Common Drug Review
Pharmacoeconomic Review Report

July 2017

Drug	Daclizumab (Zinbryta)
Indication	For the treatment of adult patients with active relapsing-remitting multiple sclerosis who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis.
Reimbursement request	As per indication
Dosage form(s)	1.0 mL pre-filled pen or syringe, 150 mg/mL
NOC Date	December 8, 2016
Manufacturer	Biogen Canada Inc.

TABLE OF CONTENTS

ABBREVIATIONS i
EXECUTIVE SUMMARY 1
INFORMATION ON THE PHARMACOECONOMIC SUBMISSION 3
1. Summary of the Manufacturer's submission 3
2. Manufacturer's Base Case 4
3. Limitations of Manufacturer's Submission 4
4. CADTH Common Drug Review Reanalyses 5
5. Issues for Consideration 7
6. Patient Input 7
7. Conclusions 8
APPENDIX 1: COST COMPARISON 9
APPENDIX 2: ADDITIONAL INFORMATION 11
APPENDIX 3: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUGS 12
APPENDIX 4: REVIEWER WORKSHEETS 14
REFERENCES 40

Tables

Table 1: Summary of the Manufacturer's Economic Submission ii
Table 2: Sequential Analysis of All Comparators 5
Table 3: Cost Comparison Table for the Treatment of Relapsing-Remitting Multiple Sclerosis 9
Table 4: Submission Quality 11
Table 5: Authors' Information 11
Table 6: Other Health Technology Assessment Findings (NICE and PBAC) 12
Table 7: Data Sources 14
Table 8: Manufacturer's Key Assumptions 17
Table 9: Manufacturer's Base Case Results — Daclizumab Versus Fingolimod 17
Table 10: Manufacturer's Base-Case Results — Daclizumab Versus Interferon (Avonex) 18
Table 11: Manufacturer's Base-Case Results — Daclizumab Versus Interferon (Betaferon) 18
Table 12: Manufacturer's Base-Case Results — Daclizumab Versus Interferon (Extavia) 18
Table 13: Manufacturer's Base-Case Results — Daclizumab Versus Glatiramer Acetate 18
Table 14: Manufacturer's Base-Case Results — Daclizumab Versus Dimethyl Fumarate 18
Table 15: Manufacturer's Base-Case Results — Daclizumab Versus Teriflunomide 19
Table 16: Manufacturer's Base-Case Results — Daclizumab Versus Natalizumab 19
Table 17: Manufacturer's Base-Case Results — Daclizumab Versus Alemtuzumab 19
Table 18: Manufacturer's Base-Case Results — Daclizumab Versus Interferon (Rebif 44) 19
Table 19: Sequential Analysis of All Comparators Excluding Alemtuzumab and Natalizumab 20
Table 20: Sequential Analysis of All Comparators Excluding Interferons, Alemtuzumab and Natalizumab 20

Figure

Figure 1: Manufacturer's Model Structure 14

ABBREVIATIONS

AE	adverse event
DAC	daclizumab
DMT	disease-modifying therapy
EDSS	Kurtzke Expanded Disability Status Scale
IFN	Interferon
MS	multiple sclerosis
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	Daclizumab beta (Zinbryta)
Study Question	"The primary objective of this analysis was to estimate the cost-effectiveness of Zinbryta compared with Gilenya in the treatment of patients with relapsing-remitting multiple sclerosis (RRMS) in Canada."
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with RRMS in Canada
Treatment	Daclizumab beta 150 mg subcutaneous every month
Outcome	QALYs
Comparators	• Fingolimod 500 mcg oral once daily The following were considered in sensitivity analyses but not in the base case: • IFN beta-1a (Avonex) 30 mcg intramuscular once weekly • IFN beta-1a (Rebif) 44 mcg subcutaneous 3 times weekly • IFN beta-1b (Betaferon) 250 mcg subcutaneous every other day • IFN beta-1b (Extavia) 250 mcg subcutaneous every other day • glatiramer acetate 20 mg subcutaneous once daily • dimethyl fumarate 240 mg oral twice daily • teriflunomide 14 mg oral once daily • natalizumab 300 mg intravenous infusion every four weeks • alemtuzumab 12 mg intravenous daily
Perspective	Canadian public payer
Time Horizon	25 years
Results for Base Case	• Daclizumab dominated fingolimod — daclizumab costs less and produces more QALYs. The probability that daclizumab was cost-effective assuming a threshold of $50,000 per QALY was 90%. **When considering all comparators:** • Daclizumab is dominated by alemtuzumab. • Compared with all IFN formulations, teriflunomide, glatiramer acetate, and dimethyl fumarate, daclizumab is estimated to be more costly and more effective with incremental cost per QALYs exceeding $50,000 (range: $54,565 to $174,026 per QALY). • In a sequential analysis, considering all comparators, alemtuzumab was dominant over all comparators. The probability that daclizumab was cost-effective given a threshold of $50,000 per QALY was 0%.
Key Limitations	• The primary limitation with the submitted analysis was the failure to present the results in a sequential manner, considering all relevant comparators in the base case. • The submitted model lacked transparency, which proved challenging to validate. • Certain assumptions relating to monitoring and administration costs did not appear appropriate for the Canadian setting, but are unlikely to significantly affect the results.
CDR Estimate(s)	• When considering all comparators, alemtuzumab dominates all therapies including daclizumab in that it is associated with lower total costs and greater QALYs. The probability that daclizumab is cost-effective given a threshold of $50,000 per QALY was 0%. • When excluding alemtuzumab and natalizumab, and comparing daclizumab to all moderately or modestly effective therapies, daclizumab would be cost-effective if a decision-maker was willing to pay $174,026 per QALY. The

	probability that daclizumab is cost-effective given a threshold of $50,000 per QALY was 0.6%. • When excluding alemtuzumab and natalizumab and all IFNs — and comparing daclizumab with fingolimod, glatiramer acetate, dimethyl fumarate, and teriflunomide — daclizumab would be cost-effective if a decision-maker was willing to pay $174,026 per QALY. The probability that daclizumab is cost-effective given a threshold of $50,000 per QALY was 1.9%.

