Canada's Drug Agency
L'Agence des médicaments du Canada

Draft Reimbursement Review

Review Report

TERIFLUNOMIDE (AUBAGIO)

(Non-Sponsored Review)

Therapeutic area: Multiple Sclerosis (MS), Radiologically Isolated Syndrome (RIS)

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Key Messages

What Is Radiologically Isolated Syndrome?

- Radiologically isolated syndrome is considered the earliest detectable pre-clinical phase of multiple sclerosis that is characterized by incidental brain or spinal cord magnetic resonance imaging findings in individuals without typical multiple sclerosis symptoms. While radiologically isolated syndrome is defined as asymptomatic, patients may present with non-specific symptoms and require increased health care resources prior to the diagnosis of multiple sclerosis.
- In 2024, there are approximately 18,000 to 210,000 patients with radiologically isolated syndrome in Canada.

What are the Treatment Goals and Current Treatment Options for Radiologically Isolated Syndrome?

- Delaying disease onset and slowing disability progression with increased tolerability and safety were identified as important outcomes of treatments in the patient group input.
- Other important outcomes identified through clinician input include targeting the disease process, preventing future relapses and preventing disability progression, and maintaining health-related quality of life.
- Currently, there are no publicly funded treatments for radiologically isolated syndrome in Canada. Patients with radiologically isolated syndrome are often untreated. Treatment options may include off-label drugs that are used for multiple sclerosis (e.g., interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide) or for other indications (e.g., minocycline).

What Is Teriflunomide and Why Did We Conduct This Review?

- Teriflunomide is a drug that is available as an oral tablet. Health Canada has approved teriflunomide, 14 mg, for relapsing remitting multiple sclerosis.
- We previously reviewed teriflunomide for relapsing remitting multiple sclerosis and issued a recommendation not to list at the submitted price. At the request of the participating drug programs, we reviewed teriflunomide to inform a recommendation on whether it should be reimbursed for adults with radiologically isolated syndrome.

How Did We Evaluate Teriflunomide?

- We reviewed the clinical evidence on the beneficial and harmful effects and compared costs of teriflunomide versus other treatments used in Canada for radiologically isolated syndrome:
- The clinical evidence was identified through systematic searches for available studies. We consulted 2 clinical specialists with expertise in the diagnosis and management of multiple sclerosis, as part of the review process. The review was also informed by 1 patient group submission and 1 clinician group submission in response to our call for input, and by input from the participating drug programs around issues that may impact their ability to implement a recommendation.

What Did We Find?

Clinical Evidence

We reviewed the following clinical evidence:

- 1 trial (TERIS) comparing teriflunomide with placebo in patients with radiologically isolated syndrome

For the comparison of teriflunomide versus placebo:

- There was a statistically significant and clinically important delayed time to first acute or progressive neurological symptom associated with a central nervous system demyelinating event. There was some uncertainty in the evidence because of concerns about potential risk of bias, the small number of patients, and the short treatment duration.

- There was insufficient evidence to show an effect on imaging outcomes, functional status, and health-related quality of life.
- There was no evidence to inform how teriflunomide compares with interferon beta, glatiramer acetate, or dimethyl fumarate.
- The safety profile of teriflunomide was as expected with no new safety signals.

Economic Evidence

- The reimbursement of teriflunomide is expected to decrease drug acquisition costs in jurisdictions that currently fund glatiramer acetate and interferon beta for the treatment of RIS. Conversely, in the majority of jurisdictions where no treatments are currently funded for the treatment of RIS, the reimbursement of teriflunomide will result in increased drug acquisition costs. Given that teriflunomide is associated with increased drug acquisition costs and incremental benefits in the majority of jurisdictions, a cost-effectiveness analysis would be required to determine the cost-effectiveness of teriflunomide relative to no active intervention.

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Abbreviations

AE	adverse event
CNS	central nervous system
CSCT	Computerised Speed Cognitive Test
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
HR	hazard ratio
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention to treat
MRI	magnetic resonance imaging
MS	multiple sclerosis
MusiQoL	Multiple Sclerosis International Quality of Life
PASAT	Paced Auditory Serial Addition Test
RCT	randomized controlled trial
RIS	radiologically isolated syndrome
SAE	serious adverse event
SD	standard deviation

Background and Review Methods

Introduction

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug (product)	Teriflunomide, 14 mg, oral tablets
Relevant Health Canada indication	Not applicable
Mechanism of action	Blocks the proliferation of stimulated lymphocytes, diminishing the numbers of activated lymphocytes in peripheral blood, which may reduce numbers of active lymphocytes available for migration into the CNS
Data protection status	End date: May 14, 2022
Status of generic drugs or biosimilars	Submitted for review by Accel Pharma Inc.: April 2024; several other generics are currently marketed and available
Information on the CDA-AMC review	
Requestor	Formulary Working Group
Indication under consideration for reimbursement	Adults with radiologically isolated syndrome
Clinical review focus	Population: As defined in the indication under consideration for reimbursement Intervention: As per recommended dosage Comparators: interferon beta, glatiramer acetate[a], dimethyl fumarate[a] Outcomes: Efficacy: time to first neurological event from CNS demyelination, time to disease progression, new and/or enlarging and/or gadolinium-enhancing lesions, functional status (e.g., Expanded Disability Status Scale), HRQoL Harms: AE, SAE, withdrawal due to AE, death due to AE, adverse events of special interest (i.e., hepatotoxicity, teratogenicity)

AE = adverse event; CNS = central nervous system; HRQoL = health-related quality of life; SAE = serious adverse event.

[a] CDA-AMC has previously issued a reimbursement recommendation for this drug for relapsing remitting multiple sclerosis.

Objective

The objective of the Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of teriflunomide, 14 mg, oral tablets in the treatment of adults with radiologically isolated syndrome (RIS). The focus will be placed on comparing teriflunomide to relevant comparators and identifying gaps in the current evidence. The Economic Review consists of a cost comparison for teriflunomide compared with relevant comparators for RIS in adults. The comparators considered relevant to the reviews were interferon beta, glatiramer acetate, and dimethyl fumarate.

