Common Drug Review
Pharmacoeconomic Review Report

June 2015

Drug	alemtuzumab (Lemtrada, intravenous)
Indication	For the management of adult patients with relapsing-remitting multiple sclerosis (RRMS), with active disease defined by clinical and imaging features, who have had an inadequate response to interferon beta or other disease-modifying therapies
Listing request	As per indication
Manufacturer	Genzyme Canada Inc.

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

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ABBREVIATIONS

AE	adverse event
BSC	best supportive care
CDR	CADTH Common Drug Review
DMT	disease-modifying therapy
EDSS	Kurtzke Expanded Disability Status Scale
GA	glatiramer acetate
ICUR	incremental cost-utility ratio
INESSS	Institut National d'Excellence en Santé et en Services Sociaux
MS	multiple sclerosis
MTC	mixed-treatment comparison
PE	pharmacoeconomic
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary-progressive multiple sclerosis

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	**Alemtuzumab (Lemtrada) 12 mg intravenous**
Study Question	"The objective of this project was to adapt a cost-effectiveness (CE) model, originally developed for the National Institute for Health and Care Excellence (NICE), to evaluate the clinical and cost benefits associated with alemtuzumab in the treatment of patients with relapsing-remitting multiple sclerosis (RRMS) who have had an inadequate response to interferon beta or other disease-modifying therapies, from both the Ministry of Health and societal perspectives."
Type of Economic Evaluation	Cost-utility analysis
Target Population	Base-case population is treatment-experienced patients; as per the Health Canada indication and patient population in CARE-MS II.
Treatment	Alemtuzumab 12 mg intravenous: • Year 1 (100% of patients): 12 mg/day, 5 consecutive days (60 mg total dose); • Year 2 (96.8% of patients): 12 mg/day, 3 consecutive days (36 mg total dose), administered 12 months after the initial treatment course. • A proportion of patients continue to receive alemtuzumab (36 mg total dose) beyond year 2
Outcomes	• Life-years (LYs) • QALYs
Comparators	• IFN beta-1a (Rebif) 44 mcg subcutaneous 3 times weekly • IFN beta-1a (Avonex) 30 mcg subcutaneous once weekly • IFN beta-1b (Betaseron) 250 mcg subcutaneous every other day • Glatiramer acetate (GA) 20 mg subcutaneous daily • Dimethyl fumarate 240 mg oral twice daily • Teriflunomide 14 mg oral once daily • Fingolimod 0.5 mg oral once daily • Natalizumab 300 mg intravenous every 4 weeks
Perspective	Public-payer perspective (societal in sensitivity analysis)
Time Horizon	25 years
Results for Base Case	Alemtuzumab dominates all comparators
Key Limitations	• Uncertainty regarding durability of effect of alemtuzumab beyond 2 treatment courses, including the need for re-treatment and application of withdrawal rates • Substantial uncertainty associated with the MTC to inform the clinical data inputs in the economic model • Inappropriate inclusion of patients in EDSS 0 • Inappropriate adjustment of mortality rates • Proportion of patients hospitalized following relapse overestimated
CDR Estimates	• The cost-effectiveness of alemtuzumab versus other DMTs is not known given the uncertainty surrounding the MTC, thus CDR focused on direct comparison with Rebif, which may not be the most appropriate comparator. • CDR reanalyses based on the key limitations resulted in an ICUR of ~$31,000 per QALY for alemtuzumab versus Rebif. • CDR conducted reanalyses on several other parameters of uncertainty that resulted in substantial variation (range: alemtuzumab dominates Rebif, to $91,000 per QALY for alemtuzumab compared with Rebif). • There is uncertainty with pattern and duration of treatment with alemtuzumab in the Canadian setting, which may substantially impact the burden on the Canadian health care system.

CDR = CADTH Common Drug Review; CE = cost-effectiveness; DMT = disease-modifying therapy; EDSS = Kurtzke Expanded Disability Status Scale; GA = glatiramer acetate; ICUR = incremental cost-utility ratio; IFN = interferon; LY = life-year; MTC = mixed-treatment comparison; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

EXECUTIVE SUMMARY

BACKGROUND

Alemtuzumab (Lemtrada) is a recombinant, humanized, monoclonal antibody available as a concentrate for solution for intravenous infusion (12 mg/1.2 mL) indicated "for the management of adult patients with relapsing-remitting multiple sclerosis (RRMS), with active disease defined by clinical and imaging features, who have had an inadequate response to interferon beta or other disease-modifying therapies."[1] The recommended dose of alemtuzumab is 12 mg/day over two treatment cycles: an initial treatment cycle over five consecutive days (60 mg in total), and a second treatment cycle given 12 months after the initial treatment over three consecutive days (36 mg in total). Patients must be followed up for 48 months after their last dose of alemtuzumab.[1] Although the product monograph indicates that the efficacy for alemtuzumab treatment duration beyond two years has not been determined,[1] alemtuzumab has been reported to have been used over a longer time period.[2,3] The manufacturer submitted a confidential price of [redacted] per 12 mg vial, for an annual per patient cost of [redacted] in year 1 and [redacted] in subsequent years. The manufacturer is requesting listing as per the Health Canada indication.

The manufacturer previously submitted alemtuzumab for consideration through the CADTH Common Drug Review (CDR) process; however, the submission was withdrawn.[4]

The manufacturer submitted a cost-utility analysis comparing alemtuzumab with interferon beta-1a (Avonex), interferon beta-1a (Rebif), glatiramer acetate (GA), dimethyl fumarate, fingolimod, and natalizumab for patients with RRMS who have had an inadequate response to interferon beta or other disease-modifying therapies. The analysis used a cohort-based Markov model of disease progression over a 25-year time horizon, from the perspective of the public health care payer. Death was captured separately from other health states. The model also incorporates differential risks of relapses, disease progression, costs, and utility values for each health state. Data on the natural progression of multiple sclerosis (MS) were derived primarily from the London, Ontario registry. Data on relative effectiveness of all comparators in terms of disease progression, annualized relapse rates and withdrawals were obtained through an unpublished mixed-treatment comparison (MTC).[5] Health state utility values were based on a published UK patient survey, while disutility values were sourced from the published literature. Costs for each state are derived from Canadian data sources. The manufacturer reported that alemtuzumab dominated (was less costly and more effective) all comparator treatments.[6]

SUMMARY OF IDENTIFIED LIMITATIONS AND KEY RESULTS

CDR identified the following primary limitations relating to the manufacturer's model:

Use of Alemtuzumab Over Time

There is uncertainty regarding durability of effect of alemtuzumab beyond two treatment courses and proportion of patients who will need re-treatment beyond year 2. CDR undertook reanalyses using data from the CARE-MS II trial for years 1 and 2, and then accounted for an expected discontinuation of treatment in year 3 based on data from a long-term UK observational study (up to 12 years of follow-up; median 7).[2] From year 4 onwards, the withdrawal rate for Rebif (~16% annually) was applied to alemtuzumab. Note, this was assessed through changes to the withdrawal rate rather than the uptake rate (proportion of patients receiving alemtuzumab in each year) as presented by the manufacturer, as uptake only considers costs (no clinical effects).

Lack of Comparative Clinical Information

Clinical efficacy inputs were based on an MTC with a [redacted] (see summary and critical appraisal of the manufacturer's MTC presented in the CDR Clinical Report). Given the substantial uncertainty with the MTC, CDR considered data from the CARE-MS II study of alemtuzumab versus Rebif, although Rebif is unlikely to be the most appropriate comparator in clinical practice.

Target Patient Population

Patients with a baseline Kurtzke Expanded Disability Status Scale (EDSS) score of 0 were included in the model, although the CDR clinical expert indicated it is unlikely that patients who failed on a disease-modifying therapy (DMT) would have an EDSS score of 0. The patient population was reweighted to exclude EDSS 0.

Mortality Inputs

A mortality rate specific to MS was sourced from the published literature and adjusted to fit the manufacturer's model structure. The method used by the manufacturer to adjust the mortality rate is inappropriate. CDR undertook reanalyses using the actual data from the published literature.

Hospitalization

The proportion of patients hospitalized following relapse was deemed to be an overestimation by the CDR clinical expert. CDR undertook reanalyses using a lower rate of hospitalization based on the CARE-MS II trial.

These primary limitations were combined to define the CDR base case, which resulted in an incremental cost-utility ratio (ICUR) of $31,000 per quality-adjusted life-year (QALY) for alemtuzumab compared with Rebif. CDR identified several other parameters of uncertainty (administration and monitoring costs, utility and disutility values, treatment waning, inappropriate use of a mid-cycle correction for alemtuzumab given up-front yearly dosing regimen, and alemtuzumab uptake rates), which were all examined using the CDR base case. The resulting ICURs ranged from alemtuzumab dominating Rebif to $91,000 per QALY for alemtuzumab compared with Rebif, suggesting substantial variability within the model. CDR undertook an exploratory analysis including treatment waning, which increased the ICUR to $231,000 per QALY for alemtuzumab versus Rebif.

