Common Drug Review
Pharmacoeconomic Review Report

October 2014

Drug	Teriflunomide (Aubagio) (14 mg film-coated tablet)
Indication	Teriflunomide is indicated as monotherapy for the treatment of patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
Listing request	For patients with relapsing forms of MS with similar listing criteria to IFNs and GA on public drug formularies, which is aligned with the anticipated Aubagio Health Canada indication
Manufacturer	Genzyme Canada

Teriflunomide (Aubagio) Common Drug Review Pharmacoeconomic Report was prepared using Pharmastat data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

BSC	best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
DMT	disease-modifying treatments
EDSS	Expanded Disabilities Status Scale
GA	glatiramer acetate
ICUR	incremental cost-utility ratio
IFN	interferon
MS	multiple sclerosis
MTC	mixed treatment comparison
NICE	National Institute for Health and Clinical Excellence
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	Teriflunomide (Aubagio)
Study Question	"The current study estimates the cost-effectiveness of oral teriflunomide compared with current Canadian standard therapies for the first line treatment of relapsing MS."
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults with relapsing forms of MS with EDSS score ≤ 5.5 who are treatment naive, or those requiring a first switch to another therapy due to intolerance
Treatment	Teriflunomide 14 mg oral daily
Outcome(s)	Life-years, QALYs, years on treatment, relapses
Comparators	• IFN beta 1a (Rebif) 44 mcg subcutaneous 3 times weekly • IFN beta 1a (Avonex) 30 mcg intramuscular once weekly • GA 20 mg subcutaneous daily • Dimethyl fumarate 240 mg twice daily
Perspective	Health care system (societal in sensitivity analysis)
Time Horizon	20 years
Manufacturer's Results (Base Case)	• Teriflunomide dominates Rebif and Avonex • Teriflunomide vs. GA: $33 per QALY • Dimethyl fumarate vs. teriflunomide: dimethyl fumarate is more costly ($20,440) and more effective (0.083 QALYs)
Key Limitations and CDR Estimate(s)	There were several limitations within the manufacturer's model that required reanalysis by CDR. The parameters included: 1. Relative effectiveness estimates from the manufacturer's MTC 2. Utility values by EDSS state 3. Persistence of treatment effect (i.e., treatment waning) 4. Side effects from treatments 5. Health care costs by EDSS state and by relapse 6. Mortality by EDSS state 7. Withdrawal rates Reanalysis addressed all points above, with the exception of persistence of treatment effect (#3): • Teriflunomide dominates Rebif and Avonex • Teriflunomide vs. best supportive care[a] (no DMT) is associated with an ICUR of $195,070 • Teriflunomide vs. GA is associated with an ICUR of $409,175 • Dimethyl fumarate vs. teriflunomide: dimethyl fumarate is more effective and more costly than teriflunomide, leading to an ICUR of $10,030 for dimethyl fumarate • Teriflunomide is subject to extended dominance through GA and dimethyl fumarate (there might be combinations of the two that would be more cost-effective) CDR reanalysis does not address either waning of treatment effect or whether confidential prices exist for other products.

CDR = Common Drug Review; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; ICUR = incremental cost-utility ratio; IFN = interferon; MS = multiple sclerosis; MTC = mixed treatment comparison; QALY = quality-adjusted life-year.

[a]Best supportive care was not considered as a relevant comparator by the manufacturer, but was included in the economic model.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

The manufacturer's submission, which was received by the Common Drug Review (CDR) before the Health Canada Notice of Compliance (NOC) was issued, relates to oral teriflunomide (Aubagio) 14 mg once daily for patients with relapsing forms of multiple sclerosis with an Expanded Disability Status Scale (EDSS) score of ≤ 5.5 who are treatment naive, or those requiring a first switch to another therapy due to intolerance.[1] The indication for teriflunomide is as monotherapy for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.[2] It should be noted that this difference in the indication (RRMS only instead of all relapsing forms of MS) had no impact on the economic evaluation, as the manufacturer's base case analysis was based on the TEMSO trial population, in which 91.5% of subjects had RRMS, and it was assumed that treatment would be discontinued when patients converted from RRMS to secondary progressive multiple sclerosis (SPMS).

The manufacturer submitted a confidential price of $[redacted] per 14 mg tablet ($[redacted] per year). The manufacturer is requesting listing with similar criteria to interferons (Avonex, Rebif) and glatiramer acetate (GA) on public drug formularies.

Summary of Economic Analysis

The manufacturer conducted a cost-utility analysis based on a Markov model of disease progression, where patients progress through EDSS levels (1 to 9) and move from RRMS to SPMS, and death.
A 20-year time horizon was considered, with cycle lengths of one year. 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. The model also incorporates differential risks of relapses, costs, and utility values for each level. The analysis is conducted from the perspective of the health care payer. Data on the natural progression of MS were derived primarily from the London, Ontario, registry, supplemented by data from the placebo arms of the TEMSO and TOWER trials.[3-5] 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) restricted to studies published since 2000 with 80% of patients with RRMS.[6] Utility values and costs for each state are derived from Canadian data sources.[7,8] The primary analysis is a cost-utility analysis comparing teriflunomide (Aubagio) with interferon beta 1a (Avonex), interferon beta 1a (Rebif), GA, and dimethyl fumarate (Tecfidera).

Results of Manufacturer's Analysis

In the manufacturer's base analysis, the following results were reported: teriflunomide is dominant over Rebif and Avonex; the incremental cost-utility ratio (ICUR) for teriflunomide versus GA is $33; dimethyl fumarate is more costly and associated with greater quality-adjusted life-years versus teriflunomide.

Interpretations and Key Limitations

There were a number of limitations within the model that required reanalysis. How these limitations were handled in CDR reanalyses is provided.

1. The MTC submitted by the manufacturer used studies published since 2000 and focused on treatment progression over a three-month period, which biased the results in favour of teriflunomide, especially in comparison with GA. CDR reanalysis employed estimates from the Canadian Agency for Drugs and Technologies in Health Therapeutic Review on drug therapies for RRMS, where the MTC considered trials in which > 50% of the trial population had RRMS and looked at progression over a three- or six-month period.[9]
2. The utility values by EDSS state used by the manufacturer (Tappenden et al.)[7] were much lower than those found in other published studies. CDR reanalysis adopted alternate utility values.
3. Analysis assumes that the effectiveness of treatment will be maintained for lifetime. The duration of follow-up in the TEMSO clinical trial was 108 weeks. It would be reasonable to assume that benefit from treatment may wane beyond this time horizon. A request was made to the manufacturer to incorporate a treatment waning effect in the model. The manufacturer indicated that a model incorporating waning of treatment effect is not available.
4. Analysis included only side effects for each therapy where the difference between active therapy and placebo was 4%. Considering the transient nature of most of the adverse events related to the RRMS treatments, CDR performed a reanalysis in which side effects were excluded.
5. Health care costs by EDSS state and for relapse were purportedly derived from Karampampa et al. (2012).[8] However, the methods of extrapolation were inappropriate. Among other limitations, the method used by the manufacturer ignored the possibility that patients with a hospitalized relapse also had a relapse not requiring hospitalization. CDR reanalysis was conducted using alternative cost estimates.[9]
6. Mortality by EDSS state was derived from a 1992 study by Sadovnick et al.,[10] 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. CDR reanalysis adopted the actual data from Sadovnick et al.[10]
7. Treatments became more cost-effective if they were associated with a higher withdrawal rate. Reanalysis assumed a constant withdrawal rate across all treatments — assumed to be 17% per annum, as per teriflunomide 14 mg.

Results of Common Drug Review Analysis

CDR reanalysis adopted the assumptions listed above and found:

- teriflunomide dominates Rebif and Avonex
- teriflunomide is more effective than best supportive care: ICUR of $195,070
- teriflunomide is more effective than GA: ICUR of $409,175
- dimethyl fumarate is more effective than teriflunomide: ICUR of $10,030.

Analysis stratified by EDSS states (i.e., for populations of EDSS states of 1, 2, 3, 4, and 5) found that the interpretation for results did not vary by EDSS state. The ICUR for teriflunomide versus GA did vary slightly, but the lowest ICUR was $281,298 for an EDSS of 5.