Review Methods

Sources of Information

The contents of the Clinical Review report are informed by study publications identified through systematic literature searches and input received from patient groups, clinician groups, the public drug programs that participate in the Non-Sponsored Reimbursement Review process, and industry.

Calls for patient group, clinician group, and industry input are issued for each Non-sponsored Reimbursement Review. The full submissions received are available in the consolidated input document <insert hyperlink or citation>. Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical evidence. Relevant patient and clinician group input and industry input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized in a separate document.

Each review team includes at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two neurologists with expertise in the diagnosis and management of multiple sclerosis (MS) participated as part of the review team, with representation from Alberta and Ontario.

Submitted Input From Patient Groups and Clinician Groups

Patient group input was submitted by MS Canada based on information in the literature and previous broad engagement of the MS community on the topic of MS treatments (number of respondents was not reported), as no patient was identified to have been diagnosed with RIS and treated with teriflunomide.

Clinician group input was submitted by the representative on behalf of Canadian Network of MS Clinics (number of clinicians was not reported) which focused on the proposed project scope.

Disease Background

MS is a heterogenous autoimmune central nervous system (CNS) disorder characterized by inflammatory demyelination and axonal transection[1,2] and symptoms including vision loss, motor weakness, and paresthesia.[2] Incidental brain or spinal cord magnetic resonance imaging (MRI) findings suggestive of MS in individuals without typical MS symptoms is defined as RIS.[3,4]

While RIS is asymptomatic by definition, increased health care resource utilization prior to the diagnosis of MS suggests a prodromal phase or non-specific symptoms preceding classical experiences among people with MS; in those with RIS, common reasons for an initial MRI scan included headache and trauma.[2,5] Patients with RIS have presented with cognitive impairment, with a similar profile to patients with relapsing remitting MS.[3]

Based on accumulating evidence about the natural history of RIS, the original 2009 RIS criteria[6] was revised in 2023 to incorporate observed CNS anomalies, risk factors, and earlier treatment; the revised criteria had better sensitivity and maintained specificity, was aligned with the existing 2017 McDonald Criteria, and provided clinicians with a broadly applicable framework.[2,7] Note that the official publication of the 2024 McDonald Criteria was not yet released at the time of writing this report; some patients who were previously diagnosed with RIS would be diagnosed with MS according to the proposed revised criteria.

The prevalence of RIS has been estimated to range from 0.06% to 0.7%,[3] approximately 18,000 to 210,000 patients in Canada in 2024. Studies that used the Okuda criteria reported that the incidence of RIS ranged from 0.05% to 0.1% per year.[8,9] Data are limited on the proportion of patients with RIS at risk of developing MS, with an estimated 30% of patients who converted to symptomatic MS.[5]

Current Management

Treatment Goals

Input from the patient group indicated that there is a need for treatments to delay disease onset and slow disability progression with increased tolerability and safety. The clinical experts and clinician group input echoed this, highlighting that as with MS, the goals of treatment are to target the disease process, prevent future relapses and disability progression, and maintain health-related quality of life (HRQoL).

Current Treatment Options

Currently, there are no publicly funded treatments for RIS in Canada. As such, the clinical experts have expressed that patients with RIS can sometimes be treated off-label with drugs that are approved by Health Canada for patients with relapsing remitting MS (e.g., interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide, ocrelizumab, ofatumumab, natalizumab), or drugs not indicated for MS but for which there is clinical evidence of effectiveness (e.g., minocycline, rituximab).

According to the clinical experts consulted for this review, patients' risk factors including clinical, MRI, and paraclinical characteristics, are used to inform whether treatment may be appropriate. Since RIS is recognized as being a subclinical precursor to clinical MS, including a prodromal phase (i.e., non-specific symptoms such as cognitive impairment, motor or dexterity impairments, fatigue), there is emerging consensus among MS clinicians that treatment with disease-modifying agents may be appropriate among certain patients with RIS.

Key characteristics of teriflunomide are summarized with other treatments available for RIS in the Working Papers, Table 2.

Unmet Needs and Existing Challenges

The following is based on input provided by patient groups, clinician groups, and the clinical experts consulted for this review.

MS Canada advocates for health equity among all who are at risk of developing MS, including patients diagnosed with RIS, by intervening early and filling a therapeutic gap of the MS disease spectrum. The patient group seeks the listing of all Health-Canada authorized drugs for MS (including different classes of drugs, different methods of administration, biosimilars, and generics), in a manner that is timely and equitable, such that patients have improved and consistent access to affordable treatments regardless of place of residence, income status, disease phase, and other factors. As such, MS Canada seeks access to disease-modifying therapies (DMTs) on behalf of patients with RIS which can significantly delay disease onset and slow disability progression, including teriflunomide.

The Canadian Network of MS Clinics did not provide input on unmet needs or existing challenges among patients with RIS.

The clinical experts consulted for this review indicated that RIS is considered to be a pre-clinical, early phase of MS, and the goals of treatment are to prevent future relapses and disability progression. Given that early treatment of a potentially disabling condition is critical, and that current guidelines recommend off-label treatments, the experts expressed that there is a clear gap in approved treatments for patients with RIS.

Clinical Review Methods

Eligibility Criteria

We included studies that adhered to the a priori eligibility criteria, detailed in Working Papers, Table 3. Eligible studies included published phase III and IV randomized controlled trials (RCTs) that included adults with RIS being treated with teriflunomide. Relevant comparators included drugs used in clinical practice in Canada to treat patients described in the indication under review and those included in the Economic Review. These included: interferon beta, glatiramer acetate, and dimethyl fumarate. Because no comparative trials were expected, placebo was also considered as a relevant comparator. Long term extension studies of included RCTs were eligible, regardless of whether there was a comparison group.

We selected outcomes (and follow-up times) for review considering clinical expert input, and patient and clinician group inputs. Selected outcomes are those considered relevant to expert committee deliberations. These included: time to first neurological event from CNS demyelination, time to disease progression, new and/or enlarging and/or gadolinium-enhancing lesions, functional status, HRQoL, and harms.