CDR = CADTH Common Drug Review; IFN = interferon; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

EXECUTIVE SUMMARY

Background

Daclizumab beta (Zinbryta, DAC) is a humanized, monoclonal antibody directed against the interleukin-2 receptor. DAC beta is indicated for the treatment of adult patients with active relapsing-remitting multiple sclerosis (RRMS) who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis (MS).[1] DAC is available as a pre-filled syringe or pen solution for subcutaneous injection (150 mg per 1 mL). At a recommended dose of 150 mg subcutaneous once monthly and a manufacturer–submitted market price of $2,308 per 150 mg pre-filled pen or syringe, DAC costs $27,700 per year.[2] The manufacturer's listing request is per the Health Canada indication.[2]

The manufacturer submitted a cost-utility analysis based on a Markov state-transition model comparing DAC with fingolimod for the treatment of adult patients with RRMS.[3] Further comparisons were made against different interferon (IFN) beta-1 formulations (Avonex, Betaferon, Extavia, Rebif 44), biologics (alemtuzumab, natalizumab), and other injectable and oral disease-modifying therapies (DMTs: glatiramer acetate, dimethyl fumarate, and teriflunomide). Patients transitioned between different Kurzke Expanded Disability Status Scale (EDSS) levels (0 to 9) and could progress from RRMS to secondary-progressive MS (SPMS). The analysis used a 25-year horizon and was undertaken from the public health care payer perspective.[3] Data on baseline disease progression and relapses were derived from the placebo arm of the pivotal SELECT trial, the British Columbia MS database, London Ontario database, and UK MS Survey.[4-6] The effects of treatment on disease progression and relapse rates were derived from a manufacturer-commissioned mixed treatment comparison.[7]

The manufacturer reported that DAC dominated fingolimod as it produced more quality-adjusted life-years (QALYs) and costs less. When compared with all treatments, DAC was dominated by alemtuzumab. DAC was more effective and more costly than all IFNs, glatiramer, dimethyl fumarate, and teriflunomide. The incremental cost per QALY gained for DAC in each of these comparisons was greater than $50,000 (range: $54,565 to $174,026). Natalizumab was more costly and more effective than DAC; no incremental cost per QALY gained was reported by the manufacturer.

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified several limitations of the manufacturer's analysis. The most notable limitation was the failure to present a sequential analysis considering all comparators simultaneously as the base case. The indication for DAC and the listing request, biologics, glatiramer, dimethyl fumarate, and teriflunomide are all relevant comparators for the base case. When considering all treatments simultaneously, alemtuzumab is the optimal treatment in that it dominates all other therapies — it is more effective and less costly.

When excluding alemtuzumab and natalizumab as comparators — only considering IFNs, fingolimod, glatiramer, dimethyl fumarate, and teriflunomide — DAC would only be considered cost-effective if a decision-maker was willing to pay $174,026 per QALY gained. When further excluding IFNs (assuming patients have tried IFNs as initial treatment) — comparing DAC to fingolimod, glatiramer, dimethyl fumarate, and teriflunomide — again, DAC would only be considered cost-effective if a decision-maker was willing to pay $174,026 per QALY gained.

Thus, presenting results against fingolimod alone does not fully capture the cost-effectiveness of DAC for treating RRMS.

There were a number of limitations with the manufacturer's model concerning assumptions related to utility values as well as monitoring and administration costs; however, given the manufacturer's reported finings with respect to the cost-effectiveness of DAC highlighted above, these are unlikely to significantly affect the results.

Conclusions

Using the manufacturer's base-case analysis, while DAC dominates fingolimod, it is dominated by alemtuzumab (DAC is more costly and less effective) and is associated with an incremental cost greater than $50,000 per QALY when compared with all IFN formulations, glatiramer, dimethyl fumarate, and teriflunomide.

Further CDR reanalyses restricting the number of comparator therapies, to consider therapies that could be considered after more effective therapies, showed that DAC was not cost-effective unless a decision-maker was willing to pay at least $174,026 per QALY gained.

When alemtuzumab is included as a comparator, the price of DAC would have to be reduced by 83.6% for it to be considered cost-effective if a decision-maker was willing to pay $50,000 per QALY gained. When alemtuzumab is not included as a comparator, the price of DAC would have to be reduced by 25.1% for it to be considered cost-effective if a decision-maker was willing to pay $50,000 per QALY gained.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S SUBMISSION

Description of Analysis

The manufacturer submitted a cost-utility analysis comparing daclizumab (DAC) beta to fingolimod among adult patients with relapsing-remitting multiple sclerosis (RRMS).[3] Further results were provided as sensitivity analyses, comparing DAC with interferon (IFN) beta-1 formulations (Avonex, Betaferon, Extavia, Rebif 44), biologics (alemtuzumab, natalizumab) and other injectable and oral disease-modifying therapies (DMTs; glatiramer acetate, dimethyl fumarate, teriflunomide). The cost-utility analysis was based on a Markov state-transition model using a 25-year horizon and one-year cycle length to which a half-cycle correction was applied. All costs and outcomes were discounted at a rate of 5% annually and the analysis was undertaken from the perspective of the Canadian publicly funded health care system.[3]

The model tracks disease progression, where patients transition between Kurzke Expanded Disability Status Scale (EDSS) levels (0 to 9), move from RRMS to secondary-progressive multiple sclerosis (SPMS), and death (Figure 1). Death was captured separately from the EDSS-based states to allow for increasing mortality risk with age. The model was designed such that results are only available pairwise comparisons (DAC compared with another treatment); it did not allow for the comparison of all treatments simultaneously. The model population was assumed to have patient characteristics similar to those in the SELECT trial, with a mean age of 36 years old, 65% female and with a mean EDSS score of 2.96.[4]

The model consisted of 21 states in total (Figure 1). Twenty of these states captured the combination of EDSS level (0, 1 to 1.5, 2 to 2.5, 3 to 3.5, 4 to 4.5 … 9 to 9.5) and disease phase (RRMS or SPMS). There was also a separate death state. Patients entering the model received either DAC or fingolimod (in the manufacturer's base case). At the end of each year, patients could experience disease progression (EDSS increase), remain at their current level of disease activity, or move to the death state. Patients experiencing an EDSS increase could also move to SPMS. Further, data on the occurrence of relapses and adverse events (AEs) were tracked. Patients were assumed to discontinue treatment at a constant value of 15% per year, encompassing all-cause discontinuation (i.e., loss of efficacy, onset of AEs, etc.) based on the value used in CADTH's therapeutic review of DMTs in RRMS.[8] Patients were further assumed to discontinue treatment upon reaching an EDSS score of greater than 5 or progressing to SPMS.