Issues for Consideration

- Reanalysis does not consider treatment waning, as the response from the manufacturer for additional analysis was still pending as of March 31, 2014.
- The results will be sensitive to any confidential prices for each of the therapies considered (dimethyl fumarate, Rebif, Avonex, and GA).
- Results do not appear to vary by baseline EDSS state.
- The population was based on TEMSO, which included a mix of treatment-naive patients (73%) and patients switched from prior injection-based therapies due to lack of tolerability. It was not possible to run separate analyses for treatment-naive or intolerant patients in the model.

Conclusions

CDR found several limitations with the manufacturer's economic analysis. A reanalysis addressing all of these limitations (except treatment waning over time) found that teriflunomide dominated Rebif and Avonex, but the ICUR for teriflunomide versus GA was $409,175.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

"The current study estimates the cost-effectiveness of oral teriflunomide compared with current Canadian standard therapies for the first line treatment of relapsing multiple sclerosis (MS)" (Manufacturer's submission page 3[1]).

1.2 Treatment

Teriflunomide (Aubagio): 14 mg once daily oral treatment

1.3 Comparators

- Interferon beta 1a (Rebif): 44 mcg subcutaneous 3 times weekly
- Interferon beta 1a (Avonex): 30 mcg intramuscular once weekly
- Glatiramer acetate (Copaxone): 20 mg subcutaneous daily
- Dimethyl fumarate (Tecfidera): 240 mg oral twice daily

The model also reports results for no treatment — i.e., best supportive care (BSC). Analysis relates to first line use of therapies. Interferon beta 1b 250 mcg subcutaneous every other day (Betaseron and Extavia) were not included, as the manufacturer indicated that these treatments are not used often in clinical practice. Rebif 22 mcg was also excluded, as it is more commonly used as a starting dose for treatment titration. Common Drug Review (CDR) analysis using Pharmastat data (IMS Health Canada Inc.) indicated that across Canadian public plans in 2013, less than 1% of claims were for Extavia, and 11% of claims were for Betaseron.

However, the model is designed such that the user can compare teriflunomide with only one other active treatment at a time. This is a limitation that should not be encouraged in future models.

1.4 Type of Economic Evaluation

A cost-utility analysis was conducted as the primary analysis. This is appropriate given that treatment may affect the progression of diseases, thus affecting disease costs, possibly life expectancy, and quality of life.

Primary analysis was from the health care system perspective. This is appropriate.

1.5 Population

The patient population is adults with relapsing forms of MS with Expanded Disability Status Scale (EDSS) score ≤ 5.5 who are treatment naive, or those requiring a first switch to another therapy due to intolerance. The indication for teriflunomide is for relapsing-remitting MS (RRMS) only.[2] It should be noted that this difference in the indication had no impact on the economic evaluation, as the manufacturer's base case analysis was based on the TEMSO trial population, in which 91.5% of subjects had RRMS, and it was assumed that treatment would be discontinued when patients converted from RRMS to secondary progressive MS (SPMS).

2. METHODS

The manufacturer's economic analysis is conducted using a Markov model of disease progression, in which patients progress through EDSS levels (1 to 9) and move from RRMS to secondary progressive multiple sclerosis (SPMS), and death. Death was captured separately from the EDSS-based states in order to allow for an increasing risk of mortality by age. The model is created within Microsoft Excel. The model is designed such that results are only available at one time for teriflunomide, one other active treatment, and BSC. It did not allow comparison of all treatment options simultaneously.

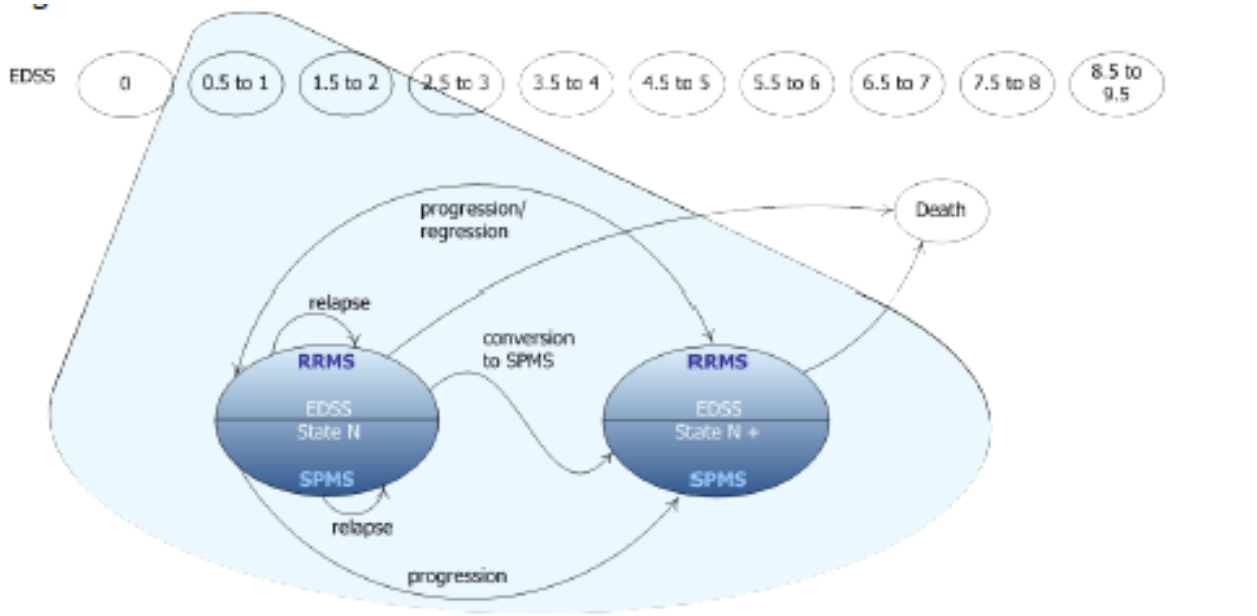
The model adopts a cycle length of one year over a 20-year time horizon. Mortality can occur at any EDSS level and the rate is assumed to increase with EDSS level. The model also incorporates differential risks of relapses, costs, and utility values for each level.

The model structure and design is cumbersome and lacks a degree of transparency but is technically correct. The limitations detailed in Table 15 relate to the choice of parameter inputs into the model rather than the methodology used in the model.

2.1 Model Structure

The model structure relates to the disease progression with MS depicted by health states relating to EDSS (1, 2, 3, 4, 5, 6, 7, 8, and 9) and type of MS (RRMS and SPMS). Death was captured separately from the EDSS-based states in order to allow for an increasing risk of mortality by age.

FIGURE 1: MODEL DESIGN



Abbreviations: MS = multiple sclerosis; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; EDSS = Expanding disability status scale.

Source: Manufacturer's submission.[1]

2.2 Clinical Inputs

2.2.1 Efficacy

Treatment efficacy was derived from an unpublished mixed treatment comparison (MTC) restricted to studies published since 2000 with trial populations of at least 80% RRMS.[6] Outcomes assessed were sustained accumulation of disability at three months, annualized relapse rates, treatment withdrawals, and the proportion of relapses requiring hospitalizations.

The justification for including only studies published after 2000 was unclear. The inclusion of only data on a sustained accumulation of data at three months may not be appropriate, given six-month data were often available and could give a greater indication of long-term treatment effect.

Analysis assumed that the treatment effect was maintained in perpetuity. This seemed inappropriate and a reanalysis was requested from the manufacturer that allowed consideration of treatment waning. At the time the draft report was sent to the manufacturer, this analysis was still pending.

Analysis assumed differential withdrawal rates. Given that results appeared highly sensitive to withdrawal rates and that results for all studies were unavailable, an assumption of equal withdrawal rates would be more appropriate.

2.2.2 Harms

Treatment-related adverse events were included in the model if they were deemed clinically significant and there was either at least a 4% difference in incidence between treatment and placebo or the adverse event had been included in previous studies. Data were obtained from relevant clinical trials.

This approach did not seem defensible. For example, the probability of headache for Avonex is 42.63%, and yet headache is not considered for any other treatment. It appears unlikely that the probability of headache with the other treatments was 0%.