CONCLUSIONS

CDR identified several key limitations with the manufacturer's economic analysis relating to the clinical data used, as well as model structure and inputs. Given the substantial uncertainty surrounding the MTC, CDR undertook reanalyses based on the CARE-MS II trial of alemtuzumab versus Rebif, although this is unlikely to be the most appropriate comparator. The CDR base-case analysis resulted in an ICUR of approximately $31,000 per QALY for alemtuzumab versus Rebif in adult patients with active RRMS who had previously failed or were intolerant to interferon beta or GA. CDR identified several other parameters of uncertainty. Testing these parameters identified substantial variability within the range of ICURs (range: alemtuzumab dominates Rebif to $91,000 per QALY for alemtuzumab compared with Rebif). The cost-effectiveness of alemtuzumab versus other DMTs is not known given the uncertainty surrounding the MTC. There is uncertainty with pattern and duration of treatment with alemtuzumab in the Canadian setting, which may substantially impact the burden on the Canadian health care system.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis comparing alemtuzumab with interferon beta-1a (Avonex), interferon beta-1a (Rebif), interferon beta-1a (Betaseron), glatiramer acetate (GA), dimethyl fumarate, fingolimod, and natalizumab. The analysis used a cohort-based Markov model of disease progression — based on the previously published School of Health and Related Research (ScHARR) model — which included 21 health states: 10 for each multiple sclerosis (MS) type (relapsing-remitting multiple sclerosis [RRMS] and secondary-progressive multiple sclerosis [SPMS]) and a death state. The 10 MS-specific health states were grouped according to Kurtzke Expanded Disability Status Scale (EDSS) levels, from 0 (normal neurological examination) to 9 (helpless bed patient). Death was captured separately from the EDSS-based states in order to allow for an increasing risk of mortality by age, and can occur at any EDSS level, with the rate increasing with EDSS levels.[6]

In the model, all patients began in an RRMS health state, ranging from EDSS 0 to 7 (based on data from the CARE-MS II trial). The model also incorporated differential risks of relapses, disease progression, costs, and utility values for each EDSS level. Data on the natural progression of MS were derived from the London, Ontario registry, as well as the AFFIRM trial of natalizumab.[7] Data on relative effectiveness of all comparators in terms of disease progression, annualized relapse rates and withdrawals were obtained through an unpublished mixed-treatment comparison (MTC).[5] Health state utility values were based on a published UK patient survey, while disutility values were sourced from the published literature. Costs for each state are derived from Canadian data sources. The model presented a 25-year time horizon, with cycle lengths of one year from the perspective of the public health care payer.[6] In the model, use of alemtuzumab was based on the proportion of patients requiring treatment (cited as based on the CARE-MS extension study), while the comparator treatments had a stable withdrawal rate. The manufacturer assumed proportion of patients receiving alemtuzumab based on data from their extension studies. Beyond year [redacted]% of patients were modelled to receive alemtuzumab; however, treatment benefits for alemtuzumab were accrued until the end of the model (25 years).

The model was designed so that results are only available at one time for alemtuzumab, one other active treatment and best supportive care (BSC). It did not allow comparison of all treatment options simultaneously.

2. MANUFACTURER'S BASE CASE

The manufacturer's base-case analysis produced the following results:

- Alemtuzumab dominated all comparator treatments: Rebif, Avonex, GA, dimethyl fumarate, fingolimod, and natalizumab.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer tested uncertainty for several parameters through both probabilistic and deterministic sensitivity analyses, with the analyses taken separately for alemtuzumab versus each of the different comparators. The probabilistic sensitivity analyses (PSAs) showed some uncertainty around

both the incremental cost and incremental quality-adjusted life-years (QALYs); reporting that in 74% of iterations, alemtuzumab dominated teriflunomide, and in 70% of iterations, alemtuzumab dominated natalizumab.[6] The results for alemtuzumab relative to the other comparators were not included in the manufacturer's pharmacoeconomic (PE) report. CADTH Common Drug Review (CDR) reran the PSA to test the manufacturer's results against the two reported comparators, and could not replicate the results within a reasonable range. The manufacturer's PE report indicated at 90% probability of cost-effectiveness, willingness to pay for alemtuzumab versus natalizumab was approximately $72,000. When CDR reviewers reran the PSA, at 90% probability, the willingness to pay was approximately $88,000.

The manufacturer reported for the deterministic sensitivity analyses, in all cases, alemtuzumab remained the lowest cost and most effective intervention, dominating all other therapies.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

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

4.1 Longer-Term Use and Potential for Re-treatment With Alemtuzumab is Uncertain

The manufacturer's model applied a proportion of patients receiving alemtuzumab (uptake), but a withdrawal rate for comparator treatments. Proportion of patients receiving alemtuzumab dropped substantially from year 2 (96.77%) to year 3 ([redacted]%), and further declined up to year [redacted]. From year [redacted] onwards, [redacted]% of patients in the model received alemtuzumab, based on data from extension studies.[6] Published data from a long-term follow-up of a small number of patients (n = 87) in the UK[2] indicated that eight patients (~9%) received at least one dose of alemtuzumab between years 6 and 10. For alemtuzumab, the proportion of patients receiving treatment was linked to costs, but not efficacy parameters, assuming a continued effect over time. For the comparator treatment, patients received BSC once treatment was stopped. Monitoring and adverse events (AEs) occurred up to four years after treatment stoppage for alemtuzumab. Given the small amount of data available and the high level of uncertainty, CDR undertook reanalyses using data from the CARE-MS II trial for years 1 and 2, and then accounted for an expected drop-off in year 3 based on data from a long-term UK study.[2] From year 4 onwards, the withdrawal rate for Rebif (~16%) was applied to alemtuzumab.

4.2 Substantial Uncertainty With the Results of the Manufacturer's MTC

The manufacturer's MTC was based on a [redacted] (see CDR Clinical Report). Consequently, CDR considered its analyses based on the single randomized controlled trial of alemtuzumab (compared with Rebif) in the treatment-experienced population to inform treatment effects (CARE-MS II).[8] Although Rebif is unlikely to be the appropriate comparator for treatment-experienced patients, information on comparative clinical effectiveness versus other disease-modifying therapies (DMTs) was not available, given the paucity of information to inform an indirect comparison.

4.3 Patients With an EDSS Score of 0 Were Included

The CDR clinical expert indicated that while it was possible that patients who have already failed on a DMT would have an EDSS score of 0, it was unlikely. The patient population was reweighted to exclude EDSS 0.

4.4 Inappropriate Adjustment of MS-Specific Mortality Rate

An MS-specific mortality rate was identified from the published literature and adjusted to fit the manufacturer's model structure. CDR undertook reanalyses using the actual data from the published literature.

4.5 Proportion of Patients Hospitalized Following Relapse is Overestimated

The manufacturer indicated that approximately 41% of patients who relapsed were hospitalized. The CDR clinical expert indicated that this figure was likely between 5% and 10%. CDR undertook reanalyses using a lower rate of hospitalization based on the Rebif group of the CARE-MS II trial (11.4%).

Other parameters of uncertainty identified with the submitted model include:

4.6 Uncertainty Surrounding Monitoring and Administration Cost

The administration cost presented by the manufacturer appears to have been miscalculated. CDR recalculation slightly increased the cost of administration. The cost of monitoring in the manufacturer's PE report was stated to be $157 for alemtuzumab (for 48 months post-treatment), which differed substantially to the model input values. CDR undertook reanalysis based on monitoring components specified in the product monograph.

4.7 Health State Utility Values are Uncertain

There is uncertainty in the methods used in the source article,[9] which informed the utility values, and the application of these data to the model. CDR undertook reanalysis using the utility values used in the CADTH Therapeutic Review of RRMS.[10]

4.8 Relapse Disutility Values are Uncertain

The manufacturer reported that relapse disutility values were based on a UK study,[9] but that values were derived from a US study.[11] CDR undertook a reanalysis using the original values from the US study.

4.9 Duration of Relapse May be Overestimated

The manufacturer reported that duration of relapse was assumed to be three months based on assumption from a UK study.[9] Inference from Canadian guidelines indicates that duration of relapse may be closer to one month.[12,13] CDR undertook reanalysis assuming one month duration of relapse.

4.10 Inappropriate Use of a Mid-Cycle Correction

The manufacturer included a mid-cycle correction for all compared treatments, including alemtuzumab. However, while other treatments are dosed continuously over the year, alemtuzumab is administered as a yearly dosing regimen; thus it is not be appropriate to apply the mid-cycle correction to costs associated with treatment, as this would not be capturing costs borne up front in each year.

4.11 Revised Alemtuzumab Uptake Rates

As indicated earlier, the uptake rate of alemtuzumab after year 2 is highly uncertain. CDR undertook a reanalysis using the same assumptions as earlier identified for years 1 and 2, and years 4 and beyond, but altering the year 3 uptake rate from 45% to [redacted]% (as per the manufacturer's stated proportion of patients from the CARE-MS extension trial).

5. CDR ANALYSES

CDR identified six primary limitations (previously stated) with the manufacturer's model that were adjusted in the CDR base-case analysis. CDR found the base case to be approximately $31,000 per QALY for alemtuzumab versus Rebif. CDR undertook further reanalysis to test other parameters of uncertainty, which resulted in substantial variability within the range of incremental cost-utility ratios (ICURs) (range: alemtuzumab dominates Rebif to $91,000 per QALY for alemtuzumab compared with Rebif). The model was most sensitive to the withdrawal/uptake rate of alemtuzumab and the utility values used.

CDR undertook an exploratory reanalysis incorporating treatment waning for both alemtuzumab and Rebif, which resulted in an ICUR of $231,000 per QALY for alemtuzumab versus Rebif.

CDR undertook an analysis presenting the ICUR for alemtuzumab versus Rebif assuming proportional price reductions for alemtuzumab. The results are sensitive to price. As the manufacturer's submission already indicates that alemtuzumab dominates Rebif, no price reduction is required to alter this result. Based on the CDR's base-case analysis, alemtuzumab dominates Rebif with a price reduction of 3.5%.

Using the CDR base case, analysis stratified by EDSS states (i.e., for populations of EDSS states of 1, 2, 3, 4, 5, and 6) found substantial variation in ICURs based on the EDSS state, with those in higher EDSS states having a higher cost per QALY (Table 2). Even in patients with EDSS 3 or higher, the cost-effectiveness of alemtuzumab is greatly reduced.