We included indirect treatment comparisons (ITCs) that adhered to the previously mentioned selection criteria, except for the study design criteria. Studies addressing gaps were those identified by the review team and/or clinical experts that did not meet the eligibility criteria but were considered to address important gaps in the Systematic Review evidence.

Search Strategy

An information specialist conducted a peer reviewed literature search of key bibliographic databases, trial registries, and grey literature sources. The initial search was completed on July 31, 2024, with alerts maintained until the Formulary Management Expert Committee meeting on November 21, 2024. The Working Papers document includes the detailed search strategies.

Study Selection

Two reviewers independently selected relevant studies for inclusion in 2 stages, first by titles and abstracts and then by full texts. Any record considered relevant by either reviewer at the title and abstract stage was reviewed by full text. The 2 reviewers achieved consensus on the studies included in the report.

Data Extraction and Critical Appraisal

One reviewer extracted relevant data from the included studies with verification by a second reviewer. One reviewer appraised the internal and external validity of the available evidence in consideration of inputs by the clinical experts, and patient and clinician groups, with input from a methodologist. Critical appraisal of the included study was guided by the revised Cochrane risk of bias tool for randomized trials (RoB 2).[10]

Clinical Evidence

From the search for primary studies, we identified 85 unique records via the searches of databases and registers, of which we excluded 84 by title and abstract. We screened 1 record by full text and included 1 report of 1 study.

From a supplemental search for ITCs, we identified 24 unique records via the searches of databases and registers, of which none met eligibility by title and abstract.

No long term extension studies nor studies addressing gaps were identified.

Systematic Review

Description of Studies

The TERIS study[11] was a multicentre (13 sites in France, 1 site in Switzerland, and 7 sites in Turkey), phase III, double-blinded, placebo-controlled, RCT that enrolled 89 patients with RIS from September 25, 2017, to October 31, 2022. Sources of support for the study included the manufacturer (Sanofi). The primary end point was time to first acute or progressive neurological event resulting from CNS demyelination. An acute neurologic event was defined by a clinical symptom localized to the optic nerve, brain stem, cerebellum, spinal cord, or long sensory or motor tracts, lasting more than 24 hours and followed by symptom improvement. A progressive event was defined by the onset of a clinical symptom with the temporal profile revealing at least a 12-month progression of neurological deficits. Relevant secondary end points included the cumulative number of new and/or enlarging T2-weighted hyperintense lesions, the cumulative number of new gadolinium-enhancing lesions, and the proportion of patients with new or newly enlarging T2-weighted hyperintense lesions and new gadolinium-enhancing lesions. Exploratory end points included the annualized change in Paced Auditory Serial Addition Test – 3 seconds (PASAT-3; measuring cognitive function), Computerised Speed Cognitive Test (CSCT; measuring attention and processing speed), and the Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL). Adverse events (AEs) were monitored throughout the study. A detailed description of the outcome measures is in the Working Files, Appendix 3.

Key inclusion criteria in the TERIS trial were adults aged 18 years and older, meeting 2009 RIS criteria[6] with structural neuroimaging abnormalities not explained by another disease process, and no historical accounts of remitting clinical symptoms that were consistent with neurologic dysfunction. An independent clinical adjudication committee verified patients' study eligibility. Key exclusion criteria were recent exposure to a DMT (past 3 months) or high dose glucocorticoid (past 30 days), lactating or pregnant individuals, and severe hepatic, kidney, or immune system impairments.

Patients were randomized in a 1:1 ratio to receive oral teriflunomide (Aubagio) 14 mg daily or placebo for at least 96 weeks, with optional continuation until week 144. MRI scans were conducted at baseline, week 48, week 96, week 144, and any time during the study at the discretion of the investigator (including for patients who stopped study treatment prior to a CNS demyelination event). An independent committee adjudicated analysis of MRI scans. The PASAT-3, CSCT, and MusiQoL were assessed at baseline, every 6 months, and at any unscheduled visit after a neurological event. An independent safety monitoring committee reviewed all safety data. Patients who completed the 96 weeks without symptoms suggestive of MS or AEs related to the allocated treatment were offered to enter the third year (total duration of 144 weeks) in the same randomization arm. Patients who converted to MS or opted to discontinue study treatment were included in the safety follow-up. Patients who were diagnosed with MS were offered to start or continue with teriflunomide. All patients who discontinued the study prematurely, or planned to or became pregnant, were recommended to undergo an accelerated elimination procedure.

Concomitant therapy that was allowed with caution included CYP2C8 substrates, drugs metabolized by CYP1A2, warfarin, substrates of (OAT)3, substrates of breast cancer resistant protein, substrates of OAT polypeptide family, known potent CYP and transporter inducers, and vaccination with non-live vaccines; non-permitted concomitant therapy included systemic corticosteroids and ACTH not used for MS relapses, immunosuppressive treatment, plasmapheresis, cytapheresis, or total lymphoid irradiation, anti-arrhythmic or heart rate-lowering systemic therapy, cholestyramine or activated charcoal, and vaccination with live vaccines.

All randomized patients were included in the intention to treat (ITT) analysis for the primary end point. Patients with at least 1 follow-up MRI were included in analyses for the secondary end points. Patients who received at least 1 dose of study drug were followed for safety assessments. No interim analyses were planned and a data cut off date for analyses was not specified.

Results

Patient Disposition

A total of 124 patients were screened for eligibility into the TERIS trial. After excluding 35 patients who did not meet inclusion criteria (n = 18), declined participation (n = 16), or were lost to follow-up (n = 1), 89 patients were allocated to teriflunomide (n = 44) or placebo (n = 45) and all received the randomized treatment. Nine (20%) patients in each treatment group discontinued the allocated treatment and their participation in the study. Reasons for discontinuation in the teriflunomide and placebo group, respectively, were due to an AE (1 patient and 2 patients), withdrawal of consent (3 patients and 1 patient), patient decision to discontinue (0 patient and 4 patients), study termination by the sponsor (0 patient and 1 patient), pregnancy (1 patient and 0 patient), and lost to follow-up (4 patients and 1 patient). Overall, 35 patients (79.5%) in the teriflunomide group and 36 patients (80.0%) in the placebo group completed the study.

