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

January 2025

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Teriflunomide

Reimbursement request: Radiologically isolated syndrome
Requester: Public drug programs
Final recommendation: Reimburse with conditions

Summary

The Formulary Management Expert Committee (FMEC) recommends teriflunomide be reimbursed for the treatment of radiologically isolated syndrome (RIS), provided certain conditions are met.

FMEC reviewed the TERIS trial identified by systematic review of the literature by Canada's Drug Agency (CDA-AMC), in which teriflunomide was compared to placebo in patients with RIS. FMEC also considered input received from external partners, including MS Canada, Canadian Network of MS Clinics, and public drug programs.

FMEC concluded there may be a clinically important delayed time to first acute or progressive neurological symptoms associated with a central nervous system demyelinating event. FMEC also concluded that improving access to oral treatment options that are supported by evidence may address a clinical unmet need in the setting of RIS.

In jurisdictions funding glatiramer acetate and interferon beta for RIS, reimbursing teriflunomide is expected to lower drug acquisition costs. However, in most jurisdictions where no therapies are funded for RIS, the reimbursement of teriflunomide will increase costs.

Therapeutic Landscape

What Is RIS?

RIS is considered the earliest detectable preclinical phase of multiple sclerosis (MS) that is characterized by incidental brain or spinal cord imaging findings in individuals without typical MS symptoms. Based on historical references, approximately 30% to 50% of patients with RIS progress to MS. However, based on input from the clinical experts consulted, these historical references likely underrepresent the proportion of patients who will develop MS later in life. Patients may require increased health care resources and present with cognitive impairment. In 2024, there were approximately 18,000 to 210,000 patients with RIS in Canada.

What Are the Current Treatment Options?

Currently, there are no marketed products with a Health Canada–approved indication of use for the treatment of RIS, and no public drug plan in Canada has funding criteria specific for RIS. Funded options are limited to MS drugs, used off-label, in jurisdictions where they are listed as open benefits. For the purpose of this review, an appropriate comparator was considered any drug listed by 1 or more drug programs, including those listed as an “open” benefit.

Why Did We Conduct This Review?

Given the emergence of evidence for drugs that delay symptoms of MS and its associated disability, public drug programs requested a review of the available evidence on the efficacy and safety of teriflunomide in the treatment of adults with RIS. Teriflunomide was eligible for a non-sponsored reimbursement review given that generic drugs are available in Canada.

Input From Partners

- **MS Canada** identified that individuals with RIS require timely, equitable, and consistent access to affordable treatments that delay disease onset, prevent future relapses, and delay disability progression while being tolerable and safe.
- One clinician group, **Canadian Network of MS Clinics,** submitted input on the proposed scope for this review.
- No input was provided by **industry** groups.
- **Public drug plans** inquired about the evidence for teriflunomide to inform a recommendation on whether it should be reimbursed for adults with RIS. The public drug plans outlined implementation questions related to treatment eligibility and potential costs.

►Refer to the main report and supplemental material for this review.

Person With Lived Experience

A person with lived experience from Ontario shared her journey with RIS, which was unexpectedly diagnosed following an MRI revealing brain lesions. Initially asymptomatic and with no family history, she hesitated to begin treatment, believing it unnecessary. After a follow-up MRIs showed lesion progression, she began treatment with another disease-modifying therapy, dimethyl fumarate, to slow disease advancement. She shared insights into treatment considerations, such as managing side effects, monitoring progress through MRIs, and navigating the financial challenges of accessing treatment. The presentation provided valuable context on how the initial diagnosis and subsequent progression from RIS to relapsing-remitting MS in November 2021 affected them personally and underscored the broader challenges faced by patients with RIS.

Note: CDA-AMC engaged with a person with lived experience living with RIS, who has experience with dimethyl fumarate, for both dimethyl fumarate and teriflunomide reimbursement reviews conducted on November 21, 2024.

Deliberation

The committee deliberated using the following 5 domains of value:

- **Clinical value:** The value that patients derive from a health technology in terms of its effect on their health and health-related quality of life. The determination of the clinical value of a health technology requires the measurement of its clinical benefits and harms and an assessment of the impact of these effects on patients. Clinical benefits and harms are assessed against relevant comparators.
- **Unmet clinical need:** Morbidity and/or mortality arising from a condition or symptom that is not addressed effectively by available treatments.
- **Distinct social and ethical considerations:** The social and ethical implications of health technologies not already assessed in the other domains and how they affect patients, caregivers, populations, and the organization of health systems. This includes nonclinical needs — social, psychological, and logistical factors affecting the appropriateness, accessibility, and acceptability of the technology beyond its direct clinical outcomes — as well as broader ethical considerations in the design, evaluation, and implementation of these technologies.
- **Economic considerations:** Economic evidence to inform the financial, human, or other resource implications associated with the technology under review, and whether it is worthwhile to allocate resources to the technology under review given its expected clinical benefits. Considerations may include the potential resource or cost impacts of the technology under review versus relevant comparator(s).
- **Impacts on health systems:** Two distinct but interrelated components: organizational feasibility of adoption is the ease with which the health technology can be implemented in the health system while

realizing its clinical value, while economic feasibility of adoption examines how the adoption of a health technology will economically impact the payer or budget holder.

