Review; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HDA = high disease activity.

CDR Reanalyses — By Individual Analysis

All-RRMS Population

Table 21: Full RRMS population – Inclusion of All Comparators

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus CLAD	Sequential Incremental Cost ($) per QALY Gained
Cladribine	$230,665	10.417		
Alemtuzumab	$266,845	11.896	$24,461	$24,461
Dominated therapies				
Fingolimod	$340,617	9.355	$399,428	Dominated by AL and CLAD
Natalizumab	$502,743	9.869	$355,475	Dominated by AL and CLAD

AL = alemtuzumab; CLAD= cladribine; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

Table 22: Full RRMS population – Inclusion of All Comparators; Use of London Natural History Data

	Total Costs ($)	Total QALYs	Incremental cost ($) per QALY Gained Versus CLAD	Sequential Incremental Cost ($) per QALY Gained
Cladribine	$227,443	8.213		
Alemtuzumab	$261,387	9.450	$27,448	$27,448
Dominated therapies				
Fingolimod	$342,270	7.334	$477,264	Dominated by AL and CLAD
Natalizumab	$503,381	7.766	$422,750	Dominated by AL and CLAD

AL = alemtuzumab; CLAD= cladribine; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

Table 23: Full RRMS Population – Inclusion of All Comparators; Equal Discontinuation (10% in Years 1 and 2 Followed by Curtailment); Equal Treatment Waning

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus FIN	Sequential Incremental Cost ($) per QALY gained
Fingolimod	$220,163	9.106		
Cladribine	$228,794	9.282	$49,182	$49,182
Alemtuzumab	$265,331	9.655	$82,381	$98,009
Dominated therapies				
Natalizumab	$272,925	9.345	$259,669	Dominated by AL and CLAD

AL = alemtuzumab; CLAD= cladribine; FIN = fingolimod; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

HDA Population

Table 24: HDA Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine)

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus CLAD	Sequential Incremental Cost ($) per QALY Gained
Non-dominated therapies				
Cladribine	$240,639	10.527		
Dominated therapies				
Alemtuzumab	$277,761	10.320	Dominated by CLAD	Dominated by CLAD
Fingolimod	$362,686	9.035	Dominated by CLAD	Dominated by AL and CLAD
Natalizumab	$516,085	9.001	Dominated by CLAD	Dominated by FIN, AL and CLAD

AL = alemtuzumab; CLAD= cladribine; FIN = fingolimod; HDA = high disease activity; QALY = quality-adjusted life-year.

Table 25: HDA Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine); Use of London Natural History Data

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus CLAD	Sequential Incremental Cost ($) per QALY Gained
Non-dominated therapies				
Cladribine	$237,141	8.334		
Dominated therapies				
Alemtuzumab	$274,456	8.158	Dominated by CLAD	Dominated by CLAD
Fingolimod	$361,639	7.137	Dominated by CLAD	Dominated by AL and CLAD
Natalizumab	$515,757	7.109	Dominated by CLAD	Dominated by FIN, AL and CLAD

AL = alemtuzumab; CLAD= cladribine; FIN = fingolimod; HDA = high disease activity; QALY = quality-adjusted life-year.

Table 26: HDA population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine); Equal Discontinuation (10% in Years 1 and 2 Followed by Curtailment); Equal Treatment Waning

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus FIN	Sequential Incremental Cost ($) per QALY Gained
Non-dominated therapies				
Fingolimod	$233,637	8.037		
Dominated therapies				
Cladribine	$241,938	8.033	Dominated by FIN	Dominated by FIN
Alemtuzumab	$278,297	8.026	Dominated by FIN	Dominated by CLAD and FIN
Natalizumab	$286,746	8.036	Dominated by FIN	Dominated by AL, CLAD and FIN

AL = alemtuzumab; CLAD= cladribine; FIN = fingolimod; HDA = high disease activity; QALY = quality-adjusted life-year.