2.2.3 Natural History

Data on the transition of patients in terms of disease progression were primarily sourced from the London MS registry relating to patients receiving BSC, and this is supplemented by data from the placebo arms of the TEMSO and TOWER trials.[3-5] Transitions relate to the probability of moving from one state to another state within RRMS on an annual basis, the probability of moving from one state to another state within SPMS on an annual basis, and the probability of moving from RRMS to SPMS on an annual basis. Note that it is possible within the model to reverse progression — e.g., patients with EDSS 3 may move to EDSS 2. Patients could also transition to EDSS 0.

This approach to modelling disease progression appears appropriate.

2.2.4 Mortality

All-cause mortality rates for the general population were obtained from Statistics Canada 2000-2002 Life Tables.

These rates were adjusted to reflect the belief that there is increased mortality with MS. Relative risks for mortality for each EDSS level are interpolated from a study by Sadovnick et al. (referred to as Pokorski by the manufacturer).[10,11]

The data from Sadovnick et al.[10] are by general MS category (mild, moderate, severe) and it would have been better to use the actual data rather than the interpolation. As an example, for severe MS, Sadovnick reported that the mortality rate was increased by 4.44 in patients with EDSS score ≥ 7.5. Rather than using this mortality multiplier for all EDSS health states ≥ 7.5, the manufacturer applied a mortality multiplier of 6.454 for EDSS = 9.

The data are quite old and it would be preferential if more recent data on the mortality by EDSS level were available.

2.2.5 Utilities

Utility values by EDSS levels for RRMS were derived from a Canadian economic evaluation by Tappenden et al. (2009) using the Health Utilities Index Mark 3.[7] For SPMS, a disutility of 0.045 was applied.

Disutility associated with a relapse both with and without hospitalization was derived from a study by Orme et al.[12] Relapse was assumed to last three months.

The submission did not use actual scores by levels but rather used modelled scores, which were only obtained by digitizing a graph from Tappenden et al.[7] Given that the values were lower than previously reported studies, additional information provided by the manufacturer on the baseline utility values from the TEMSO trial,[13] along with data provided from the MS Research Trust study in a report from ScHARR (2002), may have been more appropriate.[14] A reduction of utility of –0.085 for SPMS may also be more appropriate, as per ScHARR (2002).[14] The disutilities for relapses seem appropriate.

2.2.6 Costs

Cost data come from a study by Karampampa et al. 2012.[8] Due to lack of clarity in the original submission, the manufacturer provided further information to help clarify the methods used. Costs per relapse were obtained by looking at the difference in cost per patient with no relapses to those with only relapses not requiring hospitalization and those with relapses requiring hospitalizations. These are then adjusted for the number of relapses. These costs are then subtracted from costs provided for different broad EDSS categories. The costs per broad EDSS category are then interpolated to allow costs per EDSS level.

Although it is recognized that quality data on the costs of relapses and by EDSS level are sparse, the mathematical approach to calculate these is inappropriate and lacks face validity. The method of calculating the difference in costs between those with and without relapse ignores any differential in EDSS level across the categories. The method ignores the possibility that patients with a hospitalized relapse also had a relapse not requiring hospitalization. Furthermore, the data suggested to be the proportion of relapses that require hospitalization (40%, calculated from Karampampa et al.)[8] are in fact the proportion of patients who had a relapse who were hospitalized — not the same thing, given the average number of relapses is 1.64. Finally, the estimated cost per relapse not requiring hospitalization of $21 lacks face validity.

2.2.7 Drug Costs

Drug acquisition costs were estimated based on recommended dosing regimens and were based on unit costs obtained from the Association Québécoise des Pharmaciens Propriétaires, July 2013.

Given that drug acquisition cost from Quebec tends to be lower than other provinces and that the results are not targeted to Quebec, alternative sources of costs such as the Ontario drug formulary should have been used. The source used, however, would tend to bias results against teriflunomide, except for the comparison with dimethyl fumarate. Dimethyl fumarate was listed on the Quebec formulary in February 2014, at a unit cost of $14.3836 ($21,000 annually), which is lower than the cost that was used by the manufacturer ($22,578 in the first year and $23,019 in subsequent years).

2.2.8 Administration Costs

A dispensing cost of $8.62 was applied for each three-month supply of drugs. Monitoring was estimated based on consultation with an MS clinical expert. For teriflunomide, Rebif, and Avonex, it was assumed that a complete blood count and a liver function test were required every six months and for dimethyl fumarate, a complete blood count and a urinalysis were required every three months. No monitoring was assumed for GA.

These estimates appear reasonable.

2.2.9 Time Horizon

A time horizon of 20 years is used and is appropriate.

2.2.10 Discounting

Costs and effects are discounted at 5% per annum and this is appropriate.

2.2.11 Validation

No discussion of validation is provided.

3. RESULTS

3.1 Manufacturer's Base Case

In the manufacturer's base analysis, the following results were found:

- Teriflunomide is dominant over Rebif and Avonex.
- The incremental costs and quality-adjusted life-years (QALYs) for teriflunomide versus BSC are $53,389 and 0.381, leading to an incremental cost per QALY gained of $140,569. The incremental cost per life-year gained for teriflunomide versus BSC was $3,068,575.
- The incremental costs and QALYs for teriflunomide versus GA are $8 and 0.240, leading to an incremental cost per QALY gained of $33. The incremental cost per life-year gained for teriflunomide versus GA was $628.
- The incremental costs and QALYs for dimethyl fumarate versus teriflunomide are $20,440 and 0.083, leading to an incremental cost per QALY gained of $246,185. The incremental cost per life-year gained for dimethyl fumarate versus teriflunomide was $6,243,006.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost vs. Teriflunomide ($)	Total QALYs	Incremental QALYs vs. Teriflunomide	ICUR ($) for Teriflunomide	Total LYs	Incremental LYs vs. Teriflunomide	ICER
Teriflunomide	$189,860		4.990			12.676		
BSC	$136,271	$53,389	4.608	0.381	$140,569	12.658	0.018	$3,068,575
GA	$189,852	$8	4,750	0.240	$33	12.663	0.012	$628
Dimethyl fumarate	$210,301	–$20,440	5.073	–0.083	Dimethyl fumarate vs teriflunomide: $246,185	12.679	–0.003	Dimethyl fumarate vs. teriflunomide $6,243,006
Rebif	$196,777	–$6,917	4.861	0.128	Teriflunomide dominant	12.669	0.006	Teriflunomide dominant
Avonex	$193,304	–$3,174	4.735	0.255	Teriflunomide dominant	12.663	0.012	Teriflunomide dominant

BSC = best supportive care; GA = glatiramer acetate; ICER = incremental cost per life-year gained; ICUR = incremental cost-utility ratio; LY = life-years; QALY = quality-adjusted life-year.

Source: manufacturer's submission.[1]

Given the limitations of some of the parameter estimates used in the model as detailed above, the base case analysis is not appropriate for consideration with respect to drug reimbursement.

3.2 Summary of the Manufacturer's Sensitivity Analyses

3.2.1 One-way Sensitivity Analyses

The following table is derived from the manufacturer's submission and lists the univariate sensitivity analyses conducted and their results. In three of the seven analyses, teriflunomide dominates all but dimethyl fumarate, which is more effective but with an ICUR versus teriflunomide of greater than $200,000. In the other four analyses, GA is the least costly therapy, but the ICUR for teriflunomide versus GA is at most $20,371. Thus, the analyses suggested that teriflunomide was the most cost-effective treatment option, given current threshold values of a QALY.