TABLE 2: CADTH COMMON DRUG REVIEW ANALYSIS OF INCREMENTAL COST-UTILITY RATIOS FOR ALEMTUZUMAB VERSUS REBIF BY SPECIFIC BASELINE KURTZKE EXPANDED DISABILITY STATUS SCALE LEVELS

Baseline EDSS Level	ICUR for Alemtuzumab Versus Rebif	
	Based on Manufacturer's Analysis	Based on CDR Base Case
Combined weighted population	Alemtuzumab dominates Rebif	$31,575
EDSS level 1	Alemtuzumab dominates Rebif	Alemtuzumab dominates Rebif
EDSS level 2	Alemtuzumab dominates Rebif	$13,467
EDSS level 3	Alemtuzumab dominates Rebif	$62,080
EDSS level 4	Alemtuzumab dominates Rebif	$64,812
EDSS level 5	Alemtuzumab dominates Rebif	$89,864
EDSS level 6	Alemtuzumab dominates Rebif	$522,007

CDR = CADTH Common Drug Review; EDSS = Kurtzke Expanded Disability Status Scale; ICUR = incremental cost-utility ratio.

6. ISSUES FOR CONSIDERATION

Due to the limited long-term data available, the need for re-treatment with alemtuzumab beyond year 2 is uncertain. Data from Tuohy et al.[2] suggest that although many patients may discontinue alemtuzumab after year 2, a number of them may require additional courses of treatment. Further, it is uncertain whether patients would require dosing at the higher dose (60 mg over five days) as was indicated by the CDR clinical expert, or the lower dose (36 mg over three days). This will substantially impact the costs associated with alemtuzumab treatment in the future.

Alemtuzumab was recommended for listing by the Institut National d'Excellence en Santé et en Services Sociaux (INESSS) in Quebec in October 2014 and has since been listed on the Régie de l'assurance maladie du Québec (RAMQ) drug formulary at a price of $9,970 per 1.2 mL vial.[14] This represents a [redacted]% price reduction on the confidential price submitted to CDR. If the Quebec formulary price were to be used in CDR base-case analysis, [redacted]. INESSS recommended alemtuzumab be funded for a maximum of two treatment cycles. Given the limitations of the model, CDR did not undertake an analysis applying a stopping rule after two years (see Table 8).

7. PATIENT INPUT

Input was received from two patient groups, who undertook surveys of patients and carers. Respondents reported that RRMS had a significant impact not only on the patients' physical activity, but also on their quality of life, mental health, work or career, and their family members/caregivers.

More than half of the respondents indicated that they were using one of the 10 currently approved drugs for MS in Canada. Commonly reported side effects included injection site reactions, headache, flu-like symptoms, flushing, gastrointestinal symptoms, back pain, skin rashes or hives, infections, and abnormal blood or liver tests; GA and interferon beta were stated to have more impactful side effects than dimethyl fumarate, fingolimod, natalizumab, and teriflunomide. Many respondents (42%) reported access to DMTs was a challenge. Caregivers are an important part of the patients' ability to maintain their quality of life and independence in the community. Providing assistance to MS patients impacted the caregivers' own daily routines. Caregivers indicated that the disease and the treatment had negative impact on the patients' daily lives, work, family, and social life.

A small proportion of respondents indicated experience with alemtuzumab. These respondents reported fewer hospital visits, fewer relapses, the ability to remain in the workforce, better mobility, pain relief, and improved psychological impact from the disease and treatment. Common side effects reported were infusion-associated reactions, fatigue, bruising, and tingling sensations. Infusion-related side effects were impactful in approximately 66% of respondents. All patients indicated that they were aware of the potential long-term risks and would like to receive continuous alemtuzumab therapy.

Patient expectations for a new DMT were improved symptom relief, improved daily functioning, reduced or eliminated relapses, lower and/or limited side effects, affordability, and better convenience (e.g., no refrigeration and no need to take regular injections or medications).

8. CONCLUSIONS

CDR identified several key limitations with the manufacturer's economic analysis relating to the clinical data used, as well as model structure and inputs. Given the substantial uncertainty surrounding the MTC, CDR undertook reanalyses based on the CARE-MS II trial of alemtuzumab versus Rebif, although this is unlikely to be the most appropriate comparator. The CDR base-case analysis resulted in an ICUR of approximately $31,000 per QALY for alemtuzumab versus Rebif in adult patients with active RRMS who had previously failed or were intolerant to interferon beta or GA. CDR identified several other parameters of uncertainty. Testing these parameters identified substantial variability within the range of ICURs (range: alemtuzumab dominates Rebif to $91,000 per QALY for alemtuzumab compared with Rebif). The cost-effectiveness of alemtuzumab versus other DMTs is not known given the uncertainty surrounding the MTC. There is uncertainty with pattern and duration of treatment with alemtuzumab in the Canadian setting, which may substantially impact the burden on the Canadian health care system.

APPENDIX 1: COST COMPARISON

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may 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 3: COST COMPARISON TABLE FOR ALEMTUZUMAB FOR THE TREATMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Weekly Drug Cost ($)	Annual Drug Cost ($)
Alemtuzumab (Lemtrada)	**12 mg/1.2 mL**	**IV solution**	[redacted][a]	**12 mg/day for five days followed by 12 mg/day for 3 days after 12 months**	**Year 1:** [redacted] **Year 2:** [redacted]	**Year 1:** [redacted] **Year 2:** [redacted]
Dimethyl fumarate (Tecfidera)	120 mg 240 mg	Capsule	16.1925[b] 32.3850	120 mg twice daily; after 7 days increase to 240 mg twice daily	First week: 227 Subsequent weeks: 453	23,414
Fingolimod (Gilenya)	0.5 mg	Capsule	85.1648	0.5 mg daily	596	31,085
Glatiramer (Copaxone)	20 mg/mL	Pre-filled syringe	44.4960	20 mg SC daily	311	16,241
Interferon beta-1a (Avonex)	30 mcg/0.5 mL (6 MIU)	Pre-filled syringe or pen	405.76	30 mcg IM per week	406	21,157
Interferon beta-1a (Rebif)	22 mcg/0.5 mL (6 MIU) 44 mcg/0.5 mL (12 MIU)	Pre-filled syringe, cartridge or pen	128.8433 156.8533	22 mcg to 44 mcg SC 3 times weekly	387 to 471	20,155 24,536
Interferon beta-1b (Extavia)	0.3 mg (9.6 MIU) powder for injection	Single-use vial	99.3593	0.25 mg SC every other day	348	18,133
Interferon beta-1b (Betaseron)	0.3 mg (9.6 MIU) powder for injection	Single-use vial	110.0000	0.25 mg SC every other day	385	20,075
Natalizumab (Tysabri)	300 mg/15 mL	IV solution	3,158.62	300 mg IV infusion every 4 weeks	790	41,062
Teriflunomide (Aubagio)	14 mg	Tablet	53.9696	14 mg once daily	378	19,699

IM = intramuscular; IV = intravenous; MIU = million international units; SC = subcutaneous.
[a] Manufacturer-submitted confidential price.
[b] Saskatchewan Drug Benefit Formulary (accessed March 2015).
Note: Drug prices are taken from the Ontario Formulary Exceptional Access Program (March 2015) 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.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

CDR Base-Case Reanalysis

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS ALEMTUZUMAB RELATIVE TO REBIF?

Alemtuzumab Versus Rebif	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$31,575 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

Manufacturer's Base-Case Analysis

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS ALEMTUZUMAB RELATIVE TO THE OTHER COMPARATORS?

Alemtuzumab Versus Other Comparators	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Alemtuzumab dominates all other comparators					

CE = cost-effectiveness; NA = not applicable.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/Good	Somewhat/Average	No/Poor
Are the methods and analysis clear and transparent?			X
Comments	There were concerns with respect to the lack of transparency, and cumbersome presentation of the model with the inability to compare more than one treatment at a time. Different model input values were reported in different parts of the report, and input and output values stated in the report differed to the model (relapses, natural history, costs, PSA). An error in the formula for withdrawals was also identified.		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

PSA = probabilistic sensitivity analysis.

TABLE 7: AUTHOR INFORMATION

Authors	Affiliations		
Canadian adaptation	PIVINA Consulting Inc.		
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF ALEMTUZUMAB

TABLE 8: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	NICE	SMC	INESSS	PBAC
Date of publication	May 2014	July 2014	October 2014	July 2014[a]
Drug	12 mg/mL vial for intravenous infusion	10 mg/mL (1.2 mL) solution for intravenous infusion	10 mg/mL injection, 1 x 2 mL vial	
Price	£7,045 per 12 mg vial	Confidential	Confidential	Confidential
Treatment	Alemtuzumab (AL) – 12 mg per day for 5 consecutive days followed by 12 mg per day for 3 consecutive days administered 12 months after first treatment course	AL – 12 mg per day for 5 consecutive days followed by 12 mg per day for 3 consecutive days administered 12 months after first treatment course. A proportion of patients were maintained on AL in subsequent years.	AL initial treatment: max 5 x 10 mg/mL injections; continuing treatment: max 3 x 10 mg/mL injections (2 years of treatment total)	
Comparators	Rebif, Avonex, Betaferon, glatiramer acetate, natalizumab, and fingolimod	Interferon beta-1a 44 mcg; subgroup analysis: fingolimod and natalizumab	Interferon beta-1a 44 mcg, glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab, fingolimod. Given uncertainty in NMA, reanalyses focused on comparison with interferon beta-1a 44 mcg.	Fingolimod and natalizumab
Population modelled	Patients with active RRMS, based on the average demographic profile of patients in UK Risk Sharing Scheme; 2 subgroups: patients with highly active RRMS despite beta interferon and patients with rapidly evolving RRMS	Adult patients with RRMS with active disease defined by clinical or imaging features; 2 subgroups: patients with highly active RRMS and patients with rapidly evolving RRMS	MS patients having failed DMTs	First-line in patients with aggressive disease (rapidly evolving severe RRMS and/or highly active RRMS); second-line in patients failing other DMTs

	NICE	SMC	INESSS	PBAC
Time horizon	50 years	50 years	20 years	Not stated
Cycle length	1 year	1 year	Not specified	Not stated
Discount rate	3.5% on both costs and outcomes	Not specified	Not specified	Not stated
Type of model	CUA: Markov model with health states in either RRMS or SPMS, based on EDSS scores ranging from 0 to 9, and death from MS (score of 10)	CUA: Markov model with 20 health states in either RRMS or SPMS, based on EDSS scores ranging from 0 to 10	CUA: Markov model with health states in either RRMS or SPMS, based on EDSS scores	CMA
Key outcomes	Disability sustained for 3 months and relapse rates; health state utilities obtained from a study by Orme et al. (2007) based on EQ-5D values	Sustained accumulated disability and ARR; health states utilities from RCT comparing teriflunomide to interferon for up to EDSS 6; for higher EDSS states based on published UK study	Disability progression and relapse rate	Disability progression and relapse rate
Results	• AL dominated Betaferon, fingolimod, and natalizumab; Rebif extendedly dominated. • ICER for AL vs. glatiramer acetate: £7,017/QALY. • Results most sensitive to HR for sustained disability progression, disease costs, and discontinuation rate of Rebif (44 mcg). Also sensitive to which MTC was used. • Most plausible ICER for alemtuzumab compared with glatiramer is likely to lie between £13,600 and £24,500/QALY.	• ICUR for AL vs. interferon beta-1a 44 mcg: £209/QALY. • vs. natalizumab, AL dominant with savings of £62,461 and an incremental QALY gain of 1.791.	AL dominates interferon beta-1a 44 mcg.	AL cost-saving for the standard two courses of therapy (one course per year for two years) vs. fingolimod ($28,243) and natalizumab ($26,500).