Baseline Characteristics

At baseline, patients were overall similar between treatment groups in mean age at RIS diagnosis (mean 38 years [standard deviation (SD), 12]), females (71%) and males (29%), and family history of MS (3%). Reasons for the index MRI scan were primarily headache (52% in the teriflunomide group versus 40% in the placebo group), follow-up of other diseases (30% versus 27%), and dizziness or vertigo (7% versus 27%). The presence of gadolinium-enhancing lesions (30% in the teriflunomide group versus 27% in the placebo group), presence of spinal cord lesions (46% versus 44%), and T2-lesion volume (log-transformed) (mean 3.3 [SD, 0.4] versus mean 3.4 [SD, 0.5]) at baseline were similar between groups. Patients in the teriflunomide and placebo group, respectively, had similar scores at baseline on the Expanded Disability Status Scale (EDSS) (median 0 [SD, 0] in both groups) and the MusiQoL (mean 47.4 [SD, 9.8] and mean 42.5 [SD, 13.3]).

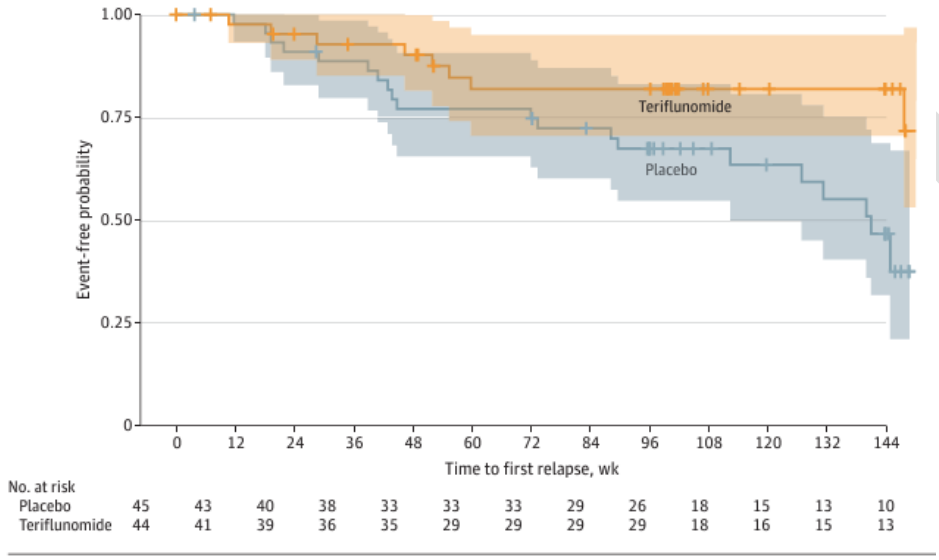
Treatment Exposure and Concomitant Medications

Treatment exposure, adherence, and concomitant medications were not reported in the TERIS trial. It is not clear how many patients remained on treatment and in the study past week 96 to week 144. Subsequent treatment, including the number of patients who continued (teriflunomide group) or started (placebo group) treatment with teriflunomide upon experiencing a primary end point event, were not specified.

Efficacy

Results for outcomes important to this review are presented in Figure 1: Kaplan-Meier Estimate of Time from Randomization to the First Demyelinating Event (Unadjusted Analysis)

Alt Text: The Kaplan-Meier curves of time to first demyelinating event in the teriflunomide group (N = 44) versus the placebo group (N = 45), showing clear separation at about 28 to 30 weeks (number of patients at risk was 36 and 38 in the teriflunomide and placebo group, respectively). The curves dropped at about 42 weeks in the teriflunomide group (number of patients at risk was 35) but were lower in the placebo group (number of patients at risk was 33), remaining the same for teriflunomide but notably lowered for the placebo group through to 144 weeks (number of patients at risk was 13 versus 10 in the teriflunomide versus placebo group, respectively).



No. = number; wk = week.

Source: Lebrun-Frénay et al. (2023).[11] Reproduced with permission from [JAMA Neurol. 2023. 80(10): 1080-1088]. Copyright © (2023) American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Table 2. The Kaplan-Meier plot for the time to first acute or progressive neurological event resulting from CNS demyelination is in Figure 1. Key results include the following:

- Length of follow-up (e.g., median weeks or months [range]) was not reported.
- The median time to event (first acute or progressive neurological event resulting from CNS demyelination) in each treatment group was not reported. The adjusted hazard ratio (HR) was 0.28 (95% CI, 0.11 to 0.71; P value = 0.007), favouring teriflunomide.
- The evidence was insufficient to show a difference between teriflunomide and placebo across all secondary and exploratory end points.

Figure 1: Kaplan-Meier Estimate of Time from Randomization to the First Demyelinating Event (Unadjusted Analysis)

Alt Text: The Kaplan-Meier curves of time to first demyelinating event in the teriflunomide group (N = 44) versus the placebo group (N = 45), showing clear separation at about 28 to 30 weeks (number of patients at risk was 36 and 38 in the teriflunomide and placebo group, respectively). The curves dropped at about 42 weeks in the teriflunomide group (number of patients at risk was 35) but were lower in the placebo group (number of patients at risk was 33), remaining the same for teriflunomide but notably lowered for the placebo group through to 144 weeks (number of patients at risk was 13 versus 10 in the teriflunomide versus placebo group, respectively).