TABLE 3: SUMMARY OF RESULTS OF THE MANUFACTURER'S SENSITIVITY ANALYSES

Base Case	Alternate Assumption	Lowest Cost Therapy	Dominated Therapies	ICURs
Only RRMS patients treated with DMTs	RRMS and SPMS patients considered as a combined population in the model (both RRMS and SPMS patients are treated with DMTs)	Teriflunomide	GA, Avonex, Rebif	Dimethyl fumarate vs. teriflunomide: $406,984/QALY
Progression rates from London, Ontario; TEMSO; & TOWER	TEMSO placebo arm only for source of natural history (assess impact of allowing EDSS improvement in the model)	GA	Avonex, Rebif	Teriflunomide vs. GA: $639/QALY; dimethyl fumarate vs. teriflunomide: $253,531/QALY
Relapse rate sourced from Patzold 1982	Relapse rate sourced from Held 2005	GA	Avonex, Rebif	Teriflunomide vs. GA: $1,029/QALY; dimethyl fumarate vs. teriflunomide: $229,193/QALY
Treatments have effect on the split between relapses in the model	All treatment effects on proportion of relapses leading to hospitalization set to 1 (assume that treatments have no effect on hospitalization for relapse)	Teriflunomide	GA, Avonex, Rebif	Dimethyl fumarate vs. teriflunomide: $237,494/QALY
Considering treatment-related withdrawal rates	Not considering treatment-related withdrawal rates	GA	Rebif	Avonex vs. GA: $8,623,000/QALY; teriflunomide vs. Avonex: $11,080/QALY; dimethyl fumarate vs. teriflunomide: $347,933/QALY
20 years	10 years	GA	Avonex, Rebif	Teriflunomide vs. GA $20,371/QALY; dimethyl fumarate vs. teriflunomide: $387,796/QALY
20 years	30 years	Teriflunomide	GA, Avonex, Rebif	Dimethyl fumarate vs. teriflunomide: $214,789/QALY

DMT = disease-modifying treatment; GA = glatiramer acetate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.
Source: Manufacturer's submission.[1]

3.2.2 Probabilistic Sensitivity Analysis

Within a probabilistic sensitivity analysis (PSA), key parameters within the model were assigned probability distribution based on its base value, uncertainty, and appropriate distribution of the uncertainty. One thousand estimates for the costs and QALYs are obtained from sampling from the distributions. For teriflunomide versus GA, the probability that teriflunomide was cost-effective at a threshold of $50,000 per QALY was approximately 60%, suggesting a considerable degree of uncertainty regarding the study results. The design of the model did not allow a PSA that would allow comparison of all treatment options simultaneously.

The PSA was conducted appropriately with respect to the choice of probability distributions and the mechanics of the simulations. However, the PSA incorporates the same limitations to the base case, due to the choice of parameter values. In addition, the inability to consider all treatments concurrently is a major weakness of the PSA.

3.3 Common Drug Review Analyses

3.3.1 Clinical Effectiveness

The MTC used studies published since 2000 only. The justification of including only studies published after 2000 may not be appropriate (Appendix VII of the CDR Clinical Report). The inclusion of only data on a sustained accumulation of disability at three months (otherwise referred to as progression) may not be appropriate when six months' data were often available and could give a greater indication of long-term treatment effect.

A CDR reanalysis addressed the first concern by using the manufacturer's estimates of treatment effect for progression and annualized relapse rate based on all trials in which > 80% of the trial population had RRMS. However, this does not address concerns over the lack of data for progression for longer time periods. Thus, a further reanalysis employed estimates from the Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review, wherein the MTC considered trials in which > 50% of the trial population had RRMS and looked at progression over a three- or six-month period.[9] Results were very sensitive to the use of alternative estimates of effectiveness. Based on the use of data from the CADTH Therapeutic Review, teriflunomide was dominated by GA (incremental cost: $2,056; incremental QALYs: –0.017), compared with the original ICUR for teriflunomide versus GA of $33 (incremental cost: $8; incremental QALYs: 0.240).

TABLE 4: COMMON DRUG REVIEW REANALYSIS: INCREMENTAL COST-UTILITY RATIOS FOR TERIFLUNOMIDE VERSUS EACH INTERVENTION BASED ON ALTERNATE ESTIMATES OF CLINICAL EFFECTIVENESS

	Base-Case Analysis Submitted by Manufacturer	Reanalysis by CDR Using Manufacturer's MTC Estimates for All Trials with RRMS ≥80%	Reanalysis by CDR Using Estimates from CADTH Therapeutic Review
BSC	ICUR for teriflunomide vs. BSC $140,569	ICUR for teriflunomide vs. BSC $132,893	ICUR for teriflunomide vs. BSC $212,582
GA	ICUR for teriflunomide vs. GA $33	ICUR for teriflunomide vs. GA $40,636	Teriflunomide is dominated
Dimethyl fumarate	ICUR for dimethyl fumarate vs. teriflunomide $246,185	ICUR for dimethyl fumarate vs. teriflunomide $316,519	ICUR for dimethyl fumarate vs. teriflunomide $143,936
Rebif	Teriflunomide is dominant	Teriflunomide is dominant	Teriflunomide is dominant
Avonex	Teriflunomide is dominant	Teriflunomide is dominant	Teriflunomide is dominant

BSC = best supportive care; CADTH = Canadian Agency for Drugs and Technologies in Health; CDR = Common Drug Review; GA = glatiramer acetate; ICUR = incremental cost-utility ratio; MTC = mixed treatment comparison; RRMS = relapsing-remitting multiple sclerosis.

3.3.2 Utilities

The utility values by EDSS state were much lower than those found in other studies. Reanalysis adopted utility values provided by the manufacturer from the TEMSO trial[13] — baseline values for all patients, up to EDSS 5 — as well as data from the UK Multiple Sclerosis Research Trust (ScHARR), which allowed estimation of utility value by EDSS level,[14] for EDSS level 6 and above. Results for the comparison of teriflunomide with BSC were sensitive to the changes in the source of utility values with the ICUR increasing from $140,569 to $159,913.

TABLE 5: COMMON DRUG REVIEW REANALYSIS: INCREMENTAL COST-UTILITY RATIOS FOR TERIFLUNOMIDE VERSUS EACH INTERVENTION BASED ON ALTERNATE ESTIMATES OF UTILITIES

	Base-Case Analysis Submitted by Manufacturer	Reanalysis by CDR Using Utility Values from TEMSO (EDSS 0 to 5) and the UK MS Research Trust Study (EDSS 6 to 9)
BSC	ICUR for teriflunomide vs. BSC $140,569	ICUR for teriflunomide vs. BSC $159,913
GA	ICUR for teriflunomide vs. GA $33	ICUR for teriflunomide vs. GA $38
Dimethyl fumarate	ICUR for dimethyl fumarate vs. teriflunomide $246,185	ICUR for dimethyl fumarate vs. teriflunomide $280,110
Rebif	Teriflunomide is dominant	Teriflunomide is dominant
Avonex	Teriflunomide is dominant	Teriflunomide is dominant

BSC = best supportive care; CADTH = Canadian Agency for Drugs and Technologies in Health; CDR = Common Drug Review; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; ICUR = incremental cost-utility ratio.

3.3.3 Exclusion of Side Effects

Given the concerns over the method for including side effects within the model, reanalysis was required. Ideally, analysis would have been conducted using incidence figures for side effects for all treatments. As this was unavailable, side effects were excluded from the analysis. Exclusion of side effects had little impact on the results of the CDR reanalysis.

TABLE 6: COMMON DRUG REVIEW REANALYSIS: INCREMENTAL COST-UTILITY RATIOS FOR TERIFLUNOMIDE VERSUS EACH INTERVENTION BASED ON ALTERNATE ESTIMATES OF SIDE EFFECTS

	Base-Case Analysis Submitted by Manufacturer	Reanalysis by CDR Excluding Side Effects
BSC	ICUR for teriflunomide vs. BSC $140,569	ICUR for teriflunomide vs. BSC $140,518
GA	ICUR for teriflunomide vs. GA $33	ICUR for teriflunomide vs. GA $49
Dimethyl fumarate	ICUR for dimethyl fumarate vs. teriflunomide $246,185	ICUR for dimethyl fumarate vs. teriflunomide $243,271
Rebif	Teriflunomide is dominant	Teriflunomide is dominant
Avonex	Teriflunomide is dominant	Teriflunomide is dominant

BSC = best supportive care; CDR = Common Drug Review; GA = glatiramer acetate; ICUR = incremental cost-utility ratio.