Decision Summary

Table 1: Summary of Deliberation

Domain	Discussion points
Clinical value	• **Given limitations in the evidence, FMEC noted the clinical value is uncertain.** • Based on the TERIS trial, 18% of patients on teriflunomide compared with 44% on placebo experienced a first acute or progressive neurological event resulting from CNS demyelination. Time to first demyelinating event was a mean of 128.2 weeks (SD = 7.25 weeks) for teriflunomide versus a mean of 109.6 weeks (SD = 7.44 weeks) for placebo, representing approximately 70% relative hazard reduction[a] with teriflunomide compared with placebo. FMEC noted this is a clinically valuable end point because delaying disease onset and slowing disability have meaningful impacts to patients. • FMEC highlighted that there are the limitations to the evidence supporting teriflunomide for RIS. These include the lack of subgroup analysis and comparative efficacy and safety compared with currently available treatments used in MS. There was uncertainty in the findings due to internal validity issues, wide confidence intervals (e.g., the adjusted hazard ratio for the primary end point was 0.28 with a 95% confidence interval of 0.11 to 0.71), and small sample size. FMEC also discussed and raised concerns about the discontinuation rates, with 9 patients (20%) for both treatment and placebo groups, which further increased the uncertainty in the evidence. • FMEC noted that patients who are currently receiving off-label injectable therapies (in which there is a lack of high-quality evidence to inform efficacy) would value an oral treatment option with evidence for benefits in RIS. In addition, the clinical guest specialists have noted that injectable therapies, such as glatiramer acetate and interferon beta, are rarely used in clinical practice.
Unmet clinical need	• **FMEC concluded there is an unmet need to offer evidence-informed treatment for RIS to delay potential progression or onset of MS symptoms and associated disability.** • FMEC highlighted there is a clinical need for patients diagnosed with RIS who prefer to start on drug therapy that would delay disease progression in addition to routine surveillance with imaging. • Because 30% to 50% of patients with RIS go on to develop MS, which is a progressive condition and has significant functional disability, delaying onset would be clinically important for patients. • Currently, patients with RIS may be offered injectable therapies commonly prescribed for MS. The clinical experts noted that these options are not adequately supported by high-quality evidence (e.g., an RCT). They are also not funded across jurisdictions. Hence, improving access to funded oral treatment options that are supported by evidence may address a major clinical unmet need in the setting of RIS. • FMEC discussed the input from patient groups and highlighted that patients value early intervention with equitable access to affordable, effective, tolerable, and safe medications to mitigate disease activity and preserve functional ability. • FMEC discussed the presentation from a person with lived experience that highlighted the difficult decision of accepting treatment with known risks while a patient is well or symptom free when the benefits of preventing or delaying onset of MS and future disability may not be realized or be needed.
Economic considerations	• FMEC noted that 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 and incremental benefits. No evidence was identified regarding the cost-effectiveness of teriflunomide relative to no active intervention for the treatment of RIS; therefore, estimates of cost-effectiveness were not available to the committee. However, FMEC discussed that because several generic versions of teriflunomide are

Domain	Discussion points
	currently marketed and available in Canada, prices are set by the generic pricing framework as opposed to value. • FMEC also noted that glatiramer acetate and interferon beta are currently open benefits in 2 participating drug plans (Canadian Armed Forces and Veterans Affairs Canada), meaning they may be accessible for the treatment of RIS in these jurisdictions. However, the guest clinical experts indicated that these treatments are not used frequently. FMEC noted that, using publicly available pricing information, teriflunomide is less costly than glatiramer acetate and interferon beta. Because 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 where therapies for the treatment of RIS are open benefits. • FMEC noted that CDA-AMC conducted a concurrent review of dimethyl fumarate for RIS. In this review, dimethyl fumarate was estimated to have an annual per-patient drug acquisition cost of $6,283 in year 1 and $6,343 in subsequent years.
Impacts on health systems	• FMEC discussed that there are limitations to the clinical evidence supporting the treatment of teriflunomide in RIS. For example, patients with RIS may not be currently identified through routine screening. As per the 2023 RIS criteria,[b] RIS is defined via MRI with incidental CNS white matter anomalies demonstrating radiological characteristics highly suggestive of demyelinating disease. The requirement for routine MRI imaging may impact trial enrolment and feasibility of adoption. • FMEC noted there are no specific concerns related to impacts on health systems. Teriflunomide treatment can be monitored with appropriate assessment scales, imaging with MRI, and other relevant lab investigations. Common adverse events for teriflunomide are not expected to require hospitalization or costly utilization of health care resources. • By delaying the time to first demyelinating event (as reported in the TERIS trial), FMEC also discussed that treatment for RIS can potentially delay disability and the burden on the health care system for caring for patients with disability.
Distinct social and ethical considerations	• FMEC discussed the input from patient groups and noted that patients diagnosed with RIS may experience psychological stress about the prospect of future disability. Delaying disease onset would delay the burden of disease for the patients' family and/or caregivers.