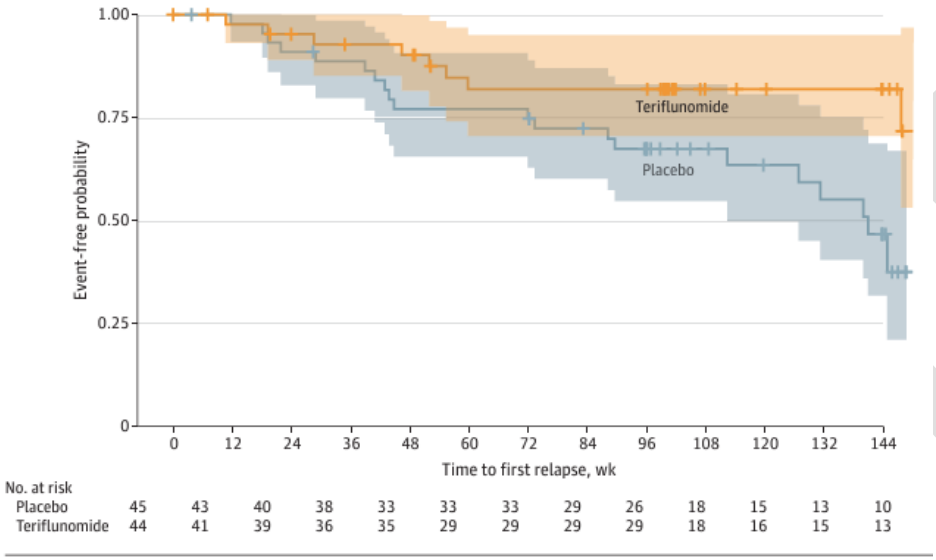


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Table 2: Summary of Key Efficacy Results in the TERIS Trial (ITT Population)

Variable	Teriflunomide N = 44	Placebo N = 45
Primary End Point: Time to first CNS demyelinating event[a]		
Number of patients with a first acute or progressive neurological event resulting from CNS demyelination, n (%)	8 (18.2)	20 (44.4)
First acute neurological event, n (%)	6 (13.6)	18 (40.0)
Initial progressive neurological event, n (%)	2 (4.5)	2 (4.4)
Time to first clinical demyelinating event (weeks), mean (SD)	128.2 (7.25)	109.6 (7.44)
Unadjusted HR (95% CI)[b]	0.37 (0.16 to 0.84)	Reference
P value[c]	0.02	Reference
Adjusted HR[d] (95% CI)	0.28 (0.11 to 0.71)	Reference

Variable	Teriflunomide N = 44	Placebo N = 45
P value[c]	0.007	Reference
Secondary End Points:		
New and/or newly enlarging T2-weighted hyperintense lesions		
Number of patients contributing to the analysis, n (%)	34 (77.3)	37 (82.2)
Number of patients with ≥ 1 new and/or newly enlarging T2-weighted hyperintense lesion(s), n (%)	20 (58.8)	24 (64.9)
Adjusted odds ratio[e] (95% CI)	0.72 (0.25 to 2.06)	Reference
P value	0.54	Reference
Cumulative number of new and/or newly enlarging T2-weighted hyperintense lesions, annualized mean (95% CI)	1.49 (0.82 to 2.69)	3.04 (1.81 to 5.09)
Adjusted rate ratio[f] (95% CI)	0.57 (0.27 to 1.20)	Reference
P value	0.14	Reference
New gadolinium-enhancing lesions		
Number of patients contributing to the analysis, n (%)	33 (75.0)	36 (80.0)
Number of patients with new gadolinium-enhancing lesions, n (%)	5 (15.1)	12 (33.3)
Adjusted odds ratio[e] (95% CI)	0.28 (0.07 to 1.13)	Reference
P value	0.07	Reference
Cumulative number of new gadolinium-enhancing lesions, annualized mean (95% CI)	0.22 (0.09 to 0.55)	0.50 (0.25 to 1.00)
Adjusted rate ratio[f] (95% CI)	0.33 (0.09 to 1.37)	Reference
P value	0.09	Reference
Functional Status: Computerised Speed Cognitive Test (score range not reported)		
Change from baseline to week 96		
Number of patients contributing to the analysis, n (%)	NR	NR
Mean change from baseline to week 96, score (SD)[g]	7.04 (16.69)	–0.52 (8.99)
Annualized change		
Number of patients contributing to the analysis, n (%)	33 (75.0)	36 (80.0)
Mean annualized change (95% CI)	1.99 (0.15 to 3.83)	1.43 (–0.33 to 3.19)
Adjusted mean difference[h] (95% CI)	0.57 (–4.40 to 5.54)	Reference
P value	0.82	Reference
Functional Status: Paced Auditory Serial Addition Test – 3 seconds (total correct responses, 0 to 60 out of 60)		
Change from baseline to week 96		
Number of patients contributing to the analysis, n (%)	NR	NR
Mean change from baseline to week 96, score (SD)[g]	6.0 (13.95)	1.18 (13.38)
Annualized change		
Number of patients contributing to the analysis, n (%)	36 (81.8)	39 (86.7)
Mean annualized change (95% CI)	1.03 (–1.34 to 3.40)	–0.09 (–2.27 to 2.08)

Variable	Teriflunomide N = 44	Placebo N = 45
Adjusted mean difference[h] (95% CI)	1.02 (–2.22 to 4.27)	Reference
P value	0.53	Reference
HRQoL: Multiple Sclerosis International Quality of Life Questionnaire (0 [worst quality of life] to 100 [best quality of life])		
Change from baseline to week 96		
Number of patients contributing to the analysis, n (%)	NR	NR
Mean change from baseline to week 96, score (SD)[g]	–4.40 (15.11)	1.65 (16.11)
Annualized change		
Number of patients contributing to the analysis, n (%)	35 (79.5)	38 (84.4)
Mean annualized change (95% CI)	–0.26 (–2.60 to 2.07)	1.12 (–1.12 to 3.36)
Adjusted mean difference[i] (95% CI)	–1.36 (–4.62 to 1.89)	Reference
P value	0.41	Reference

CI = confidence interval; CNS = central nervous system; CSCT= Computerised Speed Cognitive Test; EDSS = Expanded Disability Status Scale; HR = hazard ratio; HRQoL = health-related quality of life; ITT = intention to treat; MS = multiple sclerosis; NR = not reported; PASAT-3 = Paced Auditory Serial Addition Test – 3 seconds; RIS = radiologically isolated syndrome; SD = standard deviation.

[a] The number of patients censored, and reasons for the censoring were not reported. The method used to calculate the mean (SD) time to event was not reported and there are patients remaining at risk at the end of follow-up.

[b] Based on an unadjusted Cox proportional hazards regression model.

[c] P value from a log-rank test. The alpha has not been adjusted for multiple testing and there is an increased risk of type I error.