	NICE	SMC	INESSS	PBAC
Sources of uncertainty	• Population modelled should be based on trial populations. • Natural history estimates for disease progression (based on London, Ontario dataset) did not allow EDSS scores to improve. • Questionably low number of QALYs to be accrued by a person with MS over a 50-year time horizon. Concluded that economic model had poor face validity. • Initial assumption of constant treatment effect throughout course of MS up to EDSS state 7 or SPMS was not supported by long-term data. • Conversion rate used for patients moving from RRMS to SPMS in the model was too high; it did not reflect the people receiving first-line treatment for RRMS. • Re-treatment with AL should be based on time-dependent rate of re-treatment, which was reflected in the manufacturer's revised economic model.	• Natalizumab or fingolimod may be more relevant comparators. • Pooling of trial data in economic model may overestimate benefits of AL. • For vs. interferon, more appropriate to base this analysis on data from treatment-naive patients only. • Key assumption in model that patients continue to receive benefit with AL over time horizon while on active treatment. Results sensitive to this assumption by reducing the time horizon to 20 years. • Uncertainty about proportion of patients who would be re-treated with AL in practice.	• Important uncertainty in NMA. • Total withdrawals from NMA higher than what reported in other sources. • Relapses leading to hospitalization assumed to be less frequent with AL, but clinical trial did not show a statistically significant difference. • Risk of severe relapses, requiring hospitalization duration of moderate relapses. • INESSS ran additional sensitivity analyses using different sources of utility values, varying efficacy, half-cycle correction, and including prophylactic treatments with AL. • AL remained a dominant strategy through all sensitivity analyses conducted by INESSS.	• CUA may be more appropriate to account for differences in risk/benefit profiles (both short- and long-term). • Interferon beta-1a appropriate main comparator. • Analysis does not account for AL re-treatment beyond the standard 2 courses of therapy. • Assumes effects of AL will persist after treatment using time until re-treatment as a proxy for durability of effect (no waning considered). • Re-treatment rates may not be an adequate proxy for durability of effect as they do not account for patients switching to other therapies and patients lost to follow-up.
Recommendation	AL is recommended as an option, within its marketing authorization, for adults with active RRMS.	AL accepted for use within NHS Scotland.	AL recommended as a second-line option in patients having failed DMT. Initial authorization is for 1 year. Second course in year 2 is allowed only in responders. Maximum of two treatment courses (2 years) allowed.	PBAC recommended listing of AL for the treatment of RRMS, on basis of non-inferior effectiveness and a different safety profile to fingolimod and natalizumab.

	NICE	SMC	INESSS	PBAC
CDR assessment	The economic evaluation submitted to CDR appears similar to economic evaluations submitted to NICE and SMC, and INESSS, but different to the one submitted to PBAC. Although there are some differences regarding the information included within the model (e.g., main comparators used, populations modelled/line of therapy, and time horizon adopted), the overall outcomes appear to be the same across all four HTA agencies (including CDR). NICE, SMC, and PBAC all found several key limitations within their respective submitted model, several of which have been identified within the CDR review. It should be noted that the reviews conducted by NICE, SMC, and PBAC all considered preliminary results of the CARE-MS I/II extension study. The extension study provides input on the duration of AL treatment in only the submission to CDR.			

AL = alemtuzumab; ARR = annualized relapse rate; CDR = CADTH Common Drug Review; CMA = cost minimization analysis; CUA = cost-utility analysis; DMTs = disease-modifying therapies; EDSS = Kurtzke Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions Questionnaire; HR = hazard ratio; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; INESSS = Institut National d'Excellence en Santé et en Services Sociaux; max = maximum; MS = multiple sclerosis; MTC = mixed-treatment comparison; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; NMA = network meta-analysis; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life-year; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SMC = Scottish Medicines Consortium; SPMS = secondary-progressive multiple sclerosis; vs. = versus.

[a] Publication date not stated; date of meeting used instead.

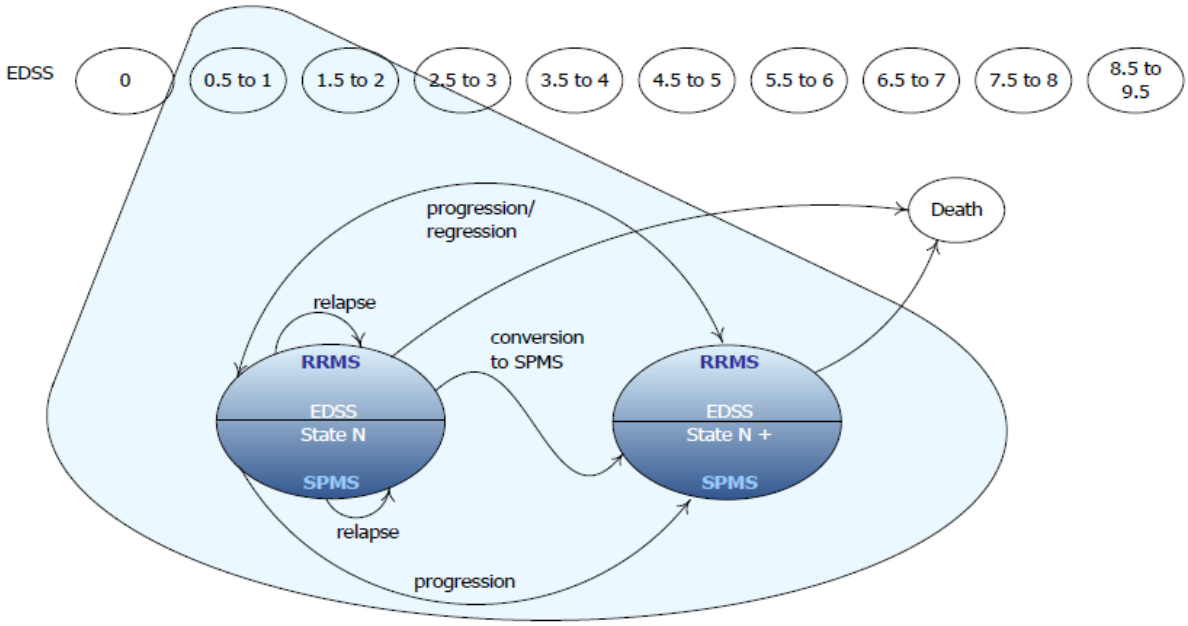
APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cohort-based Markov model originally developed for the National Institute for Health and Care Excellence (NICE) and adapted to the Canadian situation based on the previously published School of Health and Related Research (ScHARR) model.[15] The model included 21 health states: 10 for each multiple sclerosis (MS) type (relapsing-remitting multiple sclerosis [RRMS] and secondary-progressive multiple sclerosis [SPMS]) and a death state. The 10 MS-specific health states were grouped according to Kurtzke Expanded Disability Status Scale (EDSS) levels, from 0 (normal neurological examination) to 9 (helpless bed patient).[16] The model structure is presented in Figure 1.

In the model, all patients begin in RRMS. The model tracks a cohort of patients as they progress through the health states. The distribution of patients by EDSS state was defined at the outset based on the proportion of patients in each state from the CARE-MS II trial.[17] From this point onwards, and through each cycle in the model, each patient in the cohort can either progress to a higher EDSS state (disease progression), remain in the same state, or die. Patients can also progress to SPMS from RRMS; patients with SPMS are withdrawn from the model. Patients progressed or relapsed were dependent on their RRMS or SPMS status, and EDSS score. Patients can transition from any state to the death state.

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



EDSS = Kurtzke Expanded Disability Status Scale; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.

Note: EDSS State N is the EDSS state defined at the top of the figure that the patient is in, while EDSS State N+ is the EDSS state that the patient moves to upon progression/regression.