3.3.4 Costs

Given concerns over the data employed relating to the costs by EDSS level and the costs of relapses, costs employed within the CADTH Therapeutic Review[9] were used in reanalysis alongside Ontario cost for drugs (and Quebec list price for dimethyl fumarate) as found in the Cost Comparison Table (Appendix 1: Cost Comparison Table for Teriflunomide). The results of the CDR reanalysis favoured teriflunomide, with GA now being dominated and the ICUR for teriflunomide versus BSC lowered from $140,569 to $103,484.

TABLE 7: COMMON DRUG REVIEW REANALYSIS: INCREMENTAL COST-UTILITY RATIOS FOR TERIFLUNOMIDE VERSUS EACH INTERVENTION BASED ON ALTERNATE COST ESTIMATES

	Base-Case Analysis Submitted by Manufacturer	Reanalysis by CDR with Alternate Cost Estimates
BSC	ICUR for teriflunomide vs. BSC $140,569	ICUR for teriflunomide vs. BSC $103,484
GA	ICUR for teriflunomide vs. GA $33	Teriflunomide is dominant
Dimethyl fumarate	ICUR for dimethyl fumarate vs. teriflunomide $246,185	ICUR for dimethyl fumarate vs. teriflunomide $99,161
Rebif	Teriflunomide is dominant	Teriflunomide is dominant
Avonex	Teriflunomide is dominant	Teriflunomide is dominant

BSC = best supportive care; CDR = Common Drug Review; GA = glatiramer acetate; ICUR = incremental cost-utility ratio.

3.3.5 Mortality

Given concerns over the methods for interpolation of mortality over EDSS levels, reanalysis employed the actual standardized mortality ratios for each EDSS level from the Sadovnick study (i.e., same mortality ratio for all EDSS scores included in the same severity category). A further reanalysis assumed no excess mortality associated with MS as per a sensitivity analysis within the CADTH Therapeutic Review.[9]

CDR reanalysis found little effect when changing assumptions on mortality.

TABLE 8: COMMON DRUG REVIEW REANALYSIS: INCREMENTAL COST-UTILITY RATIOS FOR TERIFLUNOMIDE VERSUS EACH INTERVENTION BASED ON ALTERNATE MORTALITY EFFECTS

	Base-Case Analysis Submitted by Manufacturer	Reanalysis by CDR Using Original Data from Sadovnick	Reanalysis by CDR Assuming No Effect of MS on Mortality
BSC	ICUR for teriflunomide vs. BSC $140,569	ICUR for teriflunomide vs. BSC $140,272	ICUR for teriflunomide vs. BSC $138,195
GA	ICUR for teriflunomide vs. GA $33	Teriflunomide is dominant	Teriflunomide is dominant
Dimethyl fumarate	ICUR for dimethyl fumarate vs. teriflunomide $246,185	ICUR for dimethyl fumarate vs. teriflunomide $245,941	ICUR for dimethyl fumarate vs. teriflunomide $243,451
Rebif	Teriflunomide is dominant	Teriflunomide is dominant	Teriflunomide is dominant
Avonex	Teriflunomide is dominant	Teriflunomide is dominant	Teriflunomide is dominant

BSC = best supportive care; CDR = Common Drug Review; GA = glatiramer acetate; ICUR = incremental cost-utility ratio; MS = multiple sclerosis.

3.3.6 Withdrawals

Given concerns over using differential withdrawal rates, reanalysis was conducted assuming a withdrawal rate of 17% (the default rate for teriflunomide) for all treatments. Within the CDR reanalysis, the ICUR for teriflunomide versus GA increased from $33 to $31,303.

TABLE 9: COMMON DRUG REVIEW REANALYSIS: INCREMENTAL COST-UTILITY RATIOS FOR TERIFLUNOMIDE VERSUS EACH INTERVENTION BASED ON EQUAL WITHDRAWAL RATES

	Base Case Analysis Submitted by Manufacturer	Reanalysis by CDR Assuming a 17% Withdrawal Rate for All Treatments
BSC	ICUR for teriflunomide vs. BSC $140,569	ICUR for teriflunomide vs. BSC $140,569
GA	ICUR for teriflunomide vs. GA $33	ICUR for teriflunomide vs. GA $31,303
Dimethyl fumarate	ICUR for dimethyl fumarate vs. teriflunomide $246,185	ICUR for dimethyl fumarate vs. teriflunomide $338,068
Rebif	Teriflunomide is dominant	Teriflunomide is dominant
Avonex	Teriflunomide is dominant	Teriflunomide is dominant

BSC = best supportive care; CDR = Common Drug Review; GA = glatiramer acetate; ICUR = incremental cost-utility ratio.

3.3.7 Combination of the Above (Best Available Estimate)

A final CDR reanalysis was conducted whereby all the revised assumptions considered above were implemented:

- clinical effectiveness based on the CADTH Therapeutic Review[9]
- utility values from manufacturer data provided from TEMSO (EDSS scores 0 to 5), as well as utility values from the UK Multiple Sclerosis Research Trust (EDSS scores 6 to 9)[14]
- exclusion of side effects
- revised cost estimates
- use of the actual standardized mortality ratios for each EDSS level from the Sadovnick study[10]
- assuming a withdrawal rate of 17% (the default rate for teriflunomide) for all treatments.

Based on the above, the ICUR for teriflunomide versus GA increased from $33 to $409,175. The ICUR for teriflunomide versus BSC increased from $140,569 to $195,070. The incremental cost per life-year gained for teriflunomide versus GA increased from $628 to $6,659,855.

TABLE 10: COMMON DRUG REVIEW REANALYSIS: INCREMENTAL COST-UTILITY RATIOS FOR TERIFLUNOMIDE VERSUS EACH INTERVENTION BASED ON BEST AVAILABLE ESTIMATE

	Base-Case Analysis Submitted by Manufacturer	CDR Reanalysis (Best Available Estimate)
BSC	ICUR for teriflunomide vs. BSC $140,569	ICUR for teriflunomide vs. BSC $195,070
GA	ICUR for teriflunomide vs. GA $33	ICUR for teriflunomide vs. GA $409,175
Dimethyl fumarate	ICUR for dimethyl fumarate vs. teriflunomide $246,185	ICUR for dimethyl fumarate vs. teriflunomide $10,030
Rebif	Teriflunomide is dominant	Teriflunomide is dominant
Avonex	Teriflunomide is dominant	Teriflunomide is dominant

BSC = best supportive care; CDR = Common Drug Review; GA = glatiramer acetate; ICUR = incremental cost-utility ratio.

TABLE 11: COMMON DRUG REVIEW REANALYSIS: INCREMENTAL COST PER LIFE-YEAR GAINED FOR TERIFLUNOMIDE VERSUS EACH INTERVENTION BASED ON BEST AVAILABLE ESTIMATE

	Base-Case Analysis Submitted by Manufacturer	CDR Reanalysis (Best Available Estimate)
BSC	ICER for teriflunomide vs. BSC $3,068,575	ICER for teriflunomide vs. BSC $5,009,938
GA	ICER for teriflunomide vs. GA $628	ICER for teriflunomide vs. GA $6.659,855
Dimethyl fumarate	ICER for dimethyl fumarate vs. teriflunomide $6,243,006	ICER for dimethyl fumarate vs. teriflunomide $272,640
Rebif	Teriflunomide is dominant	Teriflunomide is dominant
Avonex	Teriflunomide is dominant	Teriflunomide is dominant

BSC = best supportive care; CDR = Common Drug Review; GA = glatiramer acetate; ICER = incremental cost-effectiveness (life-years) ratio.

3.3.8 Reanalysis Based on Price Reduction

A reanalysis presenting the ICUR for teriflunomide versus BSC and GA, assuming further price reductions for teriflunomide, was conducted. Results are very sensitive to price. Based on the manufacturer's submission, teriflunomide would dominate GA with a less than 1% price reduction. Based on the CDR's best available estimate analysis presented in Table 11, the ICUR for teriflunomide versus GA would be less than $50,000 with a price reduction of slightly more than 13%. With a price reduction of 15% or more, teriflunomide would dominate GA.