[d] Based on a Cox proportional hazards regression model that adjusted for sex, age at time or RIS diagnosis, MS family history, EDSS score at baseline, T2-weighted hyperintense lesion volume at baseline (log-transformed), and presence of gadolinium-enhancing lesions at baseline.

[e] Based on a logistic regression model that adjusted for sex, age at time or RIS diagnosis, MS family history, EDSS score at baseline, T2-weighted hyperintense lesion volume at baseline (log-transformed), and presence of gadolinium-enhancing lesions at baseline. The model included an offset term accounting for follow-up duration.

[f] Based on a negative binomial regression model that adjusted for sex, age at time or RIS diagnosis, MS family history, EDSS score at baseline, T2-weighted hyperintense lesion volume at baseline (log-transformed), and presence of gadolinium-enhancing lesions at baseline. The model included an offset term accounting for follow-up duration.

[g] The mean difference in change from baseline was not reported.

[h] Based on a generalized linear model that adjusted for sex, age at time or RIS diagnosis, MS family history, EDSS score at baseline, T2-weighted hyperintense lesion volume at baseline (log-transformed), and presence of gadolinium-enhancing lesions at baseline, and the baseline value. The model included an offset term accounting for the follow-up duration.

[i] Based on a generalized regression model that adjusted for sex, age at time or RIS diagnosis, MS family history, EDSS score at baseline, T2-weighted hyperintense lesion volume at baseline (log-transformed), and presence of gadolinium-enhancing lesions at baseline, and the baseline value. The model included an offset term accounting for the follow-up duration.

Source: Lebrun-Frénay et al. (2023).[11]

Harms

Detailed results for harms for the included study are in the following publication: Lebrun-Frénay et al. (2023).[11]

Key results include the following:

- The overall number of patients with at least 1 AE was not reported. Moderate AEs occurred in 21 of 44 patients (48%) the teriflunomide group and in 17 of 45 patients (38%) in the placebo group. Common moderate AEs in the teriflunomide group were eye disorders, chills, COVID-19 infection, and elevated liver enzymes (2 patients each). Common moderate AEs in the placebo group were multiple sclerosis and neurological pain (2 patients each).
- The number of patients with serious adverse events (SAEs) was not reported. Severe AEs occurred in 4 patients (9.1%) in the teriflunomide group including abdominal pain, hypersensitivity reaction, COVID-19 infection, renal cancer, headache, and alopecia (1 patient each). No patient experienced a severe AE in the placebo group.

- Study discontinuations due to an AE occurred in 1 patient in the teriflunomide group and 2 patients in the placebo group; details of the AEs were not reported.
- No deaths due to AE were reported.
- Notable harms identified for this review (hepatotoxicity and teratogenicity) were not prespecified in the included study. Pregnant individuals were excluded from the study and those who became or planned to become pregnant were intended to undergo an accelerated elimination procedure. Two patients (4.5%) in the teriflunomide group and none in the placebo group experienced elevated liver enzymes.

Critical Appraisal

Internal Validity

Risk of bias in the randomization process was low. Centralized allocation using a stratified randomization schedule was implemented and there were few between-group imbalances in baseline characteristics. These were likely due to chance, given the small sample size.

Treating physicians, assessors, and patients were blinded to allocated treatment to reduce potential for bias related to knowledge of assigned intervention. Patients in the placebo group were able to start treatment with teriflunomide upon developing MS, and therefore became unblinded. There was no information reported on the number of patients who were diagnosed with MS during the study and switched to teriflunomide. No information was reported on concomitant nor subsequent treatments. While unlikely to be of concern prior to cross-over (i.e., for the primary end point or secondary MRI end points), there may be a risk of bias for patient-reported outcomes due to deviations from intended intervention because patients taking placebo were permitted to cross over to the teriflunomide arm. The potential bias is likely to be directed towards the null, but no information was provided to enable the review team to appraise the presence or extent of potential bias.

Sample size calculations suggested that 80 patients per arm would result in 80% power to detect a 50% reduction in risk of first clinical event. However, patient enrolment was slow and the TERIS trial was prematurely discontinued by the sponsor for a total of 89 included patients. The primary end point was analyzed using a Cox proportional hazards model with log-rank tests to compare survival between treatment groups. The validity of the proportional hazards assumption could not be determined since results of the testing were not reported. The mean time to event was reported (instead of the median), but it is not clear how this was estimated. This would be an underestimate of the true mean because several patients remain in follow-up without an event. There was no adjustment for multiple comparisons, resulting in increased risk of type I error for the primary end point (the only statistically significant finding).

Allowing patients to select their length of treatment and participation in the study (96 or 144 weeks), in addition missing outcome assessments, resulted in varied timing of available outcome data across patients in each group. No information was reported on the number of patients who selected each length of study participation. It is not clear how patient choice to discontinue at 96 weeks was addressed in the analysis of the primary outcome. Censoring these patients could introduce a risk of bias if the choice to stop at 96 weeks was influenced by prognosis or patient perceptions of efficacy, but minimal information was reported to inform a judgment. For secondary and exploratory end points, models included an offset term for the length of follow-up. This can be considered appropriate for the analysis of the rate of new or newly enlarging lesions using the negative binomial regression model. For other secondary and exploratory end points, where generalized linear or logistic regression models were used, the inclusion of the offset assumes a 1-to-1 linear relationship between the outcome and time. This assumption is unlikely to be appropriate and challenges any meaningful interpretation of the results.

Each site conducted an MRI test scan of a patient with MS or a healthy volunteer before initiating enrolment to ensure adequacy of the site's scanning techniques, with independent review by an MS specialist and a neuro-radiologist; this centralized team also evaluated MRI scans for follow-up of clinical events using a standardized protocol at scheduled visits in addition to unscheduled visits (e.g., neurological events) such that there may be low risk of bias in evaluations of MRI data despite no details specifying within and inter-rater reliability. Patient-reported outcomes included objective (PASAT-3, CSCT) or validated (MusiQoL) measures to reduce concerns related to biased outcome measurements. As previously mentioned, blinding of patients, physicians, and outcome assessors would have mitigated any potential risk of bias in the outcome measurement. An unknown number of patients in the

placebo group converted to MS and were allowed to switch to teriflunomide, becoming unblinded. This would result in a risk of bias in subjective outcomes (notably HRQoL), likely toward the null. The extent and presence of this potential bias is unknown because the number of patients who became unblinded was not reported.