Source: Manufacturer's pharmacoeconomic submission.[6]

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment*
Efficacy		
Efficacy • Annualized relapse rate (ARR) • Disability progression (sustained accumulation of disability; SAD)	An MTC was conducted, [redacted]	The relevant MTC [redacted] Thus, CDR considered analyses based on the CARE-MS II trial to inform the efficacy parameters. CDR reviewers note that the limitation is primarily with the lack of compatibility of the studies for comparison as opposed to the conduct of the MTC.
Treatment effect on relapse leading to hospitalization	Treatment effect on the proportion of relapses leading to hospitalization was based on the proportion of hospitalizations within the CARE-MS I clinical trial (alemtuzumab and Rebif), the observed rate of hospitalization for relapses in the TEMSO phase 3 trial (teriflunomide), and extracted from a poster presentation by Haas et al. (fingolimod and Avonex).[18] Where data for certain treatments were not available, assumptions were made using data from the other treatments. Assumptions about the treatment effect on the need for hospitalization were applied onto the natural history proportion of relapses that led to hospitalization.	The value presented in the PE report differed to the value used in the model. The value in the PE report was from the CARE-MS II trial, as opposed to the stated CARE-MS I trial (the value for which was used in the model).
Probability of relapse leading to hospitalization (in absence of treatment)	The probability of relapse leading to hospitalization (i.e., relapse rates in absence of treatment) for both types of relapses across the RRMS and SPMS populations were sourced from the placebo group of the FREEDOMS clinical trial.[18] The proportion of relapses requiring hospitalization was assumed to not vary across EDSS level or disease stage.	The CDR clinical expert indicated that the proportion of relapses leading to hospitalization is likely to be less than 10%. CDR undertook an analysis using data from the CARE-MS II trial (see Table 21, CDR Clinical Report).

Data Input	Description of Data Source	Comment*
Adverse events	Data were based primarily on direct published trial evidence (Rebif, Avonex, GA), publically available reports based on trial data (fingolimod), a combination of the two (dimethyl fumarate, teriflunomide, natalizumab), and a combination of trial data and company data on file (alemtuzumab).	Data were based on a variety of different trials in different populations.
Natural history		
Disease progression	The natural history transition matrices for disability progression were stated to be based on analyzed data from the London, Ontario registry of multiple sclerosis data, and TEMSO and AFFIRM trials for teriflunomide and natalizumab, respectively (O'Connor 2011; Polman 2006), though the model worksheets indicate only data from the AFFIRM trial (for EDSS 0) and the London, Ontario registry.	While it may be assumed that data from TEMSO was excluded as ~8% of patients had progressive MS, it was not made explicit why TEMSO was not used in the model.
Relapse rate	Natural history relapse rates were derived from a study by Patzold et al.[19] Results from a study by Held et al.,[20] which were combined with UK MS survey data, were used for supplemental analyses.	The use of relapse rates from Patzold et al. appears to be appropriate.
Duration of relapse	The mean duration of relapse (3 months) was derived from a study by Orme et al.,[9] appearing to assume 3 months from the questionnaire that asked whether patients had relapsed in the past 3 months.	The duration of relapse may be shorter than 3 months,[12] though there is a dearth of data regarding this.[13]
Conversion from RRMS to SPMS	The probability of converting from RRMS to SPMS is calculated from hazard rates using a standard formula for conversion.[21] Hazard rates for conversion appear to have been based on the London, Ontario dataset, calculated using the Cox Proportional hazards model.	Data from the London, Ontario Registry are not publically available and thus this was not able to be verified.
Mortality	Relative increase in mortality rates per EDSS state were applied to all-cause mortality rates for the Canadian general population. Mortality multipliers by MS disease severity were sourced from Pokorski et al.[22] A cubic regression was fitted to the study values — reported in ranges of EDSS — to obtain a mortality adjustment for each individual EDSS state.	The values used by Pokorski were derived from a study by Sadovnick et al. 1992,[23] which presented mortality rates based on grouped EDSS categories. CDR notes that it would have been better to use actual data than interpolated values. Also of note: the data are quite old — it would be preferential if more recent data on the mortality by EDSS level were available.

Data Input	Description of Data Source	Comment*
Discontinuation/ withdrawal/uptake rate	Each comparator treatment in the model is associated with an annual rate of withdrawal [redacted] The withdrawal rate is applied to both the cost and efficacy parameters. No withdrawal rate was applied to alemtuzumab in the model, although a formula was included in the model should a withdrawal rate be included. A separate model input dictates the proportion of patients treated with alemtuzumab in each year of the model. The proportion of patients treated with alemtuzumab was assumed to decrease from 100% in year 1 to [redacted]% from year [redacted] onwards, based on data from the CARE-MS extension study. The uptake rates are applied to the cost data for alemtuzumab but not the efficacy data, which is not appropriate.	The assumptions around the withdrawal/uptake rates are questionable and applied in a way that biases the results in favour of alemtuzumab. The formula to calculate withdrawal for alemtuzumab was incorrect, resulting in increased numbers of patients if a withdrawal rate was included. This was amended in CDR reanalysis.
Utilities		
Health state utilities	Utilities were based on EDSS state (health states). Values were based on published literature (Orme et al.) reporting responses from a survey of patients with MS and their caregivers using EQ-5D utility scoring system using the UK value set. Utilities were applied to a mid-year estimate of the cohort to adjust for the half-cycle correction.	It is uncertain as to how the base values from Orme et al. were calculated. It is also uncertain whether the UK population is similar to the Canadian population. Although the health states that were collected appear to map better to the submitted model than those used in the CADTH Therapeutic Review of RRMS, values from the CADTH Therapeutic Review of RRMS were tested in CDR analysis.
Disutilities due to relapse	The utility loss for relapse was sourced from a UK study by Orme et al.[9] Data from a US study (Prosser et al. 2004)[24] were indicated to be similar to UK rates. Disutility associated with relapses not leading to hospitalization were based on Orme et al., and values for relapse associated with hospitalization were derived by applying percentage increase observed for severe relapse from the US Prosser et al. study to the UK disutility of relapse.	The CADTH Therapeutic Review of RRMS used values from Prosser et al.[24] for disutility due to relapse. CDR undertook an analysis based on values from Prosser et al.
Disutilities due to adverse events	Adverse event disutilities were sourced largely from published literature and, where available, from previous HTA submissions.	Values appear appropriate, though disutility associated with autoimmune thyroid-related adverse events appears low.
Disutilities for caregiver	Derived from the UK MS survey. Values reported in natalizumab HTA submission to NICE.	Not included in the base-case analysis, which is appropriate.
Resource use		
Adverse events	Resources associated with TRAE management were estimated based on clinical expert input. The majority of the AEs were assumed to be mild and would not require any physician visits or treatment.	Appropriate

Data Input	Description of Data Source	Comment*
Costs		
Drug	The manufacturer provided a confidential price of alemtuzumab. Drug acquisition costs unit prices for all other comparators were obtained from the Ontario Ministry of Health and Long-Term Care — Formulary for the Exceptional Access Program (EAP), October 2014.	There were some minor differences in calculations between the CDR Cost Table and manufacturer's yearly drug acquisition costs. Rebif acquisition cost was calculated to be $24,469 vs. $24,536.
Administration of oral drugs	Fingolimod, teriflunomide, and dimethyl fumarate are oral drugs, assumed to incur a dispensing fee of $8.62 every three months ($34.48 per year), though the data source of this cost is not reported.	Appropriate
Administration of self-injectables	A dispensing fee of $8.62 every three months was determined from the Ontario Schedule of Benefits. Avonex, Rebif, and GA can be self-administered in the home. Costs associated are based on an assumed nurse home-visit cost of $70.29 per visit. In subsequent years, the training would not be required, thus no cost was included.	No source of nurse costs provided. No information or rationale on the number of visits; however, the CDR clinical expert indicated that most patients would require only 1 visit.
Administration of IV infusions	Both alemtuzumab and natalizumab require IV infusion. Costs associated were poorly reported. On page 61, the report states: "as pharmaceutical companies fund this infusion, thus the cost … is assumed to be $0 in the base-case analysis"; however, it is later reported that administration costs are included in the base case (page 68), which concurs with the model. The cost of infusion was $35 per hour for nursing and $57.42 per hour for overhead, as reported by a 2002 Canadian publication. After inflating the costs to 2014 dollars and assuming a 6-hour infusion (as per product monograph),[1] a cost of $681.48 per infusion is included.	It appears the manufacturer may have miscalculated the administration cost. Revised calculations result in a slightly higher cost per administration for infusions ($683). This was adjusted in CDR's revised analysis.
Other health care resource costs associated with administration	The report stated that health care resources associated with treatment monitoring were estimated from clinical expert opinion, including lab test costs used for monitoring any treatment-specific adverse events and are shown below. Physician visits and MRI tests related to treatment monitoring were not included (included in health state costs). The model used a different monitoring cost, approximately 4 times higher than the stated cost in the report; however, there was no information in the model as to the resources included for this cost.	The manufacturer's report indicated $157 as total monitoring costs for alemtuzumab, but this does not cover the range of tests required for monitoring. However, the monitoring costs for alemtuzumab differed from the report to the model. Excluding physician and MRI costs was appropriate, as these were included in the health state costs.
Costs associated with relapses	Cost per relapse requiring hospitalization (severe relapses), and relapse not requiring hospitalization (mild/moderate relapses) were derived from the CADTH Therapeutic Review. Indirect costs associated with relapses were derived from Karampampa et al. 2012,[25] and inflated to 2014 dollars.	Appropriate

Data Input	Description of Data Source	Comment*
Costs associated with adverse events	Unit costs of physician services required to treat AEs was obtained from the Ontario Health Insurance Program Schedule of Benefits; the costs of emergency visits and hospitalization were obtained from the Ontario Case Costing Initiative (OCCI); and the costs of medications were obtained from the Ontario Ministry of Health and Long-Term Care (Ontario Disability Drug Benefit Program e-Formulary).	There was some lack of clarity over the codes that were used to associate resource costs (primarily OCCI). However, the impact of different values is unlikely to have a large impact on the relevant treatments in the CDR reanalyses (alemtuzumab and Rebif).
Costs associated with health states (EDSS)	Annual per patient direct costs of MS by EDSS scores are CPI adjusted to 2014 costs based on the values reported in the CADTH MS Therapeutic Review. Indirect costs from Karampampa et al. 2012.[25]	Appropriate