TABLE 12: COMMON DRUG REVIEW ANALYSIS OF INCREMENTAL COST-UTILITY RATIOS FOR TERIFLUNOMIDE VERSUS BEST SUPPORTIVE CARE BASED ON VARIOUS PRICE REDUCTION SCENARIOS

Scenario	ICUR Based on Manufacturer's Analysis	Revised ICUR Based on CDR "Best Available Estimate"
Manufacturer's base case	$140,569	$195,070
10% price reduction	$124,080	$168,087
20% price reduction	$107,590	$141,104
30% price reduction	$91,101	$114,122
40% price reduction	$74,612	$87,139
50% price reduction	$58,123	$60,156
60% price reduction	$41,634	$33,173
70% price reduction	$25,145	$6,190
80% price reduction	$8,655	Teriflunomide dominates BSC
90% price reduction	Teriflunomide dominates BSC	Teriflunomide dominates BSC

BSC = best supportive care; CDR = Common Drug Review; ICUR = incremental cost-utility ratio.

TABLE 13: COMMON DRUG REVIEW ANALYSIS OF INCREMENTAL COST-UTILITY RATIOS FOR TERIFLUNOMIDE VERSUS GLATIRAMER ACETATE BASED ON VARIOUS PRICE REDUCTION SCENARIOS

Scenario	ICUR Based on Manufacturer's Analysis	Revised ICUR Based on CDR "Best Available Estimate"
Manufacturer's base case	$33	$409,175
10% price reduction	Teriflunomide dominates GA	$135,231
15% price reduction	Teriflunomide dominates GA	Teriflunomide dominates GA
20% price reduction	Teriflunomide dominates GA	Teriflunomide dominates GA

CDR = Common Drug Review; GA = glatiramer acetate; ICUR = incremental cost-utility ratio.

3.3.9 Analysis by Expanded Disability Status Scale Level

The final CDR reanalysis was to present the results for the best available estimate analysis by specific EDSS level. The values of the ICURs did vary by EDSS level with the ICURs for teriflunomide versus BSC and GA and for dimethyl fumarate versus teriflunomide, all declining with more advanced EDSS level. However, the sensitivity analysis by price varied only marginally by EDSS level. For example, for an EDSS level of 1, the price for teriflunomide would have to be reduced by slightly less than 14% for the ICUR for teriflunomide versus GA to be less than $50,000 compared with 11.5% for an EDSS level of 5.

TABLE 14: COMMON DRUG REVIEW ANALYSIS OF INCREMENTAL COST-UTILITY RATIOS BY SPECIFIC EXPANDED DISABILITY STATUS SCALE LEVELS

EDSS Level	ICUR Based on Manufacturer's Analysis Revised ICUR Based on CDR "Most Likely Scenario"		
	Teriflunomide vs. BSC	Teriflunomide vs. GA	Dimethyl fumarate vs. teriflunomide
Combined weighted population	$195,070	$409,175	$10,030
EDSS level 1	$221,229	$500,055	$15,411
EDSS level 2	$204,586	$439,593	$12,185
EDSS level 3	$190,361	$397,297	$9,064
EDSS level 4	$173,534	$346,199	$5,042
EDSS level 5	$152,653	$281,298	$1,356

BSC = best supportive care; CDR = Common Drug Review; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; ICUR = incremental cost-utility ratio.

4. DISCUSSION

The key limitations associated with the manufacturer's submission are summarized in Table 15.

Based on CDR reanalyses, assumptions relating to the relative treatment effectiveness and withdrawal levels had the most impact on the results of the analysis. The failure of the analysis to consider the possible waning of treatment effects was not addressed and the impact of this on the study results is therefore unknown.

TABLE 15: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Withdrawal rates for treatments	Differential rates biased results in favour of teriflunomide	Assuming equal withdrawal rates significantly increased the ICUR for teriflunomide vs. GA
Treatment effectiveness	Restricting trials included in the MTC and focusing on treatment effectiveness at 3 months biased results in favour of GA	Assuming relative effectiveness as per the CADTH Therapeutic Review significantly increased the ICUR for teriflunomide vs. GA
Waning of treatment effect	Model did not facilitate consideration	Likely to increase ICURs for treatment vs. BSC. Impact of ICURs for comparison of therapies unknown

BSC = best supportive care; CADTH = Canadian Agency for Drugs and Technologies in Health; GA = glatiramer acetate; ICUR = incremental cost-utility ratio; MTC = mixed treatment comparison.

The model is very sensitive to relative treatment effectiveness values that have been derived through the conduct of an MTC. It should be noted that the different approaches to the definition of sustained accumulation of disability (progression) and the analysis of these data, including reporting of different effect measures (hazard ratio versus risk ratio), likely contributed to the difference observed between the manufacturer's submitted MTC and the CADTH Therapeutic Review network meta-analysis.[9] The

comparability of the manufacturer's submitted economic evaluation and the economic evaluation from the CADTH Therapeutic Review has been assessed in Appendix 5: Comparison with the Canadian Agency for Drugs and Technologies in Health Therapeutic Review .

Although CDR requested and received reanalyses from the manufacturer, upon receipt of some of these analyses, CDR determined that the information provided may not be the most appropriate, given the methodology issues in adjusting for baselines in the MTC, as well as the calculation of the EDSS and relapse costs. CDR used the manufacturer-provided utility values for EDSS levels 0 to 5 from TEMSO, as these represented an acceptable alternative to the manufacturer's original utility values, which appear to be very low.

Given the limitations and uncertainty associated with the comparisons in the MTC, the results should be interpreted with caution (see CDR Clinical Report: Appendix VII).

4.1 Issues for Consideration

The major issue not addressed with respect to the economic modelling is the potential for the waning of treatment effect. This would likely increase the ICUR for teriflunomide versus BSC, but the direction of its effect on the ICURs for comparisons of therapies is unknown.

The results will be sensitive to any confidential prices for each of the therapies considered (dimethyl fumarate, Rebif, Avonex, and GA).

The population was based on TEMSO, which included a mix of treatment-naive patients (73%) and patients switched from prior injection-based therapies due to lack of tolerability. It was not possible to run separate analyses for treatment-naive or intolerant patients in the model.

4.2 Patient Input

The Multiple Sclerosis Society of Canada (MS Society) provided input for the teriflunomide submission. Information for this submission was obtained from publicly available information about the impact of MS and from an MS Society survey (N = 1,345) conducted in English and French in February 2013 to gather data for patient input for the CADTH Therapeutic Review of MS Disease-Modifying Therapies. The patient group stated that MS is an unpredictable and often disabling disease, symptoms of which include difficulty in walking, fatigue, difficulty with coordination of arms or legs, loss of vision, numbness or tingling, memory or attention problems, and pain; each of these had an impact on patients' lives. Some of these aspects, along with overall quality of life, were included in the manufacturer's economic evaluation.

The patient group reported that burden of this disease is also felt by caregivers. Information on the impact on caregivers was provided by the manufacturer as a caregiver disutility in the societal perspective analysis.

Dislike of using a needle was second only to the high cost of MS therapies as factors preventing respondents from taking their current DMT at times. The potential benefit of oral therapy was not included in the pharmacoeconomic model.

Most of the respondents to the MS Society survey had no experience with teriflunomide. Expectations for a new DMT included lower and/or limited side effects, greater affordability, greater convenience (e.g., no refrigeration), and improvement in everyday function. Respondents also noted that an oral drug would improve compliance. The manufacturer's economic evaluation takes into account side effect profiles, although the methodology for reporting side effects appears flawed.

5. CONCLUSIONS

CDR found several limitations with the manufacturer's economic analysis. A reanalysis addressing all of these limitations (except treatment waning over time) found that teriflunomide dominated Rebif and Avonex, but the ICUR for teriflunomide versus GA was $409,175.

APPENDIX 1: COST COMPARISON TABLE FOR TERIFLUNOMIDE

Clinical experts have deemed the comparators presented in Table 16 to be appropriate. 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.