Missing baseline data were assumed to be missing at random and imputed using multiple imputations, with no imputation for missing outcome data (only observed values were included in analyses). The lack of information on the number of patients censored and censoring reasons for the primary end point, and absence of imputation for outcome data combined with a high rate of treatment and/or study discontinuations (20%) and missing follow-up MRIs for secondary end points (20%), result in a risk of bias related to missing outcome data. Findings based on a small sample size may not be generalizable to a larger population, and a complete case analysis that assumed missing data occurred completely at random was neither supported by ambiguous reasons for dropouts that differed in frequency across groups, nor lack of sensitivity analyses to verify the robustness of the findings. The direction of the potential bias cannot be predicted.

The Multiple Sclerosis Functional Composite comprising the Timed 25-Foot Walk, the PASAT, and the 9-Hole Peg Test (9-HPT) was included in the study protocol but not the SAP; it is not clear whether all components were intended as study end points. Only the PASAT component was reported in the publication.[11] It is not clear from the information available whether there was a selective non-reporting of the Timed 25-foot walk and 9-HTP measures.

External Validity

No sites in Canada were included and no information on race or ethnicity was recorded, so it is unclear whether the enrolled patients were representative of the racial or ethnic diversity of patients in Canada. Otherwise, the experts expressed no concerns with the documented baseline characteristics. Patients were evaluated for study eligibility based on meeting the 2009 RIS criteria which was more stringent than the current 2023 RIS criteria reported by the clinical experts to be used in practice; as such, a greater number of individuals may otherwise be diagnosed as having RIS and therefore, eligible for treatment with teriflunomide. No information was provided for efficacy in the expanded population of patients with RIS (those with fewer lesions but at high risk of conversion to MS due to positive CSF, presence of spinal cord lesions, and new T2 lesions on follow-up scans). Overall, the experts considered the eligibility criteria of the TERIS trial to be reasonable for capturing patients with RIS and aligned with patients who would be considered eligible for treatment with teriflunomide in clinical practice. No details were specified for prior DMT use (e.g., number of patients, reason, duration) that was reported in the discussion of the study publication, indicating the potential that these patients may differ from the overall population in their disease spectrum and/or prognosis.

In addition to the brand version (Aubagio) of teriflunomide that was used in the trial, the experts noted that the generic version is mostly applicable in clinical practice with a minority of patients using the brand name drug. Given that there are currently no approved treatments for RIS in Canada, the experts acknowledged placebo to be an appropriate comparator in the TERIS trial but expressed uncertainty on the comparative efficacy or harms of teriflunomide versus available treatments for MS, including emerging evidence on dimethyl fumarate.

The primary end point of time to first clinical demyelinating event overall captured the key outcome of interest among patients with RIS, and was overall aligned with how relapse is defined in clinical practice according to the experts. While a clinical event is the most important outcome among patients with RIS, the experts emphasized that MRI criteria are also critically important in assessing treatment response and used as part of routine clinical practice. Since the experts indicated that patients may undergo treatment for many years, there is a lack of evidence for long-term benefits and harms among patients with RIS.

Discussion

A summary of clinician input on the place in therapy of teriflunomide for RIS is available in the Working Papers, in the Place in Therapy section.

Efficacy

The patient group identified a need for patients with RIS to have timely, equitable, and consistent access to affordable treatments with demonstrated efficacy, tolerability, and safety in delaying disease onset and slowing disability progression. Clinicians also identified a need for early treatment among patients diagnosed with RIS to prevent future relapses and disability progression

Findings from the TERIS trial demonstrated that teriflunomide may increase time to a clinical event when compared to placebo among patients with RIS, although there is some uncertainty in the results based on potential risk of bias and a relatively small sample size. The clinical experts agreed that findings for time to first acute or progressive neurological symptom associated with CNS demyelinating event was considered clinically meaningful in demonstrating benefit with teriflunomide when compared with placebo, and aligned with observations of patients with MS in practice. All secondary end points (number of new and/or enlarging T2-weighted hyperintense lesions, number of new gadolinium-enhancing lesions, and proportion of patients with new or newly enlarging T2-weighted hyperintense lesions and new gadolinium-enhancing lesions) were limited in interpretability given the number of patients who had MRI findings (approximately 80%) were notably smaller than the randomized population. Relative to placebo, the point estimate suggested a direction of effect to favour teriflunomide in the number of patients with new and/or newly enlarging T2-weighted hyperintense lesions. However, the effect estimates were imprecise as evidenced by wide confidence intervals that included the possibility of harm. Furthermore, including follow-up duration as an offset in the linear and logistic regressions appeared to be inappropriate, given a lack of empiric evidence to demonstrate that rates of change would follow a 1:1 relationship (constant over time); rather, it would be more reasonable to assume rate of change would vary and account for this in analyses by including additional transformations of follow-up duration as covariates for the MRI outcomes and also applicable to patients' functional status and HRQoL. Interpretation of the findings for the secondary end points were challenging due to the method of analysis to account for follow-up duration, missing MRI data, and imprecision in effect estimates.

There was lack of evidence (e.g., stratification of patients by risk factors, subgroup analyses to verify consistency across patient groups) to inform if any subset of patients may benefit the most from treatment; the relatively small number of patients in the TERIS trial likely precluded any subgroup analyses, and this remains a gap in the evidence for prognosis and long-term follow-up of patients with RIS according to the clinical experts.