Pre-Treated population

Table 27: Pre-Treated Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine)

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus CLAD	Sequential Incremental Cost ($) per QALY Gained
Non-dominated therapies				
Cladribine	$240,178	10.201		
Dominated therapies				
Alemtuzumab	$277,117	10.137	Dominated by CLAD	Dominated by CLAD
Daclizumab	$307,893	9.541	Dominated by CLAD	Dominated by AL and CLAD
Fingolimod	$355,404	9.630	Dominated by CLAD	Dominated by AL and CLAD
Natalizumab	$504,666	9.616	Dominated by CLAD	Dominated by FIN, AL and CLAD

AL = alemtuzumab; CLAD= cladribine; FIN = fingolimod; QALY = quality-adjusted life-year.

Table 28: Pre-Treated Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine); Use of London Natural History Data

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus CLAD	Sequential Incremental Cost ($) per QALY Gained
Non-dominated therapies				
Cladribine	$237,362	7.994	$67,990	$67,990
Dominated therapies				
Alemtuzumab	$274,378	7.937	Dominated by CLAD	Dominated by CLAD
Fingolimod	$355,416	7.529	Dominated by CLAD	Dominated by AL and CLAD
Natalizumab	$506,655	7.517	Dominated by CLAD	Dominated by FIN, AL and CLAD

AL = alemtuzumab; CLAD= cladribine; FIN = fingolimod; QALY = quality-adjusted life-year.

Table 29: Pre-Treated Population – Inclusion of All Comparators With Equal Effectiveness (Equivalent to Cladribine); Equal Discontinuation (10% in years 1 and 2 followed by Curtailment); Equal Treatment Waning

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus CLAD	Sequential Incremental Cost ($) per QALY Gained
Fingolimod	$229,687	9.226		
Dominated therapies				
Cladribine	$238,312	9.221	Dominated by FIN	Dominated by FIN
Alemtuzumab	$274,556	9.214	Dominated by FIN	Dominated by CLAD, and FIN
Natalizumab	$282,310	9.225	Dominated by FIN	Dominated by AL, CLAD and FIN

AL = alemtuzumab; CLAD= cladribine; FIN = fingolimod; QALY = quality-adjusted life-year.

CDR Reanalyses – Including BSC as a Comparator

Table 30: CDR Reanalysis Including BSC: Full RRMS Population

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus BSC	Sequential Incremental Cost ($) per QALY Gained
Non-dominated therapies				
BSC	152,467	7.23		
Alemtuzumab	253,396	7.83	168,442	168,442
Dominated therapies				
Cladribine tablets	223,833	7.53	232,018	Subject to extended dominance through BSC and AL
Fingolimod	206,294	7.40	309,778	Subject to extended dominance through BSC and AL
Natalizumab	270,843	7.59	323,793	Dominated by AL

AL = alemtuzumab; BSC = best supportive care; CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

Table 31: CDR Base Case: Pre-Treated Population

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus BSC	Sequential Incremental Cost ($) per QALY Gained
Non-dominated therapies				
BSC	161,788	7.17		
Fingolimod	215,510	7.45	190,058	190,058
Dominated therapies				
Alemtuzumab	263,333	7.43	175,567	Dominated by CLAD and FIN
Cladribine tablets	232,835	7.44	232,018	Dominated by FIN
Natalizumab	280,410	7.45	323,793	Dominated by FIN

BSC = best supportive care; CDR = CADTH Common Drug Review; CLAD = cladribine; FIN = fingolimod; QALY = quality-adjusted life-year.

Table 32: CDR Base Case: High Disease Activity Population

	Total Costs ($)	Total QALYs	Incremental Cost ($) per QALY Gained Versus BSC	Sequential Incremental Cost ($) per QALY Gained
Non-dominated therapies				
BSC	168,714	6.06		
Fingolimod	220,939	6.71	79,937	79,937
Dominated therapies				
Alemtuzumab	268,631	6.70	156,401	Dominated by CLAD FIN
Cladribine tablets	238,102	6.70	107,956	Dominated by FIN
Natalizumab	286,334	6.71	180,139	Dominated by FIN

BSC = best supportive care; CDR = CADTH Common Drug Review; CLAD = cladribine; FIN = fingolimod; QALY = quality-adjusted life-year.

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