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

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Drugs Health Technologies Health Systems

Reimbursement Review

Teriflunomide (Aubagio)

Requester: Public drug programs
Therapeutic area: Multiple sclerosis, radiologically isolated syndrome

Key Messages

What Is Radiologically Isolated Syndrome?

- Radiologically isolated syndrome (RIS) is considered the earliest detectable preclinical phase of multiple sclerosis (MS). It is characterized by brain or spinal cord MRI anomalies found incidentally in individuals without typical MS symptoms. RIS is defined as asymptomatic; however, patients may present with nonspecific symptoms and require increased health care resources before a potential diagnosis of MS.
- In 2024, there were approximately 18,000 to 210,000 patients with RIS in Canada.

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

- Delaying disease onset and slowing disability progression with improved tolerability and safety were identified as important treatment outcomes in the patient group input.
- Other important outcomes identified through clinician input include targeting the disease process, preventing future relapses, preventing disability progression, and maintaining health-related quality of life.
- Currently, there are no publicly funded treatments for RIS in Canada. Patients with RIS are often untreated. Treatment options may include off-label drugs used for MS (e.g., interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide) or 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 MS.
- We previously reviewed teriflunomide for relapsing-remitting MS 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 RIS.

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 RIS:
- The clinical evidence was identified through systematic searches for available studies. As part of the review process, we consulted 2 clinical

Key Messages

specialists with expertise in the diagnosis and management of MS. 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 regarding 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) that compared teriflunomide with placebo in patients with RIS.
- 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 teriflunomide has 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 in the treatment of RIS.
  - The safety profile of teriflunomide in the treatment of RIS 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. Because 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
CDA-AMC	Canada’s Drug Agency
CNS	central nervous system
CSCT	Computerised Speed Cognitive Test
EDSS	Expanded Disability Status Scale
HRQoL	health-related quality of life
MS	multiple sclerosis
MusiQoL	Multiple Sclerosis International Quality of Life
PASAT	Paced Auditory Serial Addition Test
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 the number 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 generic drugs 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 — AEs, SAEs, withdrawals due to AEs, deaths due to AEs, AEs of special interest (i.e., hepatotoxicity, teratogenicity)

AE = adverse event; CDA-AMC = Canada's Drug Agency; 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 is on comparing teriflunomide with relevant comparators and identifying gaps in the current evidence. The Economic Review consists of a cost comparison for teriflunomide 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. Input from patient and clinician groups is considered throughout the review, including 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 the Response Summary.

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 (the number of respondents was not reported) because no patients were identified who were diagnosed with RIS and treated with teriflunomide.

Clinician group input was submitted by the representative on behalf of Canadian Network of MS Clinics (the number of clinicians was not reported) that 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] symptoms include vision loss, motor weakness, and paresthesia.[2] RIS is diagnosed when brain or spinal cord MRI anomalies suggestive of MS are found incidentally in individuals who do not have symptoms of MS[3,4]

Although RIS is asymptomatic by definition, increased health care resource utilization is common among people with RIS and suggests a prodromal phase or nonspecific symptoms preceding classical experiences among people with MS. In those with RIS, common reasons for an initial MRI scan include headache and trauma.[2,5] Patients with RIS can present 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 (Okuda diagnostic criteria)[6] was revised in 2023 to incorporate observed CNS anomalies, risk factors, and earlier treatment. The revised criteria have better sensitivity and maintains specificity, align with the existing 2017 McDonald diagnostic criteria, and provide clinicians with a broadly applicable framework.[2,7] Note the 2024 McDonald diagnostic criteria were not yet officially released at the time of writing this report; some patients previously diagnosed with RIS would now be diagnosed with MS according to the proposed revised criteria.