Some gaps were identified in the evidence. Although prespecified, data for Multiple Sclerosis Functional Composite were not reported for all 3 components to enable a complete appraisal of the degree of impairment (functions in leg and ambulation, arm and hand, and cognition) by the review team. Based on the duration of follow-up in the TERIS trial, the long term efficacy and harms of teriflunomide in patients with RIS is unknown. The comparative efficacy and harms of teriflunomide compared with currently available treatments used in MS is unknown in the absence of evidence. Additionally, the concurrent emergence of trial evidence for dimethyl fumarate as a treatment option for patients with RIS necessitates an evaluation of its efficacy and safety as a relevant comparator for teriflunomide.[12]

Harms

The patient group input did not identify any individuals with RIS who had experience with teriflunomide. Nevertheless, patients expressed a desire for treatments that were tolerable and safe. In the TERIS trial, more patients in the teriflunomide group experienced moderate AEs and SAEs (abdominal pain, hypersensitivity reaction, COVID-19 infection, renal cancer, headache, and alopecia) compared with the placebo group. A very small number of patients discontinued the study due to AEs with similar between-group proportions. No information was provided on overall AEs regardless of severity and if any study discontinuations or withdrawals were due to AEs. The experts acknowledged that the AEs observed were unsurprising and manageable based on teriflunomide use in patients with MS and that there were no new safety signals. The experts outlined some considerations with teriflunomide including risk of teratogenic effects, risk of hepatoxicity, and known AEs (e.g., hair loss). Therefore, patients who plan to become pregnant, or are lactating or nursing, may prefer to avoid treatment with teriflunomide. SAEs with teriflunomide were noted to occur in a small number of patients with RIS. Considering the available treatment options, the experts weighed in that injectable medications have additional considerations aside from patient preference. Interferons have been associated with AEs including cytopenia, liver function abnormality, thyroid dysfunction, migraine exacerbation, and injection site reactions; patients may instead opt for treatment with glatiramer acetate if limited to these conventional treatments. Overall, an oral medication is likely to be preferred over either glatiramer acetate or interferon beta, according to the experts.

Conclusion

Patient group advocates and clinicians identified a need for approved treatments in patients with RIS to delay disease onset, prevent future relapses, and delay disability progression, with tolerable side effects and maintenance of quality of life. Evidence from a randomized, phase III, double-blinded, trial (TERIS) that included 89 adult patients with RIS demonstrated that compared with placebo, treatment with teriflunomide resulted in a statistically significant and clinically important delayed time to first acute or progressive neurological symptom associated with CNS demyelinating event; there is some uncertainty in the findings based on potential risk of bias, small sample size, and relatively short duration of treatment. The evidence was insufficient to show a difference between teriflunomide and placebo in MRI outcomes, functional status, or HRQoL. The safety profile of teriflunomide was as expected with no new safety signals. The comparative efficacy and safety of teriflunomide compared with currently available treatments used in MS is unknown in the absence of evidence.

Economic Review

The economic review consisted of a cost comparison for teriflunomide compared with glatiramer acetate and interferon beta (Avonex, Plegridy, Rebif, Betaseron) for patients with RIS, as deemed appropriate based on consultations with clinical experts and feedback from drug plans. However, feedback obtained by CADTH indicated that glatiramer acetate and interferon beta are off-label treatments that are infrequently used for the treatment of RIS in clinical practice. Further, only 2 CADTH participating drug plans (Canadian Armed Forces and Veterans Affairs Canada) currently fund glatiramer acetate and interferon beta for the treatment of RIS.

Based on public list prices, teriflunomide is expected to have a per patient cost of $5,449 per year (Working Files, Appendix 5). Glatiramer acetate is expected to have a per patient cost of $10,168 annually and interferon beta is expected to have a per patient cost ranging from $20,075 to $49,001 annually. Therefore, the incremental cost savings of teriflunomide are $4,719 per patient per year compared to glatiramer acetate and $14,626 to $43,552 per patient per year compared to interferon beta. As such, the reimbursement of teriflunomide is expected to decrease drug acquisition costs in jurisdictions that currently fund glatiramer acetate and interferon beta for the treatment of RIS. Conversely, in the majority of jurisdictions where no treatments are currently funded for the treatment of RIS, the reimbursement of teriflunomide will result in increased drug acquisition costs.

Additional items for consideration are provided in the following bullets:

- Evidence from TERIS,[11] a randomized, phase III, double-blinded trial, demonstrated that treatment with teriflunomide resulted in delayed time to first acute or progressive neurological symptom associated with CNS demyelinating event.
- The comparative efficacy and safety of teriflunomide compared with currently available treatments used in MS is unknown in the absence of evidence.
- Several generics of teriflunomide are currently marketed and available in Canada.
- Four formulations of interferon beta are available in Canada (Brands: Avonex, Plegridy, Rebif, Betaseron). Unit drug costs and dosages vary by brand. Clinical expert input noted that the 4 brands are interchangeable but patient preference may determine which brand is prescribed.
- Clinical expert input indicated that delaying the onset of neurological symptom associated with CNS demyelination could potentially lead to future healthcare savings by reducing the need for healthcare resources associated with the treatment of MS.
- A concurrent review is being conducted by CADTH for use of dimethyl fumarate in the treatment of RIS based on the results of the ARISE clinical trial.[12] Dimethyl fumarate is expected to have a per patient cost of $6,283 in year 1 and $6,343 in subsequent years.
- No relevant Canadian cost-effectiveness studies were identified based on a literature search conducted on August 7, 2024.

Conclusion

In jurisdictions that currently fund therapies for the treatment of RIS, the reimbursement of teriflunomide is expected to decrease drug acquisition costs, in comparison to glatiramer acetate and interferon beta. Based on the clinical review conclusions, the comparative efficacy and safety of teriflunomide compared with currently available treatments used in MS is unknown in the absence of evidence. Given that teriflunomide is associated with decreased drug acquisition costs and unknown clinical benefit, the reimbursement of teriflunomide may result in cost savings with uncertain benefit in jurisdictions that currently fund therapies for the treatment of RIS.

In the majority of jurisdictions where no therapies are currently funded for the treatment of RIS, the reimbursement of teriflunomide will result in increased drug acquisition costs. Based on the clinical review conclusions, treatment with teriflunomide delayed the onset of the first acute or progressive neurological symptom associated with CNS demyelination compared with placebo. Given that teriflunomide is associated with increased drug acquisition costs and incremental benefits in the majority of jurisdictions, a cost-effectiveness analysis would be required to determine the cost-effectiveness of teriflunomide relative to no active intervention. As

this was not available, the cost-effectiveness of teriflunomide relative to no active intervention for the treatment of RIS could not be determined.

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