The natural history rates of disease progression and conversion from RRMS to SPMS were informed by the placebo arm of the SELECT trial, the British Columbia MS database, and the London, Ontario database.[4-6] Natural history annualized relapse rate was informed by the UK MS Survey as well as British data from Patzold and Pocklington.[9,10] Treatment effects on disease progression and relapse rates were informed by manufacturer's mixed treatment comparison.[7] The drug-specific annual incidence of AEs were derived from the pivotal clinical trials for each drug as referenced in the manufacturer's economic submission.[3] Mortality rates were determined by age, sex, and EDSS level. While age– and sex-specific mortality rates were informed by data from Statistics Canada,[11] MS-specific and EDSS-specific rate ratios were derived from literature sources.[12,13]

Health state utilities in the model were based on disease severity (as measured by EDSS), disease phase (RRMS or SPMS), and whether or not patients relapsed. AEs were associated with disutilities that were informed by a mixture of literature sources[14-21] and input from key opinion leaders. Costs included were those for disease management (excluding costs of DMTs and relapses), administration and monitoring costs, and drug acquisition. Costs of treating AEs were derived from the patient cost estimator published by the Canadian Institute for Health Information.[22]

2. MANUFACTURER'S BASE CASE

The manufacturer reported in their base case that DAC was associated with a cost of $286,977 and 6.03 QALYs. DAC was $10,601 less costly and associated with a gain of 0.22 QALYs when compared with fingolimod, making it an economically dominant option.

Summary of Manufacturer's Sensitivity Analyses

In a secondary analysis, the manufacturer compared DAC against each of the other comparators.

DAC was dominated by alemtuzumab. DAC was more effective and more costly than all IFN formulations, glatiramer, dimethyl fumarate, and teriflunomide — and was associated with an incremental cost per QALY gained ranging from $54,565 (versus Avonex) to $174,026 per QALY (versus teriflunomide). DAC was less costly and less effective than natalizumab; the manufacturer did not report an incremental cost-effectiveness ratio. The manufacturer did not report a sequential analysis as their base case, instead reporting only on pairwise comparisons (Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, Table 16, Table 17, and Table 18).

The manufacturer conducted both one-way sensitivity analyses and a probabilistic sensitivity analysis. The one-way sensitivity analyses showed that the effect of treatment on disability progression had consistently the largest impact on results, as were assumptions regarding waning of treatment efficacy and the utility of the RRMS states. The manufacturer reported that in the probabilistic sensitivity analysis, DAC had a 90% chance of being cost-effective when compared with fingolimod based on 5,000 simulations.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Failure to Present a Sequential Analysis Considering All Comparators in the Base Case

The manufacturer provided base-case results comparing DAC to fingolimod; however, for the proposed indication and likely place in therapy (i.e., failure of previous DMTs and use as a second– or third-line agent), all comparators considered in secondary analyses should have been considered in the base case. Failure to consider all relevant comparators does not provide sufficient information on the cost-effectiveness of DAC, and instead results provide a misleading assessment.

Lack of Transparency and Functionality of the Manufacturer's Submitted Model

The model had numerous issues that made validation and evaluation more difficult than it needed to be. Coding was overly complicated and lacked transparency. Despite a number of requests by CADTH for the manufacturer to provide the results for all comparators simultaneously, run probabilistically, and with sequential incremental cost-effectiveness ratios, the manufacturer was unable to provide this information. The numerous problems with model functionality required multiple requests to correct,

including a nonfunctional sequential analysis macro and multiple nonfunctional probabilistic sensitivity analysis macros.

Concerns with Data Inputs

There were a number of limitations with the model concerning assumptions related to monitoring and administration costs. Namely, the assumptions regarding neurologist visits, and the number and types of tests that patients would undergo as part of monitoring, appear to be biased in favour of DAC.

In particular:

- Patients on DAC have one neurologist visit in the first year and no further visits, while patients receiving all other drugs require four visits in the first year and one or four in subsequent years. The clinical expert noted that patients on DAC would likely have four visits in the first year and two to four visits in subsequent years.
- Patients on DAC only undergo a complete blood count as part of their monitoring, similar to patients receiving IFNs and glatiramer; however, all other treatments are associated with a variety of additional tests. The clinical expert noted that patients would undergo blood tests and liver function tests in addition to an annual MRI.

Given the negative findings with respect to the cost-effectiveness of DAC, these limitations are unlikely to significantly affect the results.

4. CADTH COMMON DRUG REVIEW REANALYSES

The focus of the manufacturer's base-case results are for the comparison of DAC and fingolimod, which provides a misleading assessment of the cost-effectiveness of DAC for the treatment of RRMS.

Given concerns with the model and issues with running probabilistic analyses of all treatment simultaneously, CADTH did not conduct reanalyses considering changes to model parameters, but rather considered a sequential analysis of cost-effectiveness. This represents best practices when there are more than two interventions being considered, as it allows for the identification of therapies that are subject to dominance or extended dominance.

Three separate set of combinations of comparators were considered based on clinician input and suggested place in therapy:

1. All comparators: DAC, fingolimod, IFNs (Avonex, Betaferon, Extavia, Rebif 44), alemtuzumab, natalizumab, glatiramer, dimethyl fumarate, and teriflunomide
2. All comparators excluding highly effective therapies (i.e., alemtuzumab and natalizumab): DAC, fingolimod, IFNs (Avonex, Betaferon, Extavia, and Rebif 44), glatiramer, dimethyl fumarate, and teriflunomide
3. All comparators excluding highly effective therapies and interferons: DAC, fingolimod, glatiramer, dimethyl fumarate, and teriflunomide.

All Comparators

When considering all comparators, alemtuzumab is dominant over all other therapies in that it is more effective and less costly (Table 2). The probability that DAC would be cost-effective at a threshold of $50,000 per QALY was 0%.

TABLE 2: SEQUENTIAL ANALYSIS OF ALL COMPARATORS

	QALYs	Cost	Incremental Cost per QALY Gained Versus Alemtuzumab	Sequential Incremental Cost per QALY Gained
Alemtuzumab	6.673	$216,297	NA	NA
Dominated strategies				
Extavia	5.443	$239,924	Dominated by alemtuzumab	Dominated by alemtuzumab, glatiramer
Betaferon	5.443	$245,429	Dominated by alemtuzumab	Dominated by alemtuzumab, glatiramer, Extavia
Glatiramer	5.509	$232,520	Dominated by alemtuzumab	Dominated by alemtuzumab
Avonex	5.602	$264,105	Dominated by alemtuzumab	Dominated by teriflunomide, alemtuzumab
Fingolimod	5.676	$293,487	Dominated by alemtuzumab	Dominated by alemtuzumab, teriflunomide, dimethyl fumarate, Rebif, daclizumab
Teriflunomide	5.718	$253,841	Dominated by alemtuzumab	Dominated by alemtuzumab
Dimethyl fumarate	5.784	$266,180	Dominated by alemtuzumab	Dominated by alemtuzumab
Rebif	5.823	$275,483	Dominated by alemtuzumab	Dominated by alemtuzumab
Daclizumab	**5.888**	**$283,401**	**Dominated by alemtuzumab**	**Dominated by alemtuzumab**
Natalizumab	5.983	$359,100	Dominated by alemtuzumab	Dominated by alemtuzumab

NA = not available; QALY = quality-adjusted life-year.