AE = adverse event; ARR = annualized relapse rate; CDR = CADTH Common Drug Review; CPI = Consumer Price Index; EDSS = Kurtzke Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions Questionnaire; HTA = health technology assessment; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; MTC = mixed-treatment comparison; NICE = National Institute for Health and Care Excellence; OCCI = Ontario Case Costing Initiative; PE = pharmacoeconomic; RRMS = relapsing-remitting multiple sclerosis; SAD = sustained accumulation of disease; SPMS = secondary-progressive multiple sclerosis; TRAE = treatment-related adverse event; vs. = versus.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	CDR Comments
Model structure	
Model did not include transitions to EDSS state 10 (i.e., MS-related death).	Appropriate. Patients experienced an age-related risk of mortality adjusted for the probability of MS-related death.
The model allowed patients to enter in EDSS state 0 (i.e., normal neurological examination).	Feedback from the CDR clinical expert was that it was possible but unlikely that patients in EDSS 0 would be treated with alemtuzumab. CDR reweighted the proportion of patients in each EDSS state in CDR analysis.
Patients either progress to a higher EDSS state, remain in the same state, or die.	This is a conservative approach.
Patients can progress to SPMS from RRMS.	This is appropriate.
The comparators were modelled individually versus alemtuzumab.	A sequential analysis would have been preferred. CDR was unable to conduct reanalyses given the structure of the model.
Mid-year correction was applied to alemtuzumab.	Given treatment costs and withdrawals are accrued at the start of the year (when patients are dosed), it is not appropriate to apply half-cycle corrections to alemtuzumab.
Treatment effect	
Data for treatment effect of DMTs was based on different populations from a manufacturer-funded MTC.	Efficacy values for some comparators were not available from the MTC for the treatment-experienced population, thus data from the pooled all-RRMS MTC values were used. Given the high uncertainty with the MTC as previously described, CDR considered analyses based on the CARE-MS II trial to inform the efficacy parameters.
Disability progression was based on 3-month sustained	Use of 6-month sustained accumulation of disability is preferred,[26] as it is likely to be more

Assumption	CDR Comments
accumulation of disability and assumed to be appropriate for a 1-year cycle.	reflected of results over a 1-year cycle.
The proportion of relapses requiring hospitalization was assumed to not vary across EDSS level or disease stage.	Based on feedback from the CDR clinical expert, this does not appear to be appropriate as patients with a higher EDSS score are more likely to be hospitalized after a relapse than those with lower EDSS scores. Severity of relapse is an important factor that has not been considered, as more severe relapses increase the likelihood of hospitalization. CDR was not able to test variances due to either factor given the model structure.
Treatment effect on the proportion of relapses leading to hospitalization for natalizumab was assumed to be the same as fingolimod; GA and teriflunomide were stated to be based on values for Rebif.	The treatment effect for teriflunomide appears to have been based on dimethyl fumarate. No justification was provided as to why different values were applied to each of the comparators listed.
Treatment waning was incorporated in a sensitivity analysis for alemtuzumab, though no waning effect was considered for the comparators.	It is a conservative approach to suggest treatment waning for alemtuzumab versus comparator treatments. The inclusion of user-defined treatment waning in the model for all treatments is appropriate.
When patients stop treatment in the model, they move onto BSC.	Feedback from the CDR clinical expert is that if a patient failed on treatment, that patient would be switched to another DMT, if possible. A "user option" that allows patients to move onto a second-line treatment was included in the model; however the user would have to enter input values for this second-line treatment including treatment efficacy, adverse event rates, and costs. Given the lack of data to inform later line treatment, this was not tested in CDR reanalyses.
Withdrawals/uptake	
Alemtuzumab costs were based on the uptake of the drug in each year (100% in year 1, 97% year 2, [redacted] and beyond). For all comparators proportion of patients treated was based on withdrawals.	The different methodology in use of withdrawal compared with uptake rates is not appropriate, given the differential way in which withdrawal and uptake rates were applied within the model. CDR analysis applies withdrawal rates to alemtuzumab.
Alemtuzumab will only be used for [redacted] years, with an additional 4 years of monitoring.	Not appropriate. Published data from a long-term follow-up of a small number of patients (n = 87) indicates that 8 patients (9%) required doses of alemtuzumab between year 6 and year 10).[2]
Proportion of patients receiving alemtuzumab was not linked to the efficacy of alemtuzumab, thus benefit was still being accrued after treatment was stopped.	This is not appropriate. The manufacturer states that clinical data indicates treatment with alemtuzumab persists for [redacted] years post-treatment; however, the treatment effect is being seen throughout the model (up to 25 years) even though patients were not receiving treatment after year [redacted] in the model.
The probability of withdrawal for the comparators remained constant over all years of the model.	May not be appropriate.
Natural history	
Data from the London, Ontario Registry were used to inform the natural history disease progression data.	Data from the London, Ontario Registry are not publically available and thus this was not able to be verified.
Duration of relapse is 3 months.	May be overestimated. CDR undertook reanalyses based on McDonald et al.'s[12] 30-day interval criterion separating relapses.

Assumption	CDR Comments
Utility values	
Utilities were based on published literature from a survey of patients from the UK, which captured data from 2,048 carers or patients with RRMS, SPMS and PPMS (36%, 37%, and 27% of the population, respectively).	Although the UK population may differ from the Canadian population, the health states that were collected do map better to the submitted model than those used in the CADTH Therapeutic Review of RRMS.[10] However, the values appear to be based on results for all patients, inflated to RRMS values, and then a decrement based on SPMS and PPMS. Thus, values from the CADTH Therapeutic Review of RRMS were tested in CDR analysis.
Manufacturer stated that patients who received at least 1 dose of alemtuzumab experienced adverse events up to 4 years after last dose and were at risk of adverse events other than infusion-associated reactions for the remainder of their lifetime.	Adverse events applied only to year [redacted]. It is uncertain how risk is applied beyond year [redacted]. CDR undertook analysis based on treatment, disutilities associated with adverse events were applied to all years of the model.
Adverse events	
Adverse events were included if ≥ 4% difference between treatment and placebo, and/or were previously reported in an HTA submission.	Appropriate.
Rate of AEs was constant over model.	May not be appropriate.
Costs	
Costs associated with administration for alemtuzumab included in the base-case analysis.	Appropriate.
The annual monitoring costs listed in the PE report for alemtuzumab indicate only a hematological consult ($157).	The costs reported in the PE report associated with monitoring for alemtuzumab differ from those used in the model ($627 in year 1, $535 in subsequent years). No breakdown of these costs was reported. CDR undertook reanalysis based on monitoring components identified by the CDR clinical expert and product monograph.[1]

BSC = best supportive care; CDR = CADTH Common Drug Review; DMT = disease-modifying therapy; EDSS = Kurtzke Expanded Disability Status Scale; GA = gadolinium; HTA = health technology assessment; MS = multiple sclerosis; MTC = mixed-treatment comparison; PE = pharmacoeconomic; PPMS = primary-progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.

Manufacturer's Results

The manufacturer's base-case analysis produced the following results:

- Alemtuzumab dominated all comparator treatments.
- There were no large survival differences predicted between comparators, with survival estimates ranging from 14.23 years (alemtuzumab) to 14.16 years (Betaseron) over the 25-year time horizon.

The manufacturer did not explicitly report a cost for life-year; however, as the base-case results were individually reported, this information could be easily determined.

TABLE 11: MANUFACTURER'S BASE-CASE RESULTS

	Total Costs ($)	Incr. Cost vs. Alemtuzumab ($)	Total QALYs	Incr. QALYs vs. Alemtuzumab	ICUR ($) for Alemtuzumab vs. Comparator	Total LYs	Incr. LYs vs. Alemtuzumab	ICER
Alemtuzumab	$402,266		5.248			14.23		
Teriflunomide	$428,060	$25,794	4.661	–0.587	Alemtuzumab dominates	14.19	–0.04	Alemtuzumab dominates
GA	$431,866	$29,600	4.430	–0.818	Alemtuzumab dominates	14.18	–0.05	Alemtuzumab dominates
Rebif	$433,204	$30,938	4.640	–0.608	Alemtuzumab dominates	14.19	–0.04	Alemtuzumab dominates
Avonex	$444,349	$42,083	4.596	–0.652	Alemtuzumab dominates	14.19	–0.04	Alemtuzumab dominates
Dimethyl fumarate	$541,754	$139,488	4.537	–0.711	Alemtuzumab dominates	14.19	–0.04	Alemtuzumab dominates
Betaseron	$468,634	$66,368	4.091	–1.157	Alemtuzumab dominates	14.16	–0.07	Alemtuzumab dominates
Fingolimod	$481,434	$79,168	4.735	–0.513	Alemtuzumab dominates	14.20	–0.03	Alemtuzumab dominates
Natalizumab	$528,249	$125,983	4.851	–0.397	Alemtuzumab dominates	14.21	–0.02	Alemtuzumab dominates

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Incr. = incremental; LY = life-year; QALY = quality-adjusted life-year; vs. = versus.
Source: Summarized from Tables 37 (page 69) and 39 (page 71) from the manufacturer's pharmacoeconomic submission.[6]

Summary of the Manufacturer's Sensitivity Analyses

Probabilistic Sensitivity Analysis

The manufacturer undertook a probabilistic sensitivity analysis (PSA), altering the following parameters using either dirichlet, beta, lognormal, or gamma distributions:

- transition matrix for natural history data
- relapse rates
- proportion of relapses leading to hospitalization and not leading to hospitalization for natural history data
- hazard ratio for disease progression
- annual treatment effect on relapse rate
- proportion of relapses leading to hospitalization for natural history data for treatment effect data
- withdrawal rates
- natural history costs
- treatment costs
- utility values.

The manufacturer reported that the PSA showed some uncertainty around both the incremental cost and quality-adjusted life-years (QALYs), reporting that in 74% of iterations, alemtuzumab dominated teriflunomide, and in 70% of iterations, alemtuzumab dominated natalizumab. The results relative to the other comparators were not reported in the pharmacoeconomic (PE) report.