TABLE 16: COST COMPARISON TABLE FOR TERIFLUNOMIDE

Drug/Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose	Average Weekly Drug Cost ($)	Average Yearly Drug Cost ($)
Teriflunomide (Aubagio)	**14 mg**	**tablet**	[redacted][b]	**14 mg once daily**	[redacted]	[redacted]
Dimethyl fumarate (Tecfidera)[c]	120 mg	capsule	14.3836[d]	2 x 120 mg twice daily	403	21,000
Fingolimod (Gilenya)	0.5 mg	capsule	85.1648	0.5 mg daily	596	31,085
Glatiramer acetate (Copaxone)	20 mg/mL	pre-filled syringe	44.4960	20 mg SC daily	311	16,241
Interferon beta-1a (Avonex)	30 mcg (30 MIU)	pre-filled syringe or pen	405.76	30 mcg IM per week	406	21,157
Interferon beta-1a (Rebif)	22 mcg (6 MIU) 44 mcg (12 MIU)	pre-filled syringe	128.8433 156.8533	22 mcg or 44 mcg 3 times weekly	387 471	20,155 24,536
Interferon beta-1b (Extavia)	0.3 mg (9.6 MIU) powder for injection	single use vial	99.3593	250 mcg 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	250 mcg SC every other day	385	20,075
Natalizumab (Tysabri)	300 mg per 15 mL	IV solution	3,158.62	300 mg IV infusion every four weeks	790	41,080

IM = intramuscular; IV = intravenous; MIU = million international units; SC = subcutaneous.
[a]Drug prices are taken from the Ontario Formulary Exceptional Access Program (April 2014) unless otherwise indicated and do not include prescription fees, costs of dose preparation, or injection administration.
[b]Manufacturer confidential submitted price.
[c]Initial recommended dose of dimethyl fumarate is 120 mg twice daily for 7 days ($28.77 daily), followed by the usual dose as listed above.
[d]Quebec Formulary (April 2014).

APPENDIX 2: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

In 2013, the Canadian Agency for Drugs and Technologies in Health (CADTH) completed a therapeutic review in the area of relapsing-remitting multiple sclerosis.[9] Key similarities and differences between CADTH and the manufacturer's economic evaluations are presented in Appendix 5: Comparison with the Canadian Agency for Drugs and Technologies in Health Therapeutic Review.

No additional published economic evaluations were identified. Two technology appraisals from the Scottish Medicines Consortium and the National Institute for Health and Clinical Excellence (NICE) were identified.[15,16]

The appraisal by the Scottish Medicines Consortium was based on a cost-minimization analysis submitted by the company based on the assumption of equal efficacy between teriflunomide, Rebif 44 mcg, Avonex 30 mcg, and GA 20 mg. Although in the base analysis teriflunomide was more expensive than each of the other treatment options, a Patient Access Scheme was offered that reduced the price to make it as cost-effective as the other treatment options.

The appraisal by NICE involved a Markov model that appears to have the same design as that based on the submission to the Common Drug Review. Teriflunomide was compared with a blended comparator of other drugs and teriflunomide dominated this comparator in the base case. NICE requested reanalyses based on the utility values employed in the model and the clinical effectiveness estimates from the MTC — similar concerns aired in this review for the Common Drug Review.

APPENDIX 3: SUMMARY OF KEY OUTCOMES

TABLE 17: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS TERIFLUNOMIDE COMPARED WITH GLATIRAMER ACETATE?

Teriflunomide vs. GA	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone		X				
Clinical outcomes		X				
Quality of life			X			
ICUR or net benefit calculation	$409,175					

GA = glatiramer acetate; ICUR = incremental cost-utility ratio; NA = not applicable.

The above is based on the Common Drug Review (CDR) reanalysis.

TABLE 18: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS TERIFLUNOMIDE COMPARED WITH REBIF?

Teriflunomide vs. 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			
ICUR or net benefit calculation	Teriflunomide dominates Rebif					

ICUR = incremental cost-utility ratio; NA = not applicable.

The above is based on the CDR reanalysis.

TABLE 19: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS TERIFLUNOMIDE COMPARED WITH AVONEX?

Teriflunomide vs. Avonex	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes		X				
Quality of life			X			
ICUR or net benefit calculation	Teriflunomide dominates Avonex					

ICUR = incremental cost-utility ratio; NA = not applicable.

The above is based on the CDR reanalysis.

TABLE 20: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS TERIFLUNOMIDE COMPARED WITH DIMETHYL FUMARATE?

Teriflunomide vs. Dimethyl Fumarate	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical Outcomes				X		
Quality of life			X			
ICUR or net benefit calculation	The ICUR for dimethyl fumarate versus teriflunomide is $10,030					

ICUR = incremental cost-utility ratio; NA = not applicable.

The above is based on the CDR reanalysis using Quebec Formulary price ($14.3836 per tablet, $21,000 annually).

APPENDIX 4: ADDITIONAL INFORMATION

TABLE 21: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments *Reviewer to provide comments if checking "no"*	Major concerns are with respect to the cost by Expanded Disability Status Scale level and the cost of relapses and to the overly cumbersome presentation of the model with the inability to compare more than one treatment at a time.		
Was the material included (content) sufficient?			X
Comments *Reviewer to provide comments if checking "poor"*	The manufacturer was asked to allow for treatment waning in their model. These were not provided		
Was the submission well organized and was information easy to locate?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 22: AUTHOR INFORMATION

Authors	Affiliations
[redacted]	Oxford Outcomes Toronto

	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 5: COMPARISON WITH THE CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH THERAPEUTIC REVIEW

In 2013, the Canadian Agency for Drugs and Technologies in Health (CADTH) completed a therapeutic review in the area of relapsing-remitting multiple sclerosis.[9] Teriflunomide was excluded from the base economic analysis, given that the cost of teriflunomide was unknown. In an exploratory analysis, an annual cost of $24,184 for teriflunomide was adopted based on the relative price of teriflunomide and fingolimod in the US (compared with $[redacted] per year, based on the manufacturer's submitted confidential price). A comparison of the two economic analyses was undertaken to attempt to explain differences in the reported incremental cost-utility ratio of teriflunomide 14 mg compared with reference comparator, GA 20 mg.

TABLE 23: COMPARISON OF THE MODEL STRUCTURE, INPUTS, AND RESULTS FROM THE MANUFACTURER'S SUBMISSION AND THE CADTH THERAPEUTIC REVIEW ON DISEASE-MODIFYING TREATMENTS

	Manufacturer's Submission	CADTH Therapeutic Review
Population	Mean age 38 years 72% females EDSS score ≤5.5 who are treatment naive, or those requiring a first switch to another therapy due to intolerance	Mean age 36 years 68% females Mean EDSS score: 2.3 Time since onset: 5 years
Stopping rule	EDSS of 7, conversion from RRMS to SPMS, or have treatment discontinued due to lack of efficacy or tolerability	Once patients progress to an EDSS of 7.0 or SPMS, treatment is withdrawn
Comparator treatments	IFN beta 1a 30 mcg (Avonex) IFN beta 1a 44 mcg (Rebif) GA 20 mg Dimethyl fumarate 240 mg b.i.d Extavia and Betaseron were not included in the manufacturer's analysis as clinical advice and IMS Brogan data indicate that these treatments are used in <10% of patients Fingolimod and Natalizumab were not included as these treatments are not indicated for first line treatment of RRMS	<u>Primary analysis:</u> IFN beta-1a 30 mcg (Avonex) IFN beta-1a 22 mcg (Rebif) IFN beta-1a 44 mcg (Rebif) IFN beta-1b 250 mcg (Betaseron) IFN beta-1b 250 mcg (Extavia) GA 20 mg/mL Dimethyl fumarate 240 mg Fingolimod 0.5 mg Natalizumab 300 mg/15 mL <u>Exploratory analysis:</u> Alemtuzumab 12 mg and 24 mg Teriflunomide 7 mg and 14 mg
Model type	Cost-utility analysis	Cost-utility analysis
Time horizon	20 years	25 years
Cycle length	1 year	3 months
Model structure	Markov model (based on ScHARR model) 21 health states defined by MS type (RRMS or SPMS)	Markov cohort approach 5 health states, defined according to the Kurtzke EDSS, also based on severity of relapse
Natural history: transitioning between states	Transition matrices were developed based on the London, Ontario, MS registry of patients receiving best supportive care and the	Transitional probabilities were based on estimates reported in the published literature from London Ontario MS registry cohort