All Comparators Excluding Alemtuzumab and Natalizumab

When considering all comparators except alemtuzumab and natalizumab, three comparators could be cost-effective dependent on a decision-maker's willingness to pay for a QALY: glatiramer acetate, teriflunomide and DAC. DAC would be cost-effective only if a decision-maker was willing to pay $174,026 per QALY gained (Table 19). The probability that DAC would be cost-effective at a threshold of $50,000 per QALY was 0.6%.

All Comparators Excluding Interferons, Alemtuzumab, and Natalizumab

When considering all comparators except IFNs, alemtuzumab, and natalizumab, the same three comparators could be cost-effective dependent on a decision-maker's willingness to pay for a QALY: glatiramer acetate, teriflunomide, and DAC. DAC would again only be cost-effective only if a decision-maker was willing to pay $174,026 per QALY gained (Table 20). The probability that DAC would be cost-effective at a threshold of $50,000 per QALY was 1.9%.

Price-reduction scenarios related to the impact on the three specific scenarios above. Analysis is presented in terms of under what conditions DAC would be considered cost-effective based on a threshold of $50,000 per QALY gained.

When including all comparators, DAC would be cost-effective given a threshold of $50,000 per QALY gained if the price was reduced by 83.6%. Under such a price reduction, alemtuzumab would be more

effective and more costly than DAC and the incremental cost per QALY gained for alemtuzumab versus DAC would be greater than $50,000. Thus, DAC would not be more effective than alemtuzumab; rather, given the additional cost required for the additional QALYs gained by alemtuzumab, it would not be considered cost-effective.

When excluding the highly effective therapies (natalizumab and alemtuzumab), DAC would be cost-effective given a threshold of $50,000 per QALY gained if the price was reduced by 25.1% regardless of whether the IFNs were included. Under such a price reduction, DAC would be more effective and more costly than glatiramer with an incremental cost per QALY gained of $50,000. DAC would dominate teriflunomide, dimethyl fumarate, fingolimod, and IFN regimens.

5. ISSUES FOR CONSIDERATION

Ocrelizumab is another monoclonal antibody that may become available on the Canadian market in the near future. In its pivotal trials,[23] it displayed a comparable hazard ratio to Rebif 44 (hazard ratio: 0.54 [ocrelizumab versus Rebif 44] versus 0.56 [DAC versus Avonex]) and demonstrates a more favourable hazard ratio when considering disability progression at three months (hazard ratio: 0.60 [ocrelizumab versus Rebif 44] versus 0.84 [DAC versus Avonex]). Of note, Rebif 44 has demonstrated higher efficacy than Avonex in terms of relapse prevention and MRI parameters.[24] Thus, even when considering biologics, DAC may not be an optimal treatment choice.

Subsequent entry glatiramer may be available soon. This would require the price reduction for DAC to be even higher than previously suggested.

6. PATIENT INPUT

Input was received from the Multiple Sclerosis Society of Canada. Patients noted that MS is an unpredictable and often disabling disease with a diverse symptomatology. Given that onset is during peak economic, schooling, and interpersonal life, MS exerts a significant impact on all aspects of life including quality of life, psychosocial functioning, and the ability to maintain employment and undertake the activities of daily living. This was accounted for by including progressively lower utilities with increasing EDSS level. Patients also noted that there is a substantial burden on caregivers (emotional, physical, financial, time commitment). Caregiver burden was not accounted for in the model.

Patients noted that a number of DMTs are available in addition to symptomatic therapy and non-pharmacological options. Side effects were generally well managed with over-the-counter options; however, patients noted that it is important to have more options available given that not all drugs work for all people. The majority of patients (97%) indicated that they had no experience with the drug and only one patient indicated that they wanted to switch to it if the option becomes available. Anticipated benefits of DAC include not having to go for infusion and a potentially lower risk of progressive multifocal leukoencephalopathy compared with other DMTs.

7. CONCLUSIONS

Sequential analyses based on the manufacturer's base-case results found that DAC was not cost-effective when all treatment regimens were considered. In particular, alemtuzumab was a dominant option when considering all comparators. Where alemtuzumab is a treatment option, DAC would require a price reduction of 83.6% for it to be considered cost-effective if a decision-maker was willing to pay $50,000 per QALY gained. If alemtuzumab was not considered a treatment option through contraindication, DAC may be considered cost-effective if a price reduction of 25.1% can be obtained.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 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 THE TREATMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Weekly Drug Cost ($)	Average Annual Drug Cost ($)
Daclizumab beta (Zinbryta)	**150 mg**	**SC syringe/pen**	**2,308.3333**	**150 mg monthly**	**533**	**27,700**
Other interferons						
Peg-interferon beta-1a (Plegridy)	63 mcg 94 mcg 125 mcg	SC syringe/pen	856.2600	Every two weeks: Dose 1: 63 mcg Dose 2: 94 mcg Dose 3 and thereafter: 125 mcg	428	22,263
Interferon beta-1a (Avonex)	30 mcg/0.5 mL (6 MIU)	Pre-filled syringe or pen	423.3925	30 mcg IM per week	423	22,016
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	20,020
Interferon beta-1b (Extavia)	0.3 mg (9.6 MIU) powder for injection	Single-use vial	102.3400	0.25 mg SC every other day	358	18,626
Interferon beta-1a (Rebif)	22 mcg/0.5 mL (6 MIU) 44 mcg/0.5 mL (12 MIU)	Pre-filled syringe, cartridge or pen	131.4202 159.9904	22 mcg 44 mcg SC 3 times weekly	394 480	20,502 24,959

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Weekly Drug Cost ($)	Average Annual Drug Cost ($)
Biologics						
Alemtuzumab (Lemtrada)	12 mg/1.2 mL	IV solution	1,045.8333 per mg	12 mg/day for five days followed by 12 mg/day for 3 days after 12 months	Weekly average, year 1: 1,207; year 2: 724	Year 1: 62,750; year 2: 37,650
Natalizumab (Tysabri)	300 mg/15 mL	IV solution	3,295.8900	300 mg IV infusion every 4 weeks	824	42,847
Other Injectable Immunomodulatory						
Glatiramer (Copaxone)	20 mg/mL	Pre-filled syringe	44.4960	20 mg SC daily	311	16,197
Oral medications						
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: 24,293; subsequent years: 24,528
Fingolimod (Gilenya)	0.5 mg	Capsule	85.1650	0.5 mg daily	596	31,000
Teriflunomide (Aubagio)	14 mg	Tablet	55.6875	14 mg daily	390	20,270

IM = intramuscularly; IV = intravenous; MIU = million international units; peg = pegylated; SC = subcutaneous.
Note: Drug prices are taken from the Ontario Formulary Exceptional Access Program (March 2017) unless otherwise indicated and do not include prescription fees, costs of dose preparation, or injection administration. Annual period assumes 52 weeks, or 13*4 weeks per year (364 days for all comparators).