CADTH Common Drug Review (CDR) tested the PSA results from the manufacturer's base case, and could not replicate the two results reported from the manufacturer's PSA. Although the values were not expected to be the same as the manufacturer's, given the probabilistic nature of the analysis, the results differed substantially from the manufacturer's analysis. For example, the manufacturer's report indicated that at a 90% probability of cost-effectiveness, the willingness-to-pay threshold for alemtuzumab versus natalizumab was approximately $72,000. However, when CDR reran the PSA on the manufacturer's base-case model for alemtuzumab versus natalizumab, the willingness-to-pay threshold was approximately $88,000. It is uncertain as to the reasons for this.

Deterministic Sensitivity Analyses

The manufacturer undertook a series of deterministic sensitivity analyses, altering the following parameters:

- inclusion of revised treatment effects (waning) for patients with an EDSS < 7 (patients with EDSS > 7 are not treated)
- alemtuzumab administration and monitoring costs funded by the manufacturer
- time horizon set to 15 years
- time horizon set to 35 years
- discounting set to 0%
- discounting set to 3%
- EDSS costs increased by 25%
- EDSS costs decreased by 25%
- EDSS utility values from Prosser (CADTH Therapeutic Review of RRMS)
- EDSS utility values from Karampampa et al. 2012
- use of sustained accumulation of disease and annualized relapse rate values from CADTH Therapeutic Review of RRMS
- direct comparison with Rebif from CARE-MS II.

The manufacturer reported that in all cases, alemtuzumab remained the lowest cost and most effective intervention, dominating all other therapies.

CDR Reanalysis

As noted in the limitations, CDR identified several important limitations relating to the manufacturer's model. CDR presents a revised base-case analysis (Table 12) with alterations based on these limitations.

Longer-Term Use and Potential for Re-treatment With Alemtuzumab Is Uncertain

The manufacturer's model applied a proportion of patients receiving alemtuzumab (uptake), but applied a withdrawal rate to the comparator treatments. The manufacturer assumed that the proportion of patients receiving alemtuzumab would decrease substantially after the initial two years in the model. In year 2, approximately 96.77% of patients received alemtuzumab, while this proportion dropped substantially in year 3 ([redacted]%), declining further [redacted]. From year [redacted] onwards, [redacted]% of patients in the model received alemtuzumab. This was stated to be based on data from extension studies.[6] However, published data from a long-term follow-up of a small number of patients (n = 87) in the UK[2] indicates that eight patients (9%) received at least one dose of alemtuzumab between years 6 and 10. The proportion of patients receiving alemtuzumab was linked to the costs that were adjusted based on proportion of patients using alemtuzumab in each year, but did not impact the efficacy parameters in the model, thus assumed a continued effect throughout the model time period for alemtuzumab. For the comparator treatment, patients received best supportive care (BSC) after treatment was stopped.

Given the small amount of data available and the high level of uncertainty, CDR undertook reanalyses using the proportion of patients treated with alemtuzumab from the CARE-MS II trial for years 1 and 2 (year 1: 100%; year 2: rounded to 96.77%), but adjusted the uptake rate to a withdrawal rate. From year 3 onwards, CDR adopted a conservative approach, accounting for an assumed drop-off in year 3 using data from a long-term UK study that indicates that 45% of patients required dosing beyond year 2.[2] From year 4 onwards, the withdrawal rate for Rebif (16%) was applied to the proportion of alemtuzumab patients remaining on treatment after the previous year. That is, 45% of patients received alemtuzumab in year 3, and then to determine the proportion of patients in year 4, the withdrawal rate of 16% was applied to the year 3 cohort (45%).

The manufacturer indicated that treatment-related adverse events (AEs) were only applied up to four years after the last dose of alemtuzumab. It was determined to be appropriate that AEs related to alemtuzumab could occur up to four years after treatment, thus the proportion of AEs was applied to the proportion of patients receiving alemtuzumab four years earlier. That is, the proportion for each AE from years 1 to 4 was based on the 100% of patients receiving alemtuzumab in year 1. In year 5, the proportion of AEs was weighted based on the proportion of patients receiving alemtuzumab in year 2. In year 6, the proportion of AEs was weighted based on the proportion of patients receiving alemtuzumab in year 3, and so on, throughout the model. This approach was used in relation to monitoring costs, which were extrapolated to 25 years. These revisions to monitoring and AEs required altering the inputs and formulas in several sheets in the workbook. As noted in the earlier Table 9: Data Sources section, CDR identified an error in the manufacturer's formula for withdrawals for alemtuzumab, which inverted results. CDR corrected this error in the reanalysis.

Substantial Uncertainty With the Results of the Manufacturer's Mixed-Treatment Comparison

The CDR Clinical Report appraised the manufacturer's mixed-treatment comparison (MTC). The appraisal focused primarily on the treatment-experienced population, and identified several inherent uncertainties that made it too difficult to draw any conclusions from the comparisons. Further,

information from the all-RRMS population was used to populate the results for treatments that did not have information to populate the treatment-experienced population. Therefore, given the [redacted], it was deemed inappropriate to inform the economic model. See Appendix 8 of the CDR Clinical Report for the full appraisal.

Consequently, CDR considered clinical data based on the single randomized controlled trial of alemtuzumab (compared with Rebif) in the treatment-experienced population to inform treatment effects (CARE-MS II) as reported in the manufacturer's pharmacoeconomic report[6] and the CDR Clinical Report. Although Rebif is unlikely to be the appropriate comparator for treatment-experienced patients, information on comparative clinical effectiveness versus other disease-modifying therapies (DMTs) was not available given the paucity of information to inform an indirect comparison.

Patients With a Kurtzke Expanded Disability Status Scale Score of 0 Were Included
The proportion of patients in each of the health states based on EDSS score at the start of the model was based on the proportion of patients in each of these health states in the CARE-MS II trial. Approximately 3% of patients were reported to have an EDSS score of 0. The CDR clinical expert indicated that while it was possible that patients who have already failed on a DMT would have an EDSS score of 0, this was unlikely for the patient population expected to receive alemtuzumab.

CDR undertook reanalysis, reweighting the patient population to exclude patients with an EDSS score of 0. Thus, there were slightly higher proportions of patients in EDSS states 1 through 6.

Inappropriate Adjustment of Multiple Sclerosis-Specific Mortality Rate
The manufacturer derived mortality by EDSS state from a 1992 study by Sadovnick et al.,[23] which presented mortality rates for three grouped EDSS categories: 0 to 3.5, 4 to 7, and 7.5 to 9. The manufacturer applied different mortality rates for each EDSS state using cubic regression.

CDR undertook analysis adopting the actual data from Sadovnick et al.

Proportion of Patients Hospitalized Following Relapse Is Overestimated
The manufacturer reported that in the natural history population, 40.7% of relapses required hospitalization based on information from a poster reporting the results of the placebo group of the FREEDOMS trial of fingolimod.[18] The CDR clinical expert indicated that this value appeared to be high, and the proportion of patients requiring hospitalization was likely to be less than 10%, and probably closer to 5%.

Given the lack of published data for this parameter, CDR undertook reanalyses using the hospitalization rate based on the Rebif group of the CARE-MS II trial (11.4%). Although this is in a treated population, the rate used is higher than the proportion of patients hospitalized in the alemtuzumab group (7.3%).

The CDR reanalysis base case addresses each of these issues simultaneously.

TABLE 12: CADTH COMMON DRUG REVIEW ANALYSIS BASE CASE: ALEMTUZUMAB VERSUS REBIF

Alemtuzumab vs. Rebif	Difference in QALYs	Difference in Life-Years	Difference in Costs	CDR base case ICUR vs. Rebif
Amendments to the withdrawal/uptake rates based on uncertain long-term use	0.0863	0.0086	2,401	27,833
Revised clinical data based on CARE-MS II	0.6078	0.0446	–30,838	Alemtuzumab dominates
Reweight to exclude patients with EDSS 0	0.6008	0.0443	–30,298	Alemtuzumab dominates
Revised adjustment of mortality rate	0.6103	0.0326	–31,467	Alemtuzumab dominates
Revised proportion of patients hospitalized post relapse	0.5904	0.0446	–27,051	Alemtuzumab dominates
Combined base-case analysis	**0.0839**	**0.0065**	**2,648**	**31,575**

CDR = CADTH Common Drug Review; EDSS = Kurtzke Expanded Disability Status Scale; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Secondary CADTH Common Drug Review Reanalyses

Several other parameters of uncertainty were identified with the manufacturer's economic evaluation. These are briefly discussed below with reanalyses presented in Table 13 based on the revised CDR base case.

Miscalculations and Uncertainty With the Administration and Monitoring Costs

The manufacturer included infusion costs for alemtuzumab in the base-case analysis; however, there appeared to be a miscalculation with the costs. CDR recalculated the administration costs, which increased slightly, from $681 to $683. The manufacturer's PE report states that the monitoring costs were assumed to be $157 for each year for alemtuzumab (hematological consultation); however, the economic model reports a cost of $627 in year 1 and $535 in subsequent years. The model text offers no explanation of these costs and what components are included. Feedback from the CDR clinical expert and information from the Lemtrada product monograph[1] indicated that monitoring costs would also include the following tests: monthly complete blood counts, monthly creatinine levels, monthly urinalysis tests, and thyroid tests (four in year 1, three in subsequent years).

Costs for these tests were sourced from the Ontario Schedule of Benefits and Fees. Using these values, the cost of monitoring has been calculated to be $349 in year 1 and $335 in subsequent years. The revisions to the administration and monitoring costs resulted in a lower incremental cost-utility ratio (ICUR) for alemtuzumab compared with Rebif. Were kidney and liver test costs included, the total cost of monitoring is likely similar to the costs reported by the manufacturer.

Health State Utility Values

The manufacturer sourced health state utility values from Orme et al.[9] While the UK population used by the manufacturer to inform the utility values in the model may map better to health states in the submitted model, it is unclear as to the methodology used to determine the base utility values by Orme.