CDA-AMC = Canada's Drug Agency; CNS = central nervous system; FMEC = Formulary Management Expert Committee; HRQoL = health-related quality of life; MS = multiple sclerosis; RCT = randomized controlled trial; RIS = radiologically isolated syndrome; SD = standard deviation.

[a]Information about absolute risk reduction (or absolute effect) was not reported or available.

[b]Lebrun-Frénay C, Okuda DT, Siva A, et al. The radiologically isolated syndrome: revised diagnostic criteria. *Brain*. 2023 Aug 1;146(8):3431-3443. doi: 10.1093/brain/awad073. PMID: 36864688; PMCID: PMC11004931.

Full Recommendation

With a vote of 6 to 2, FMEC recommends that teriflunomide for RIS be reimbursed if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Teriflunomide should be reimbursed in patients with RIS who meet all the following criteria:	While limitations of the evidence from the TERIS trial were noted, the study demonstrated a benefit of treatment with	At the time of the FMEC review, the 2023 RIS Criteria include: • Fulfillment of 2009 RIS

Reimbursement condition	Reason	Implementation guidance
1.1. aged 18 years or older 1.2. diagnosed with RIS by a neurologist based on the most current RIS criteria.	teriflunomide in adult patients who met the 2009 RIS criteria. Additionally, FMEC noted there are unmet clinical needs that can be potentially addressed by teriflunomide. Although current practice follows the 2023 RIS criteria, the clinical experts and FMEC noted that new RIS criteria will be published imminently.	dissemination in space criteria: Incidentally identified CNS white matter lesions that appear typical for inflammatory demyelination with ≥ 3 of the following: ◦ > 9 T2-weighted hyperintense lesions or ≥ 1 gadolinium-enhancing lesion ◦ ≥ 1 juxtacortical lesion ◦ ≥ 1 infratentorial lesion ◦ ≥ 3 periventricular lesions OR ● The presence of at least 1 lesion in a location typical for MS and 2 of the 3 following factors: ◦ spinal cord lesion ◦ CSF-restricted oligoclonal bands ◦ new asymptomatic T2 or gadolinium-enhancing lesion demonstration dissemination in time.
Discontinuation and renewal		
2. Teriflunomide should be discontinued for the treatment of RIS if the patient has any of the following: 2.1. disease that is consistent with the current diagnostic criteria for MS 2.1. significant intolerance or toxicity to teriflunomide.	Consistent with clinical practice, patients in the TERIS trial discontinued treatment upon experiencing a first acute or progressive neurological event resulting from CNS demyelination or upon experiencing significant intolerance.	Patients should be monitored for clinical response and safety per usual local practice.
Prescribing		
3. Prescribing should be limited to clinicians with expertise in the diagnosis and management of RIS.	This will ensure that treatment is prescribed for appropriate patients and adverse events are optimally managed.	Prescribing may be in consultation with a neurologist, including MS clinic–based neurologists for individuals residing in geographic regions with limited access to a MS clinic. Note that the use of teriflunomide is contraindicated in pregnant individuals and those of childbearing age due to its risk of teratogenicity.
4. Teriflunomide should be used as monotherapy for the treatment of RIS.	There is no evidence to support the use of teriflunomide concurrently with other DMTs.	DMT is typically used for treatment of MS and related conditions.

Reimbursement condition	Reason	Implementation guidance
Cost		
5. Teriflunomide must represent good value to drug plans.	In jurisdictions where no therapies are funded for RIS, reimbursing teriflunomide will increase drug acquisition costs. No evidence was identified regarding the cost-effectiveness of teriflunomide relative to no active intervention for the treatment of RIS; therefore, estimates of cost-effectiveness were not available to the committee. A cost-effectiveness analysis would be needed to determine whether teriflunomide is cost-effective. Additionally, in the absence of comparative clinical evidence against other therapies for RIS, teriflunomide should also be priced no higher than the least costly therapy for RIS in jurisdictions where such treatments are currently funded.	Pricing should be in accordance with pan-Canadian Pharmaceutical Alliance generic pricing framework.

CNS = central nervous system; CSF = cerebrospinal fluid; DMT = disease-modifying therapy; MS = multiple sclerosis; RIS = radiologically isolated syndrome.

Feedback on Draft Recommendation

One clinician group from the Canadian Network of MS Clinics provided feedback supporting the reimbursement recommendation conditions. This clinician group also highlighted that interferon and glatiramer acetate are not clinically relevant comparators because of the lack of available evidence from randomized controlled studies. Public drug programs have also provided comments which have been incorporated during editorial revision.

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and 2 guest specialists from Alberta and Ontario.

Meeting date: November 21, 2024

Conflicts of interest: None

Special thanks: CDA-AMC extends special thanks to the individuals who presented directly to FMEC on behalf of patients with lived experience and to patient organizations representing the community of those living with RIS and MS, notably MS Canada, which includes Jennifer McDonell, Christina Andaya, and Julie Kelndorfer.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in reimbursement reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.

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