APPENDIX 2: ADDITIONAL INFORMATION

TABLE 4: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	As noted in the limitations section, there were numerous problems with the model and the coding was cumbersome.		
Was the material included (content) sufficient?			X
Comments	CADTH made multiple requests to the manufacturer to include necessary material to evaluate the submission. There were no citations for specific publications from the London Ontario or British Columbia databases. While these are standard data sources, there are multiple publications available.		
Was the submission well organized and was information easy to locate?			X
Comments	Many pages in the pharmacoeconomic report were "page 1," which made it cumbersome to retrieve specific pieces of information. Results were not consolidated in any single location given the choice to report pairwise comparisons exclusively. As such, information was at times difficult to find. Responses to requests for additional information did not include updated sections of the report, at times making it unclear as to which results should be used.		

TABLE 5: 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 HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUGS

The cost-effectiveness of daclizumab for the treatment of active RRMS has previously been assessed by international Health Technology Assessment organizations, including the National Institute for Health and Care Excellence (NICE)[25] in the UK and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia.[26] The NICE and PBAC reviews are summarized in Table 6.

Daclizumab is also being reviewed by the Scottish Medicines Consortium[27] in the UK for the treatment of relapsing forms of multiple sclerosis (MS); however, SMC advice relating to this product is not yet publicly available.

TABLE 6: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS (NICE AND PBAC)

	NICE (March 2017)[25]	PBAC (July 2016, November 2017)[26]
Treatment	DAC (Zinbryta), 150 mg once monthly	DAC (Zinbryta), 150 mg monthly
Price	£1,596.67 per pre-filled syringe	Price information was redacted
Indication/ request	Tx of relapsing forms of MS in adult patients	Authority required PBS listing for DAC for the Tx of RRMS
Comparator(s)	Untreated active disease: IFN, GA, DF, TER, AL Previous Tx active disease: DF, TER; AL Rapidly evolving severe disease: natalizumab, AL Highly active disease despite previous Tx: fingolimod, AL	Fingolimod 0.5 mg once daily
Similarities with CDR submission	• CUA • Efficacy inputs based on SELECT and DECIDE, as well as MTC	• Main Tx comparator was fingolimod • Efficacy inputs based on SELECT and DECIDE, and ITC with fingolimod using either placebo or IFN beta-1 as common comparator (FREEDOMS, FREEDOMS-II, TRANSFORMS trials)
Differences with CDR submission	• Markov cohort model based on four patient subgroups (two groups with active disease, and two groups with rapidly evolving disease) • Waning of Tx effect considered in base case and applied equally for all comparators • Trial-based Tx stopping rates applied in first three years, then extrapolated	• Cost-comparison analysis • Model did not consider comparators other than fingolimod
Manufacturer's results	Cost-effectiveness results not reported owing to confidentiality of comparator discounts	Cost comparison results redacted owing to confidentiality
Issues noted by the review group	• Investment costs, community, and social care costs not modelled; NHS and PSS are likely to pay for some of these costs • Model assumed that transitioning to secondary-progressive disease was associated with a 1.0-point worsening in EDSS • Model did not incorporate a utility	• Unclear clinical place for DAC; comparison with fingolimod uncertain • Substantial uncertainty with ITC results • Injectable therapies may be appropriate comparators, likely replaced by DAC • Cost comparison not justified, unsupported claim of noninferior for safety

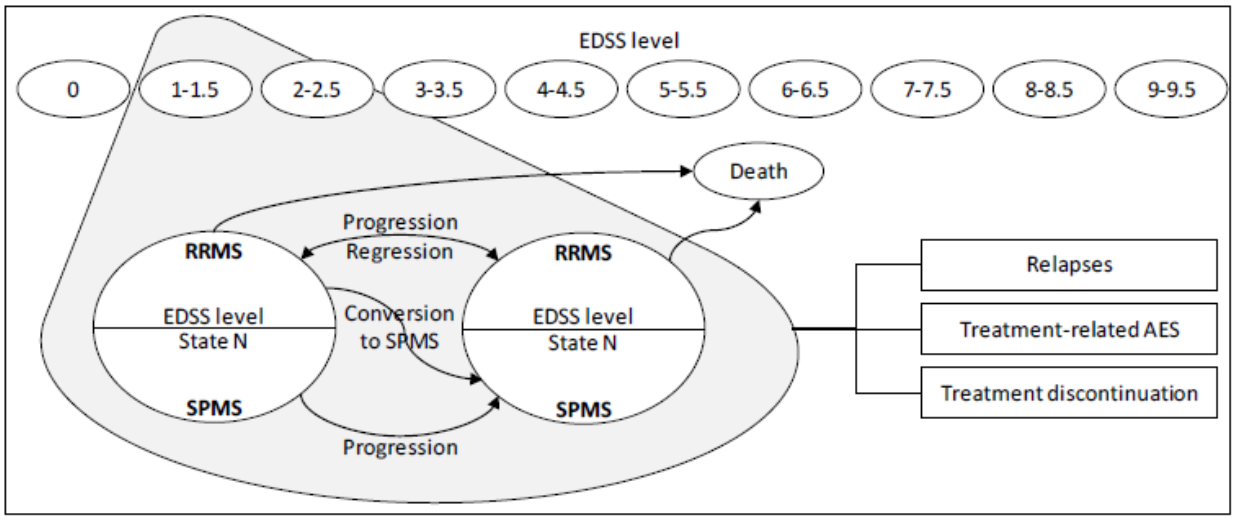
	NICE (March 2017)[25]	PBAC (July 2016, November 2017)[26]
	decrement for caregiver burden	• DAC 150 mg likely administered every 28 days vs. monthly intervals
Review group reanalysis results	***When AL is an option:*** • Untreated active disease and rapidly evolving severe disease: AL dominated DAC • Previous Tx active disease: £789 saved per QALY lost for DAC vs. AL • Highly active disease despite previous Tx: £18,004 per QALY gained for AL vs. DAC (AL more cost-effective vs. DAC in incremental analysis) ***When AL is contraindicated/unsuitable:*** • Untreated active disease: above £30,000 per QALY gained for DAC vs. IFNs, GA, DF, TER • Previously Tx active disease: between £20,000 and £30,000 per QALY gained for DAC vs. DF • Highly active disease despite previous Tx: less than £20,000 saved per QALY lost for DAC vs. fingolimod • Rapidly evolving severe disease: DAC dominated natalizumab	None reported
Recommendation	**Recommended** for treating MS in adults, only if: • active RRMS previously Tx with DMT or rapidly evolving severe RRMS (i.e., at least two relapses in previous year and at least one gadolinium-enhancing lesion at baseline MRI) • AL is contraindicated or otherwise unsuitable • company provides drug with discount agreed in patient access scheme	July 2016: **Deferred** listing decision owing to unclear clinical place of DAC pending the finalization of TGA registration, resulting in uncertainty in choice of comparator and any possible restriction November 2016 (minor submission): **Recommended** listing of DAC based on claims of likely superiority to IFN beta-1a and possible noninferiority to fingolimod according to direct and indirect comparisons, respectively