	Manufacturer's Submission	CADTH Therapeutic Review
(disease progression)	placebo arms of the teriflunomide trials TEMSO and TOWER Improvements in EDSS state were recorded in the TOWER and TEMSO trials	study reported by ScHARR (Tappenden et al. 2001) Improvements in lower health states (EDSS 0 and 5.5) in the EDSS score were modelled based on Tremlett et al. (British Columbia MS database)
Natural history: relapses	Relapse rates were estimated from the literature. Base case analysis, mean ARR by year since diagnosis were derived from Patzold et al.[17] Relapse rates were distributed over all EDSS states and MS types using patient distribution for each year of diagnosis, sourced from a UK MS survey. Two types of relapses were considered in the model: relapses leading to hospitalization and relapses not leading to hospitalization. Proportions of these two types of relapses were based on data from the TEMSO trial	The base estimate from ScHARR of 0.835 for EDSS 0 to 2 in combination with the rate of decrease by Patzold and Pocklington was used to estimate the relapse rate for health state 1 (EDSS 0 to 2.5) for patients with 5 years since onset and onwards. The regression analysis from the Patzold and Pocklington study was used as the basis for estimating the decrease of the relapse rate over time for patients in health state 2 (EDSS 3.0 to 5.5), adjusting such that the patients enter the model with an average time since disease onset of five years
Natural history: mortality	All-cause mortality is calculated using the Statistics Canada life table for the data-years 2000 to 2002 MS-associated mortality was derived from a study published by Pokorski et al.,[11] the relative increase in mortality rate per EDSS level was applied to the all-cause mortality. Mortality risks were assumed to be the same for RRMS and SPMS	All-cause mortality is calculated using the Statistics Canada life table for the data-years 2000 to 2002 MS-associated mortality was not included in the model
Treatment effectiveness	Based on an unpublished MTC funded by the manufacturer, focusing on trials starting recruitment in or after the year 2000 and including ≥80% RRMS patients. The manufacturer's pharmacoeconomic report states that 29 trials were included in the MTC base case analysis The MTC evaluated rate ratio for the ARR, HR for disease progression, and OR on discontinuation rate A random-effects model was employed for the analysis	Based on an MTC conducted by CADTH. Overall, 68 reports describing 30 unique studies were selected for inclusion. Monotherapy (27) and combination therapy (4) studies were both included. Studies were published between 1993 and 2013 The MTC derived relative risk of sustained disability progression for each treatment, rate ratio of ARR A random-effects model was employed for the analysis
Treatment effectiveness: hospitalization	Assumptions about treatment effect on hospitalization were applied to natural history proportion of relapses leading to hospitalization	Hospitalization wasn't included in the model — relapses were assessed as severe or mild/moderate. It was assumed that 23% of relapses are severe (Prosser et al 2004)
Treatment effectiveness:	Different withdrawal rates applied to each treatment	Constant annual rate of discontinuation was assumed across all treatments for the first

	Manufacturer's Submission	CADTH Therapeutic Review
withdrawal		two years of 15% (based on clinical trial data and clinical opinion). After 2 years, discontinuation rate was assumed to be 0
Treatment effectiveness: adverse events	The frequency and duration of the selected adverse events were obtained from the corresponding clinical trials, with selection based on whether there was ≥4% difference between treatment and placebo, and/or the adverse event has been included in previous HTA submissions	Due to the transient nature of most of the adverse events related to the RRMS treatments, adverse events were not included in the model
Utility values	Utility values for EDSS states were obtained from a Canadian study, Tappenden et al.[7] Utilities for SPMS are calculated from the EDSS-specific utility for RRMS states, by subtracting 0.045 from each data point as reported in the UK literature (Orme et al.[12]) Disutility of relapse not requiring hospitalization (–0.0710) and relapse requiring hospitalization (–0.2356) were obtained from literature using UK utility values (Orme et al.[12]) The model includes the disutility of adverse events associated with each treatment. Disutility values for adverse events were obtained from the literature	The base case utilities values used were from Prosser et al. because it considered the same health state definitions and was based on community-based preferences The values from Prosser et al. were substantially higher than those of the alternative sources in most circumstances
Costs: drug	Annual drug acquisition costs were calculated based on Quebec unit prices. Quebec costs were lower than those in the ODBF	Drug costs were obtained from the ODBF (2013) where possible The assumed price of teriflunomide differed from the manufacturer's submitted price [redacted] therefore the model was rerun using this price (see results)
Costs: administration	For Avonex, Rebif, and GA: assumption was made that a nurse home visit was required for training patients on how to self-administer the drugs. Second visit for additional training required in 10% of patients (cost source not stated)	Not reported.
Costs: EDSS state	Annual per patient costs of MS by EDSS scores were estimated from the literature, based on a Canadian costing study (Karampampa et al.[8]). Costs captured in 3 groups by EDSS score in study – linearly extrapolated in submission. Costs of DMT and relapses were removed to avoid double-counting of these costs. Calculations unclear	The cost associated with EDSS health states were sourced from Grima et al (2000) and Karampampa et al.[8] up to an EDSS of 5.5 and extrapolated for the more severe health states
Costs: relapse	Cost per relapse requiring no hospitalization and relapse requiring hospitalization were stated to have been derived from Karampampa et al.[8] Calculations unclear	Cost of relapse was stratified as mild or moderate relapse (Grima et al 2000), or severe relapse (estimated based on Patwardhan et al. 2005)

	Manufacturer's Submission			CADTH Therapeutic Review		
Costs: adverse events	Resource use assumptions based on clinical expert input. Costs obtained from online pharmacy (Well ca 2013), OHIP Schedule of Benefits (2013), and OCCI (2013)			Adverse events were not included in the model		
	Drug Teriflunomide Rebif Avonex GA Dimethyl fumarate	**QALYs** 4.990 4.861 4.735 4.750 5.073	**Costs** $189,860[a] $196,777 $193,034 $189,852 $210,301	**Drug** Teriflunomide (14 mg) Rebif (22 mcg) Rebif (44 mcg) Avonex GA Dimethyl fumarate Extavia Betaseron Natalizumab Fingolimod	**QALYS** 11.299 11.187 11.262 11.167 11.272 11.442 11.376 11.376 11.580 11.422	**Costs** $375,782[b] $337,766[a] $349,937 $377,759 $357,658 $321,589 $361,688 $333,589 $347,292 $482,436 $416,414
Results: base case	**Drug** GA = Teriflunomide = Rebif = Avonex = Dimethyl fumarate =	**ICUR[a]** Reference $33 Dominated Dominated $246,185		**Drug** GA = Extavia = Dimethyl fumarate = Natalizumab = Betaseron = Rebif (22 mcg) = Avonex = Rebif (44 mcg) = Fingolimod = Teriflunomide (14 mg)= Teriflunomide (14 mg)=	**ICUR** Reference $118,242 $236,518 $522,472 $246,411 Dominated Dominated Dominated $632,608 $2,037,065[b] $608,070[a]	

ARR = annualized relapse rate; b.i.d. = twice daily; CADTH = Canadian Agency for Drugs and Technologies in Health; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; HR = hazard ratio; HTA = health technology assessment; ICUR = incremental cost per QALY gained; IFN = interferon; MS = multiple sclerosis; MTC = mixed treatment comparison; MS = multiple sclerosis; OCCI = Ontario Case Costing Initiative; ODBF = Ontario Drug Benefit Formulary; OHIP = Ontario Health Insurance Plan; OR = odds ratio; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

[a]Based on manufacturer's submitted confidential price of $[redacted] per year.

[b]Based on CADTH's assumed annual cost of $24,184 per year.

Summary

There are several differences in the structure and the inputs of the economic models used in the CADTH Therapeutic Review and the manufacturer's submission. The CADTH Therapeutic Review economic model adopted more conservative assumptions. These differences led to substantial variation in the ICUR of teriflunomide compared with glatiramer acetate. Key differences between the two models appear to result from the differing utility values used, and the difference in the methods and results from the mixed treatment comparison that were used to inform treatment effectiveness, especially for the outcome of disability progression. Other differences, such as inclusion of adverse events and excess mortality related to MS in the manufacturer's model but not in the CADTH Therapeutic Review, or different assumptions on discontinuation rate, were also noted.

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