The prevalence of RIS is estimated to range from 0.06% (Australia, Germany, Japan, the Netherlands, Taiwan, and the US) to 0.7% (Pakistan)[3] and to have affected approximately 18,000 to 210,000 people in Canada in 2024. Studies that used the Okuda diagnostic criteria reported that the incidence of RIS ranged from 0.05% to 0.1% per year (Sweden).[8,9] Data are limited on the proportion of patients with RIS who are at risk of developing MS; an estimated 30% of patients converted to symptomatic MS.[5]

Current Management

Treatment Goals

Input from the patient group indicated there is a need for treatments that delay disease onset and slow disability progression with improved 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 expressed that patients with RIS can sometimes be treated off-label with drugs that are approved by Health Canada for relapsing-remitting MS (e.g., interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide, ocrelizumab, ofatumumab, natalizumab) or drugs that are 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. Because RIS is recognized as being a subclinical precursor to clinical MS, including a prodromal phase (i.e., nonspecific symptoms such as cognitive impairment, motor or dexterity impairments, fatigue), there is an emerging consensus among MS clinicians that treatment with disease-modifying drugs may be appropriate among certain patients with RIS.

Key characteristics of teriflunomide are summarized with those of other treatments available for RIS in the Table 2 in the Supplemental Material.

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 generic drugs), 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 on behalf of patients with RIS to disease-modifying therapies, including teriflunomide, which can significantly delay disease onset and slow disability progression.

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 preclinical, early phase of MS, and the goals of treatment are to prevent future relapses and disability progression. Because early treatment of a potentially disabling condition is critical and current guidelines recommend off-label treatments due to no publicly funded treatments for RIS, the experts expressed there is a clear gap in available treatments for patients with RIS.

Clinical Review

Methods

Eligibility Criteria

We included studies that adhered to the a priori eligibility criteria, which are detailed in Table 3 in the Supplemental Material. Eligible studies included published phase III and IV randomized controlled trials that included adults with RIS treated with teriflunomide. Relevant comparators included drugs used in clinical practice in Canada to treat RIS 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 a relevant comparator. Long-term extension studies of the included randomized controlled trials 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 were 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 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 literature search of key bibliographic databases, trial registries, and grey literature sources, using a peer-reviewed search strategy. The initial search was completed on July 31, 2024, with alerts maintained until the Formulary Management Expert Committee meeting on November 21, 2024. The Supplemental Material 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 text. 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, registries, and grey literature, 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 indirect treatment comparisons, we identified 24 unique records via the searches of databases and registries; none met eligibility by title and abstract.

No long-term extension studies or 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 Türkiye), phase III, double-blinded, placebo-controlled, randomized controlled trial 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 neurological 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 Appendix 3 in the Supplemental Material.

Key inclusion criteria in the TERIS trial were adult aged 18 years or older, meeting 2009 RIS diagnostic criteria[6] with structural neuroimaging abnormalities not explained by another disease process, and no historical accounts of remitting clinical symptoms that were consistent with neurological dysfunction. An independent clinical adjudication committee verified patients' study eligibility. Key exclusion criteria were recent exposure to a disease-modifying treatment (past 3 months) or high-dose glucocorticoid (past 30 days), lactation or pregnancy, 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 before 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 organic anion transporter 3 (OAT3), substrates of breast cancer–resistant protein, substrates of OAT polypeptide family, known potent CYP and transporter inducers, and vaccination with nonlive vaccines. Nonpermitted concomitant therapy included systemic corticosteroids and adrenocorticotropic hormone (ACTH) not used for MS relapses, immunosuppressive treatment, plasmapheresis, cytapheresis, or total lymphoid irradiation; antiarrhythmic 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 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. Of these, 35 patients were excluded, including those 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 groups, respectively, were due to an AE (1 patient and 2 patients), withdrawal of consent (3 patients and 1 patient), patient decision to discontinue (0 patients and 4 patients), study termination by the sponsor (0 patients and 1 patient), pregnancy (1 patient and 0 patients), 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 similar overall between treatment groups in mean age at RIS diagnosis (mean = 38 years; standard deviation [SD] = 12 years), proportion of females (71%) and males (29%), and proportion with a family history of MS (3%). Reasons for the index MRI scan in the teriflunomide and placebo groups, respectively, were primarily headache (52% and 40%), follow-up of other diseases (30% and 27%), and dizziness or vertigo (7% and 27%). In the teriflunomide and placebo groups, respectively, the presence of gadolinium-enhancing lesions (30% and 27%), presence of spinal cord lesions (46% and 44%), and T2-lesion volume (log-transformed) (mean = 3.3 mm^3 [SD = 0.4 mm^3] and mean = 3.4 mm^3 [SD = 0.5 mm^3]) at baseline were similar between groups. Patients in the teriflunomide and placebo groups, respectively, had similar scores at baseline on the Expanded Disability Status Scale (EDSS) (median = 0 points [SD = 0 points] in both groups) and the MusiQoL (mean = 47.4 points [SD = 9.8 points] and mean = 42.5 points [SD = 13.3 points]).