AL = alemtuzumab; CUA = cost-utility analysis; DAC = daclizumab; DF = dimethyl fumarate; DMT = disease-modifying therapy; EDSS = Kurzke Expanded Disability Status Scale; GA = glatiramer acetate; HTA = Health Technology Assessment; ICER = incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; ITC = indirect treatment comparison; MRI = magnetic resonance imaging; MS = multiple sclerosis; MTC = mixed treatment comparison; NHS = National Health Service; PBS = Pharmaceutical Benefits Scheme; PSS = Personal Social Services; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TGA = Therapeutic Goods Administration; Tx = treatment.

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



AE = adverse event; EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis; State N, current EDSS state
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 7: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Effects of treatment on disability progression and relapse rates were derived from the manufacturer's MTC.[7] Disability progression was measured in terms of cumulative disability progression at six months where available; when unavailable, disability progression at three months was used. The efficacy of DAC itself was assessed by two pivotal phase III clinical trials, SELECT (placebo-controlled) and DECIDE (Avonex as active comparator).[4,28]	As noted in CDR's clinical review, there were numerous issues identified with the MTC, including heterogeneity in patient populations, differences in trial inclusion/exclusion criteria, and inconsistent or absent reporting of key data in the included studies. A concern with the trials is the large proportion of treatment-naive patients and the inclusion of a population less severe than what might be assessed in clinical practice.
Natural history	**Transition probabilities between RRMS EDSS levels** were derived from the placebo arm of the SELECT trial and data from the British Columbia MS database.[4,5] **Transition probabilities between SPMS EDSS levels** were derived from the London, Ontario data set.[6]	These were noted to be standard, widely used sources that have been used in previous publications, including CADTH's therapeutic review.[8] Concerns included the presence of non-RRMS in the London, Ontario registry and the public unavailability of data from MS databases for verification.

Data Input	Description of Data Source	Comment
	ARRs for both RRMS and SPMS patients were derived from the UK MS Survey and data from Patzold and Pocklington.[9,10]	
Utilities	Utility scores by EDSS levels came from British literature values collected as part of a UK cost-of-illness study.[9] AE-related disutilities were informed by literature values[14-21] and expert opinion input.	Alternative utility values are available from CADTH's therapeutic review of MS drugs;[8] however, use of these values does not materially affect results. Technique for elicitation of expert opinion for AE disutilities was not explained. The appropriateness of the literature sources was unclear, although sensitivity analyses revealed that disutilities did not impact results.
Resource use	Includes costs of direct disease management, drug acquisition, administration, monitoring, relapses, and AE management costs. Disease-management costs are input by EDSS level and disease phase (i.e., RRMS or SPMS).	
Adverse events	The following AEs were considered: increased ALT, arthralgia, back pain, bronchitis, cough, depression, dizziness, fatigue, headache, hypoesthesia, influenza/influenza-like illness, injection site pain, lymphadenopathy, nasopharyngitis, oral herpes, oropharyngeal pain, pain in extremity, pharyngitis, pyrexia, rash, upper respiratory tract infection, and urinary tract infections. The set of AEs considered were those that occurred at an incidence of ≥ 5% in DECIDE and SELECT[4,28] and that occurred ≥ 2% for DAC compared with Avonex. Incidence of AEs were drug-specific and were based on rates reported in the pivotal trials of each drug, as referenced in the manufacturer's economic submission.[3] The proportion of serious AEs for each treatment was based on the annual incidence of serious AEs as a proportion of all AEs.	The criteria used to select AEs for consideration neglects the most severe hepatic and cutaneous AEs occurring with DAC, thereby giving a misleading picture of its safety (and association costs and QALYs).
Mortality	Age– and sex-specific mortality were based on Statistics Canada tables.[11] An MS-specific rate ratio was derived from British Columbia observational data[13] while EDSS-specific rate ratios were derived from a large Danish observational cohort.[12]	Appropriate. While inclusion of both disease-specific and severity-specific rate ratios may be double counting, this does not affect results.

Data Input	Description of Data Source	Comment
Costs		
Drug	The price of DAC was the manufacturer's submitted market price while the prices of all other drugs were obtained from the Ontario Drug Benefit Formulary Exceptional Access Program list.[29]	Appropriate.
Administration	Subcutaneously administered medications had a first-year charge for self-administration training while infused medications had infusion charges; all costs were based on the Ontario schedule of benefits.[30]	Appropriate.
Disease management	Annual per patient direct costs of RRMS by EDSS scores are based on the values reported in the CADTH MS Therapeutic Review, inflated to 2016 values. Annual costs for management of SPMS patients by EDSS scores were based on Grima et al. for EDSS scores 0 to 6 and Karampampa et al. for EDSS scores 7 to 9.[31,32]	Appropriate.
Relapse management	Costs for management of relapse were derived from CADTH's therapeutic review.[8] Proportion of severe and moderate relapses were based on values used in Prosser et al.'s economic evaluation of IFNs and GA in progressive MS.[33]	Appropriate.
Monitoring	While the pharmacoeconomic submission states that monitoring resource use was based on the "tecfidera HE," no citation is provided and no further information is provided as to the identity of this document. Costs for neurologist visits and tests were derived from the Ontario schedule of benefits.[30]	As noted in the limitations section, the type and quantity of tests and neurologists visits was biased in favour of DAC, although this did not substantially impact results.
AEs	Costs for management of non-serious AEs consisted of a follow-up neurologist visit, derived from the Ontario schedule of benefits.[30] Costs for management of serious AEs was based on the CIHI patient cost estimator.[22]	It is unlikely that patients would visit a neurologist for each non-serious AE. However, sources were otherwise noted to be appropriate.