Thus, values from the CADTH Therapeutic Review of RRMS (originally from Prosser et al.)[11] were tested in CDR analysis.[10] A disutility of –0.085 was assumed for SPMS based on figures used by ScHARR.[27] Variation in health state utility values used has a substantial effect on the ICUR.

Relapse Disutility Values
The manufacturer indicated that utility loss for relapse for both hospitalized and non-hospitalized patients were based on studies by Orme et al.[9] (UK) and Prosser et al.[24] (US). The manufacturer indicated that Orme reported only one value for disutility due to relapse, but that Prosser reported disutilities for both hospitalization and non-hospitalization. The manufacturer reported the results for Orme correspond well with the non-hospitalization disutility reported by Prosser, and then derived a hospitalization disutility based on the Orme population.

Given the availability of the data from Prosser et al., and that these data for disutility due to relapse were used in the CADTH Therapeutic Review of RRMS, CDR undertook a reanalysis using the values from Prosser et al. reported in the CADTH Therapeutic Review of RRMS. Use of the revised disutilities had a minimal impact on the ICUR.

Duration of Relapse
The manufacturer reported that the mean duration of relapse (three months) was derived from a study by Orme et al.[9] CDR assumes that the reference to three months is based on the questionnaire performed by Orme that asked whether patients had relapsed in the past three months.

Given the ambiguity around the assumption that the duration of relapse is three months, CDR undertook reanalyses based on inference from an earlier article by McDonald et al.[12] who indicated a 30-day interval criterion separating relapses. Variation in duration of relapse had little effect on the ICUR.

Lower Withdrawal/Uptake Rate for Alemtuzumab in Year 3
CDR highlighted the uncertainty surrounding the assumptions of longer-term use of alemtuzumab earlier in the document.

CDR applied a revised uptake rate for alemtuzumab in year 3 based on the CARE-MS II trial ([redacted]%). Year 1 and 2 uptake rates remain the same as the CDR base-case reanalysis, and from year 4 onwards, the withdrawal rate for Rebif (16%) was applied to the proportion of alemtuzumab patients remaining on treatment after the previous year. The reduction of the use of alemtuzumab in year 3 (and thus, in later years) substantially alters the ICUR, with alemtuzumab dominating Rebif.

Inappropriate Use of a Mid-Cycle Correction
The manufacturer included a mid-cycle correction for all compared treatments, including alemtuzumab. However, while other treatments are dosed continuously over the year, alemtuzumab is administered as a yearly dosing regimen; thus, it is not appropriate to apply the mid-cycle correction to costs associated with treatment, as this would not be capturing costs borne up front in each year. CDR undertook an analysis excluding mid-cycle correction for alemtuzumab for both costs and effects; however, this is likely to overestimate the benefits associated with alemtuzumab in comparison with Rebif. Given the lack of transparency and cumbersome structure of the model, there is uncertainty with the results of this reanalysis.

CADTH Common Drug Review Exploratory Analysis: Treatment Waning

The manufacturer did not consider treatment waning within its base case, but considered several treatment waning scenarios within sensitivity analyses. In each of these scenarios, treatment waning was applied only to the alemtuzumab group.

Although CDR removed the manufacturer's unrealistic extension of benefit beyond treatment conclusion with the use of withdrawal rates, given the potential of treatment waning after use over a

longer time period, CDR applied a treatment waning effect to both treatment groups. CDR applied a rate suggested by the manufacturer in one of its sensitivity analysis: 100% in years 1, 2, and 3, 70% in years 4 and 5, 50% in years 6 to 9, and 30% from year 10 onwards. The results indicate the ICUR increased substantially with this amendment (Table 13).

TABLE 13: CADTH COMMON DRUG REVIEW ANALYSIS SUMMARY TABLE OF ICURS: ALEMTUZUMAB VERSUS REBIF

Alemtuzumab vs. Rebif	Difference in QALYs	Difference in Costs	ICUR vs. Rebif
CDR base case	0.0839	$2,648	$31,575
Sensitivity analyses on CDR base case			
Revised administration costs	0.0839	$2,071	$24,694
Revised health state utility values	0.0288	$2,648	$91,895
Revised relapse utility values	0.0853	$2,648	$31,034
Revised duration of relapse	0.0804	$2,648	$32,932
[redacted]% uptake rate (CARE-MS II) for alemtuzumab in year 3	0.0304	–$5,201	Alemtuzumab dominates Rebif
Exclude mid-cycle correction	0.3013	$4,095	$13,593
Exploratory analysis on CDR base case			
Inclusion of treatment waning	0.0243	$5,608	$231,233

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

REFERENCES

1. [Pr]Lemtrada™ (alemtuzumab): 12 mg/1.2 ml doses and administration [product monograph]. Mississauga (ON): Genzyme Canada; 2013 Dec 12.
2. Tuohy O, Costelloe L, Hill-Cawthorne G, Bjornson I, Harding K, Robertson N, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. J Neurol Neurosurg Psychiatry. 2014 May 21. Epub ahead of print.
3. Hartung HP, Arnold DL, Cohen JA, Coles AJ, Fox EJ, Giovannoni G, et al. Efficacy and safety of alemtuzumab in patients with relapsing-remitting MS who relapsed on prior therapy: Four-year follow-up of the CARE-MS II study. Poster presented at: 2014 Joint Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) - European Commitee for Treatment and Research in Multiple Sclerosis (EXTRIMS) Meeting. 2014 Sep 10-13; Boston (MA).
4. Common Drug Review. Submission status: Lemtrada (alemtuzumab) [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014 Aug 15. [cited 2015 Feb 26]. Available from: https://www.cadth.ca/sites/default/files/cdr/tracking/cdr_SR0355_Lemtrada.pdf
5. Blieden M, Huelin R, Travers K, Fahrbach K, Wissinger E, Strand L, et al. Mixed treatment comparison of the clinical efficacy and safety of disease-modifying therapies for multiple sclerosis in support of alemtuzumab **[CONFIDENTIAL** internal report**]**. Lexington (MA): Evidera; 2014.
6. Pharmacoeconomic evaluation. In: CDR submission: Lemtrada™ (alemtuzumab) 12 mg/1.2 mL concentrate for solution for intravenous (IV) infusion. Company: Genzyme Canada [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Genzyme Canada; 2014.
7. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):899-910.
8. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380:1829-39.
9. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health. 2007 Jan;10(1):54-60.
10. Canadian Agency for Drugs and Technologies in Health. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: CADTH; 2013. [cited 2015 Feb 26]. (CADTH therapeutic review, volume 1, issue 2b). Available from: http://www.cadth.ca/media/pdf/TR0004_RRMS_ScienceReport_e.pdf Updated March 2014.
11. Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Patient and community preferences for treatments and health states in multiple sclerosis. Mult Scler. 2003 Jun;9(3):311-9.
12. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001 Jul;50(1):121-7.
13. Freedman MS, Selchen D, Arnold DL, Prat A, Banwell B, Yeung M, et al. Treatment optimization in MS: Canadian MS Working Group Updated Recommendations. Can J Neurol Sci. 2013 May;40(3):307-23.
14. Liste de médicaments publiée par la Régie de l'assurance maladie du Québec [Internet]. Quebec: Régie de l'assurance maladie Québec; 2015. [cited 2015 Mar 15]. Available from: http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/medicaments/liste-medicaments55.pdf

15. Chilcott J, McCabe C, Tappenden P, O'Hagan A, Cooper NJ, Abrams K, et al. Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosis. Commentary: evaluating disease modifying treatments in multiple sclerosis. BMJ. 2003 Mar 8;326(7388):522.

16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

17. CDR submission: Lemtrada™ (alemtuzumab) 12 mg/1.2 mL concentrate for solution for intravenous (IV) infusion. Company: Genzyme Canada [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Genzyme Canada; 2014 Nov.

18. Haas J, Hartung HP, von Rosenstiel P, Karlsson G, Tang DJ, Francis G, et al. Fingolimod reduces the number of severe relapses in patients with relapsing multiple sclerosis: Results from phase III TRANSFORMS and FREEDOMS studies [Internet]. Poster presented at: ENS 2011. Twenty-first meeting of the European Neurological Society, May 28-31st 2011; 2011; Lisbon (PT). [cited 2015 Mar 19]. Available from: http://f1000.com/posters/browse/summary/1550

19. Patzold U, Pocklington PR. Course of multiple sclerosis. First results of a prospective study carried out of 102 MS patients from 1976-1980. Acta Neurol Scand. 1982 Apr;65(4):248-66.

20. Held U, Heigenhauser L, Shang C, Kappos L, Polman C, Sylvia Lawry Centre for MS Research. Predictors of relapse rate in MS clinical trials. Neurology. 2005 Dec 13;65(11):1769-73.

21. Fleurence RL, Hollenbeak CS. Rates and probabilities in economic modelling: transformation, translation and appropriate application. PharmacoEconomics. 2007;25(1):3-6.

22. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. J Insur Med. 1997;29(2):101-6.

23. Sadovnick AD, Ebers GC, Wilson RW, Paty DW. Life expectancy in patients attending multiple sclerosis clinics. Neurology. 1992 May;42(5):991-4.

24. Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Cost-effectiveness of interferon beta-1a, interferon beta-1b, and glatiramer acetate in newly diagnosed non-primary progressive multiple sclerosis. Value Health. 2004 Sep;7(5):554-68.

25. Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (TRIBUNE) in multiple sclerosis: the costs and utilities of MS patients in Canada. J Popul Ther Clin Pharmacol. 2012;19(1):e11-e25.

26. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis (draft) [Internet].London; 2012 Sep 20. European Medicines Agency. [cited 2015 Feb 24]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133438.pdf

27. MS appraisal addendum to ScHARR final report on economic modelling [Internet]. London: National Institute for Health and Clinical Excellence; 2002. [cited 2015 Feb 26]. Available from: http://www.nice.org.uk/guidance/ta32/documents/addendum-to-scharr-report2