Treatment Exposure and Concomitant Medications

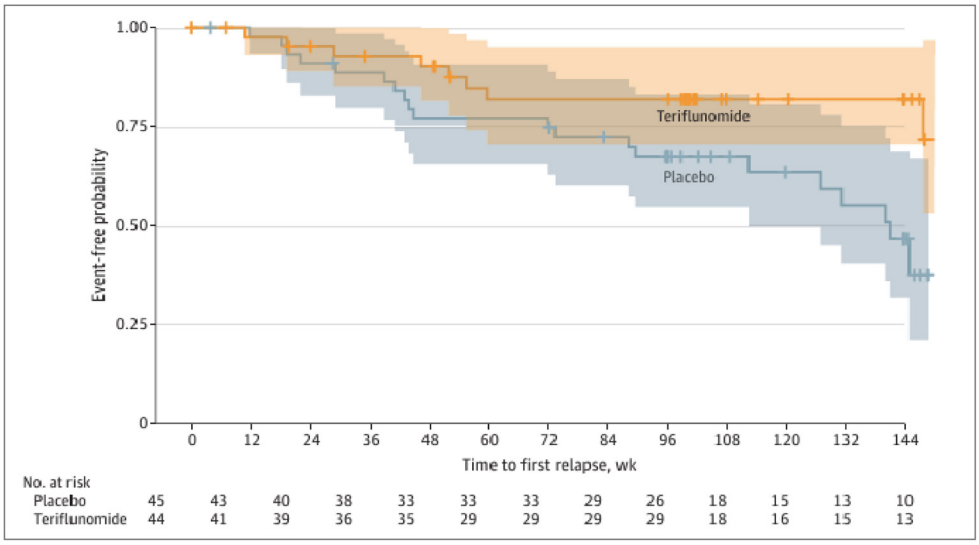
Treatment exposure, adherence, and concomitant medications were not reported in the TERIS trial. It is not clear how many patients remained on treatment and in the study past week 96 to week 144. Subsequent treatment, including the number of patients who continued (teriflunomide group) or started (placebo 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 Table 2. The Kaplan-Meier plot for the time to first acute or progressive neurological event resulting from CNS demyelination is presented 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 was 0.28 (95% confidence interval, 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)



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 Retechnologies.

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]		
Patients with a first acute or progressive neurological event resulting from CNS demyelination, n (%)	8 (18.2)	20 (44.4)
First acute neurological event	6 (13.6)	18 (40.0)
Initial progressive neurological event	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
P value[c]	0.007	Reference
Secondary end points		
New and/or newly enlarging T2-weighted hyperintense lesions		
Patients contributing to the analysis, n (%)	34 (77.3)	37 (82.2)
Patients with ≥ 1 new and/or newly enlarging T2-weighted hyperintense lesion(s), n (%)	20 (58.8)	24 (64.9)

Variable	Teriflunomide N = 44	Placebo N = 45
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		
Patients contributing to the analysis, n (%)	33 (75.0)	36 (80.0)
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		
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		
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		
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		
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		
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		
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; HR = hazard ratio; HRQoL = health-related quality of life; ITT = intention to treat; NR = not reported; 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 were 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 was not 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 of radiologically isolated syndrome (RIS) diagnosis, family history of MS, Expanded Disability Status Scale (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 of RIS diagnosis, family history of MS, 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 of RIS diagnosis, family history of MS, 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 of RIS diagnosis, family history of MS, 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 of RIS diagnosis, family history of MS, 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 in 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%) in 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 MS and neurological pain (2 patients each).

- The number of patients with serious AEs (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 (a patient could experience > 1 severe AE). No patients in the placebo group experienced a severe AE.
- 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 an 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 underwent 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 due to 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 or subsequent treatments. Although unlikely to be of concern before crossover (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 the placebo were permitted to cross over to the teriflunomide arm. The potential bias is likely to be directed toward the null, but no information was provided to enable the review team to appraise the presence or extent of potential bias.