AE = adverse event; ALT = alanine transaminase; ARR = annualized relapse rate; CDR = CADTH Common Drug Review; CIHI = Canadian Institute for Health Information; DAC = daclizumab; EDSS = Kurzke Expanded Disability Status Scale; GA = glatiramer acetate; HE= IFN = interferon; MS = multiple sclerosis; MTC = mixed treatment comparison; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis; QALY = quality-adjusted life-year.

TABLE 8: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Patients receive monotherapy and upon discontinuation receive no pharmacotherapy.	In reality, patients would move on to further therapies; however, CDR acknowledges a paucity of data on treatment sequences and their efficacy.
Patients discontinue upon exceeding an EDSS level of five and upon developing SPMS.	Different submissions have used different stopping rules (e.g., stopping at EDSS level of seven in CADTH's previous therapeutic review[8]). Assessed and found not to impact results.
Fingolimod is the most appropriate base-case comparator.	While considering fingolimod is appropriate, consideration of fingolimod to the exclusion of other second- and third-line therapies is inappropriate and gives a misleading account of DAC's cost-effectiveness.
No waning of treatment effect.	Uncertain. While biologic fatigue is a known phenomenon in other disease areas, there is more uncertainty in MS.
Patients who discontinue treatment experience relapses at the natural history rate.	Uncertain whether appropriate.
Patient characteristics reflected the SELECT trial.	Felt to be appropriate by expert.
Assumption that transition probabilities between RRMS EDSS states was constant over time.	Uncertain.
All non-serious AEs require a follow-up neurologist visit.	Likely inappropriate, serves to overestimate costs of treating AEs.
DAC confers a mortality benefit when compared with fingolimod.	Uncertain in the absence of direct evidence, however differential LYs and impact on ICERs is negligible.

AE = adverse event; DAC = daclizumab; EDSS = Kurzke Expanded Disability Status Scale; ICER = incremental cost-effectiveness ratio; LY = life-year; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.

Manufacturer's Results

As the manufacturer reported results separately for each comparator, the results were presented as follows:

TABLE 9: MANUFACTURER'S BASE CASE RESULTS — DACLIZUMAB VERSUS FINGOLIMOD

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	286,977	6.03	-	-	-
Gilenya®	297,578	5.81	-10,601	0.22	Zinbryta™ dominates

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 10: MANUFACTURER'S BASE-CASE RESULTS — DACLIZUMAB VERSUS INTERFERON (AVONEX)

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	286,977	6.03	-	-	-
Avonex®	264,350	5.61	22,628	0.41	54,565

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 11: MANUFACTURER'S BASE-CASE RESULTS — DACLIZUMAB VERSUS INTERFERON (BETAFERON)

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	283,401	5.89	-	-	-
Betaferon®	245,429	5.44	37,973	0.44	85,335

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 12: MANUFACTURER'S BASE-CASE RESULTS — DACLIZUMAB VERSUS INTERFERON (EXTAVIA)

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	283,401	5.89	-	-	-
Extavia®	239,924	5.44	43,477	0.44	97,705

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 13: MANUFACTURER'S BASE-CASE RESULTS — DACLIZUMAB VERSUS GLATIRAMER ACETATE

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	286,977	6.03	-	-	-
Copaxone®	231,896	5.44	55,082	0.59	92,804

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 14: MANUFACTURER'S BASE-CASE RESULTS — DACLIZUMAB VERSUS DIMETHYL FUMARATE

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	286,977	6.03	-	-	-
Tecfidera®	265,806	5.77	21,172	0.26	80,453

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 15: MANUFACTURER'S BASE-CASE RESULTS — DACLIZUMAB VERSUS TERIFLUNOMIDE

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	283,401	5.89	-	-	-
Aubagio®	253,841	5.72	29,561	0.17	174,026

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 16: MANUFACTURER'S BASE-CASE RESULTS — DACLIZUMAB VERSUS NATALIZUMAB

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	286,977	6.03	-	-	-
Tysabri®	369,369	6.19	-82,392	-0.16	Zinbryta™ less costly, less effective

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 17: MANUFACTURER'S BASE-CASE RESULTS — DACLIZUMAB VERSUS ALEMTUZUMAB

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	283,401	5.89	-	-	-
Lemtrada®	216,297	6.67	67,105	-0.78	Zinbryta™ dominated

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 18: MANUFACTURER'S BASE-CASE RESULTS — DACLIZUMAB VERSUS INTERFERON (REBIF 44)

Treatment	Total Cost ($)	Total QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($)
Zinbryta™	283,401	5.89	-	-	-
Rebif® 44	275,483	5.82	7,918	0.07	121,052

ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life year; $= Canadian dollar.
Source: Manufacturer's pharmacoeconomic submission.[3]

Additional CADTH Common Drug Review Reanalyses

TABLE 19: SEQUENTIAL ANALYSIS OF ALL COMPARATORS EXCLUDING ALEMTUZUMAB AND NATALIZUMAB

	QALYs	Cost	Incremental Cost per QALY Gained vs. GA	Sequential Incremental Cost per QALY Gained
GA	5.509	$232,519.51	REF	NA
Teriflunomide	5.718	$253,840.66	$101,748.59	$101,748.59
Daclizumab	5.888	$283,401.26	$134,107.56	$174,026.48
Dominated Strategies				
DMF	5.784	$266,180.32	$122,234.21	Subject to extended dominance
Rebif	5.823	$275,482.95	$136,827.37	Subject to extended dominance
Avonex	5.602	$264,104.66	$338,047.40	Dominated by teriflunomide
Fingolimod	5.676	$293,486.52	$363,858.00	Dominated by teriflunomide, DMF, Rebif , daclizumab
Extavia	5.443	$239,924.26	Dominated by GA	Dominated by GA
Betaferon	5.443	$245,428.60	Dominated by GA	Dominated by Extavia, GA

DMF = dimethyl fumarate; GA = glatiramer acetate; NA = not available; QALY = quality-adjusted life-year; REF = reference.

TABLE 20: SEQUENTIAL ANALYSIS OF ALL COMPARATORS EXCLUDING INTERFERONS, ALEMTUZUMAB AND NATALIZUMAB

	QALYs	Cost	Incremental cost per QALY gained vs. GA	Sequential incremental cost per QALY gained
GA	5.509	$232,519.51		
Teriflunomide	5.718	$253,840.66	$101,748.59	$101,748.59
Daclizumab	5.888	$283,401.26	$134,107.56	$174,026.48
Dominated Strategies				
DMF	5.784	$266,180.32	$122,234.21	Subject to extended dominance
Fingolimod	5.676	$293,486.52	$363,858.00	Dominated by teriflunomide, DMF, daclizumab

DMF = dimethyl fumarate; GA = glatiramer acetate; QALY = quality-adjusted life-year.

REFERENCES

1. Zinbryta™ (daclizumab beta): 150 mg/mL solution for injection [product monograph]. Mississauga (ON): Biogen Canada Inc.; 2016 Dec 7.
2. CDR submission: Zinbryta™ (daclizumab beta), 150 mg/mL and solution for injection. Company: Biogen Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Biogen Canada Inc.; 2016 Dec 13.
3. Pharmacoeconomic evaluation. In: CDR submission: Zinbryta™ (daclizumab beta), 150 mg/mL and solution for injection. Company: Biogen Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Biogen Canada Inc.; 2016 Dec 13.
4. Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, Radue EW, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. Lancet. 2013 Jun 22;381(9884):2167-75.
5. Palace J, Bregenzer T, Tremlett H, Oger J, Zhu F, Boggild M, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open [Internet]. 2014 Jan 17 [cited 2017 Mar 30];4(1):e004073. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3902459
6. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain. 1989 Dec;112 (Pt 6):1419-28.
7. Birnie R, Wolff R, Duffy S, Worthy G, Leadley R, Kleijnen J. A systematic review and mixed treatment comparison of daclizumab compared to other disease modifying treatments for relapsing-remitting multiple sclerosis: final report [**CONFIDENTIAL** manufacturer's submission]. Escrick (United Kingdom): Kleijnen Systematic Reviews Ltd; 2016 Jul 11.
8. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: CADTH; 2013 Oct; updated March 2014. [cited 2017 Mar 6]. (CADTH Therapeutic Review vol.1, no. 2b). Available from: https://www.cadth.ca/media/pdf/TR0004_RRMS_ScienceReport_e.pdf
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. 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.
11. Life tables, Canada, provinces and territories, 2010-2012 [Internet]. Ottawa: Statistics Canada; 2016 May 19. [cited 2017 Mar 30]. Available from: http://www.statcan.gc.ca/daily-quotidien/160519/dq160519c-eng.htm
12. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. J Insur Med. 1997;29(2):101-6.
13. Kingwell E, van der Kop M, Zhao Y, Shirani A, Zhu F, Oger J, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J Neurol Neurosurg Psychiatry. 2012 Jan;83(1):61-6.

14. Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. Br J Cancer [Internet]. 2009 Aug 4 [cited 2017 Mar 30];101(3):387-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720221

15. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes [Internet]. 2010 May 18 [cited 2017 Mar 30];8:50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2890699

16. van Hoek AJ, Underwood A, Jit M, Miller E, Edmunds WJ. The impact of pandemic influenza H1N1 on health-related quality of life: a prospective population-based study. PLoS ONE [Internet]. 2011 Mar 2 [cited 2017 Mar 30];6(3):e17030. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3047534

17. Xu R, Insinga RP, Golden W, Hu XH. EuroQol (EQ-5D) health utility scores for patients with migraine. Qual Life Res. 2011 May;20(4):601-8.

18. Sander B, Hayden FG, Gyldmark M, Garrison LP Jr. Post-exposure influenza prophylaxis with oseltamivir: cost effectiveness and cost utility in families in the UK. PharmacoEconomics. 2006;24(4):373-86.

19. Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis [Internet]. London: National Institute for Health and Care Excellence; 2007 Aug 22. [cited 2017 Mar 30]. (Technology appraisal guidance; no.TA127). Available from: https://www.nice.org.uk/guidance/ta127/resources/natalizumab-for-the-treatment-of-adults-with-highly-active-relapsingremitting-multiple-sclerosis-82598138383813

20. Depression in adults: recognition and management [Internet]. London: National Institute for Health and Care Excellence; 2009 Oct 28. [cited 2017 Mar 30]. (Clinical guideline; no.90). Available from: https://www.nice.org.uk/guidance/cg90/resources/depression-in-adults-recognition-and-management-975742636741

21. Parsons S, Carnes D, Pincus T, Foster N, Breen A, Vogel S, et al. Measuring troublesomeness of chronic pain by location. BMC Musculoskelet Disord [Internet]. 2006 Apr 5 [cited 2017 Mar 30];7:34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1459155

22. Patient cost estimator [Internet]. Ottawa: Canadian Institute for Health Information; 2017. [cited 2017 Mar 30]. Available from: https://www.cihi.ca/en/patient-cost-estimator

23. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017 Jan 19;376(3):221-34.

24. Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002 Nov 26;59(10):1496-506.

25. Appraisal consultation document: daclizumab for treating relapsing-remitting multiple sclerosis [Internet]. London: National Institute for Health and Care Excellence; 2016 Sep. [cited 2017 Mar 30]. Available from: https://www.nice.org.uk/guidance/GID-TA10013/documents/appraisal-consultation-document

26. Pharmaceutical Benefit Advisory Committee. Public summary document: daclizumab, 150 mg pre-filled injection pen or syringe, Zinbryta®, Biogen [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2016 Jul. [cited 2017 Mar 30]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-07/files/daclizumab-psd-july-2016.pdf

27. Forthcoming submission: daclizumab (Zinbryta) [Internet]. Glasgow (GB): Scottish Medicines Consortium; 2017. [cited 2017 Mar 30]. Available from: https://www.scottishmedicines.org.uk/SMC_Advice/Forthcoming_Submissions/daclizumab_Zinbryta

28. Kappos L, Wiendl H, Selmaj K, Arnold DL, Havrdova E, Boyko A, et al. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2015 Oct 8;373(15):1418-28.

29. Ontario Ministry of Health and Long-Term Care. Formulary: Exceptional Access Program (EAP) [Internet]. Toronto: The Ministry; 2017 Jan. [cited 2017 Mar 6]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx

30. Ontario Ministry of Health and Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective December 21, 2015 [Internet]. Toronto: The Ministry; 2015. [cited 2017 Mar 6]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html

31. Grima DT, Torrance GW, Francis G, Rice G, Rosner AJ, Lafortune L. Cost and health related quality of life consequences of multiple sclerosis. Mult Scler. 2000 Apr;6(2):91-8.

32. 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.

33. 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.