Sample size calculations suggest 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 (both due to site regulations and the COVID-19 pandemic that resulted in slow patient recruitment) 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 because 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 remained in

follow-up without an event. There was no adjustment for multiple comparisons, resulting in an 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 to 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 study participation length. 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, for which 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 neuroradiologist. This centralized team also evaluated MRI scans for follow-up of clinical events using a standardized protocol at scheduled visits as well as unscheduled visits (e.g., neurological events); therefore, there may be low risk of bias in the evaluations of MRI data despite no details specifying within-rater and interrater 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). There was a lack of information on the number of patients censored and the censoring reasons for the primary end point, an absence of imputation for outcome data, a high rate of treatment and/or study discontinuations (20%), and missing follow-up MRIs for secondary end points (20%). Altogether, these resulted 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 not 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 statistical analysis plan, so it is not clear if 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 nonreporting 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 of patients. Patients were evaluated for study eligibility based on meeting the 2009 RIS diagnostic criteria, which were 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 now be diagnosed with RIS and, therefore, eligible for treatment with teriflunomide. No information was provided regarding efficacy in the expanded population of patients with RIS (those with fewer lesions but at high risk of conversion to MS due to positive findings in cerebrospinal fluid, 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 appropriate for selecting patients with RIS and to align with patients who would be considered eligible for treatment with teriflunomide in clinical practice. In the study publication, the discussion reported that some patients in the TERIS trial were already exposed to a disease-modifying treatment. However, no details were specified about prior disease-modifying treatment (e.g., number of patients, reason, duration), indicating the potential that these patients may differ from the overall population in their disease spectrum and/or prognosis.

The brand version (Aubagio) of teriflunomide was used in the TERIS trial. The experts noted that the generic version is used by most patients in clinical practice with the brand-name drug used by a minority of patients. Because there are currently no approved treatments for RIS in Canada, the experts acknowledged that placebo is an appropriate comparator in the TERIS trial but expressed uncertainty about 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 captured the key outcome of interest among patients with RIS and was aligned overall with how relapse is defined in clinical practice, according to the experts. Although 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 are used as part of routine clinical practice. The experts indicated that patients may undergo treatment for many years, but 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 Place in Therapy section in the Supplemental Material.

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 compared to placebo among patients with RIS, although there is some uncertainty in the results based on potential risk of bias and the relatively small sample size. The clinical experts agreed that findings for time to first acute or progressive neurological symptom associated with a CNS demyelinating event was considered clinically meaningful in demonstrating benefit with teriflunomide 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 because MRI findings were available for a subset (approximately 80%) of 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, because of the lack of empiric evidence to demonstrate that rates of change would follow a 1:1 relationship (constant over time). It would be more reasonable to assume the rate of change would vary and to account for this in the analyses by including additional transformations of follow-up duration as covariates for the MRI outcomes, 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 a 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 most from treatment. The relatively small number of patients in the TERIS trial likely precluded any subgroup analyses; there 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 the Multiple Sclerosis Functional Composite were not reported for all 3 components to enable a complete appraisal of the degree of impairment (leg function and ambulation, arm and hand function, 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 severe AEs (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. Severe AEs 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. According to the experts, an oral medication is likely to be preferred over either glatiramer acetate or interferon beta.

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 that have tolerable side effects and maintain 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 a CNS demyelinating event. However, there is some uncertainty in the findings based on the 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 of teriflunomide 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 Canada's Drug Agency (CDA-AMC) indicated that glatiramer acetate and interferon beta are off-label treatments that are infrequently used for the treatment of RIS in clinical practice. Furthermore, only 2 CDA-AMC 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 (Appendix 5 in the Supplemental Material). 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 is $4,719 per patient per year compared with glatiramer acetate and $14,626 to $43,552 per patient per year compared with 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 include the following:

- 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 a 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 generic formulations 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 symptoms associated with CNS demyelination could potentially lead to future health care savings by reducing the need for health care resources associated with the treatment of MS.
- A concurrent review is being conducted by CDA-AMC 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 in 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 compared with 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. This was not available; therefore, the cost-effectiveness of teriflunomide relative to no active intervention for the treatment of RIS could not be determined.

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