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

CDA-AMC REIMBURSEMENT REVIEW

Patient/Clinician/Industry Input

teriflunomide

(non-sponsored review)

Indication: Radiologically Isolated Syndrome (RIS).

Jan 3, 2025

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Teriflunomide
Indication: Radiologically Isolated Syndrome (RIS)
Name of Patient Group: MS Canada
Author of Submission: Jennifer McDonell

MS Canada

MS Canada provides programs and services for people with MS and their families, advocates for those living with MS, and funds research to help improve the quality of life for people living with MS and ultimately find a cure. The mission of MS Canada is to connect and empower the MS community to create positive change. Since 1948 MS Canada has contributed over $218 million towards MS research. This investment has enabled the advancement of critical knowledge of MS and the development of a pipeline of exceptional researchers.

Multiple Sclerosis

Multiple sclerosis (MS) is the most common neurological disease of the central nervous system (CNS). Approximately 90,000 Canadians are living with the disease, which most commonly is diagnosed between the ages of 20 and 49 years of age, and is up to three times more likely to occur in women than men. MS impacts each person differently over their lifetime.

Symptoms of MS can be unpredictable and vary greatly from person to person. Many symptoms are invisible to everyone but the person living with the disease. Symptoms will depend on the area within the CNS that has been damaged and may cause fatigue, problems with balance, weakness, odd sensations such as tingling or numbness, vision problems, bladder and bowel problems, and cognitive and mood changes.

MS is now better understood as a continuous disease process, driven by the underlying biological mechanisms that vary across individuals and over time. Mechanisms of injury and compensatory mechanisms and the interaction and balance between these mechanisms change across the MS disease course. Factors such as age, biological sex, genetic and environmental factors, and disease duration are likely to influence the ability of an individual to compensate for injury caused by MS.

Subclinical inflammatory, demyelinating, and neurodegenerative processes occur at the earliest stages of MS before symptoms are present. Radiologically isolated syndrome (RIS) is the earliest detectable phase of MS. People with RIS have lesions in their central nervous system (i.e. brain and spinal cord) suggestive of MS as seen by magnetic resonance imaging (MRI), but do not have any clinical symptoms of MS. Nearly half of people with RIS will be diagnosed with MS within ten years.

Approximately 85-90% of people living with MS are initially diagnosed with a relapsing disease course, characterized by acute inflammatory attacks (relapses) followed by periods of remission. About 10% of people are diagnosed with progressive MS and experience a continuous worsening of symptoms from the beginning. People with RIS can be diagnosed with relapsing or progressive courses of MS.

Currently Available Treatments for MS

There is no cure for MS however there are 15 Health Canada-approved disease-modifying therapies (DMT) by active ingredient indicated for relapsing MS. DMTs target some aspect of the inflammatory process of MS to reduce the frequency and severity of relapses; reduce the number of new lesions in the brain and spinal cord as seen on MRI, and slow down the accumulation of disability. Early intervention is vital to avoid many of the long-term health, economic and personal costs that result from unnecessary irreversible disability.

MS Canada believes that Canadians living with MS have a right to access all Health Canada-approved DMTs, including biosimilar and generic MS medications. Their patient voice is central to the goals of eliminating or reducing symptoms, slowing, preventing, and ultimately curing the disease. This requires timely, equitable, affordable, and consistent access to the full array of approved treatments, ranging from longstanding compounds to more recently approved innovative agents because no two people have the same disease course or respond in the same way to the same medication.

A central premise must include the concept of "the right medication at the right time", enabling Canadians living with MS, and those at highest risk of developing MS, to benefit from those medications most appropriate for them regardless of where they live or their income status, and their patient voice is integral in this decision-making in collaboration with their healthcare team.

Canadian drug programs must list all Health Canada-authorized medicines for MS. This includes different classes of medications and administrations as the clinical response to each of these drugs will vary greatly from person to person based on their unique patient journey including disease phase, type and course, stage of life, and personal preferences driven by lifestyle, health, and economic factors.

MS Canada's feedback stems from the strong engagement of the MS community on the topic of MS treatments. For example, in 2022, over 3000 individuals signed onto a letter to the Federal Minister of Health and all provincial/territorial Ministers of Health asking for improved access to all Health Canada approved disease-modifying therapies. This need for improved access to DMTs was reflected in research conducted by the Conference Board of Canada, who found that for Canadians affected by MS[i], where they live, their employment status, and how much money they earn has a significant impact on their ability to access the life-changing DMTs they need.

Improved Outcomes of Treatments for People Diagnosed with RIS

Diagnosis of RIS presents a significant therapeutic window to mitigate disease activity and preserve brain health at the earliest phase of the disease. Clinical trials in people with RIS treated with teriflunomide as compared with placebo have shown a statistically significant reduction in the risk of a first clinical event.

Diagnostic criteria for RIS were first established in 2009, updated in 2017 and most recently in 2023. Additionally, in 2021 international consensus recommendations proposed a standardized MRI protocol for use in MS that is also applied in RIS.[ii]

Longitudinal studies on RIS show that the risk of a first clinical event or progression onset increases over time. Around 14% of people with RIS will have a first clinical event within two years, and over half after 10 years. Factors such as younger age (≤ 37 years), being male, the presence of oligoclonal bands (OCBs) and elevated levels of Immunoglobulin G (IgG) in CSF analysis, both key indicators of MS, increase the risk. The presence of all three risk factors increases the risk of a first clinical event.[iii]

Established diagnostic criteria in tandem with known prognostic factors of those with RIS at the highest risk of experiencing a first clinical event creates an optimal and unprecedented opportunity to manage the disease at its earliest detectable stage. With these foundational components in place, revisions to public drug plans to expand the indication of teriflunomide to include RIS should be relatively straightforward.

Canadian public and private drug plans provide reimbursement of MS DMTs for people who have experienced a single demyelinating event and have lesions typical of MS on brain MRI (clinically isolated syndrome) to decrease the frequency of clinical exacerbations and reduce the number and volume of active brain lesions identified on MRI. From a health equity perspective, all Canadians at risk of developing MS; those diagnosed with CIS and RIS, must have access to medications that can significantly delay disease onset and slow disability progression.

Experience With Teriflunomide

Branded teriflunomide was approved in Canada in 2013 and has since been joined by ten generic options, making teriflunomide a cost-effective treatment for RIS. Long term safety data of more than 80,000 people treated with teriflunomide did not show an increased risk of adverse events of special interest[iv], indicating a favorable safety profile as treatment in people diagnosed with RIS. MS Canada does not have lived experience data from people diagnosed with RIS who are or were treated with teriflunomide. In

Final Thoughts

Teriflunomide has a well-established safety profile and demonstrated efficacy in relapsing MS and those at risk of MS including CIS and RIS. Available as a generic, it is cost effective to public and private payers and as a once daily oral tablet, carries a high ease of administration for individuals. To achieve health equity, all Canadians at risk of developing MS; those diagnosed with CIS and RIS, must have access to medications that can significantly delay disease onset and slow disability progression. Teriflunomide has the potential to fill a significant therapeutic gap within the MS disease spectrum, to help delay the onset of symptoms and improve long-term outcomes by intervening at the earliest stage of the disease.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Table 1: Financial Disclosures

No industry help was received from outside MS Canada to collect, analyze data, or complete this submission. The following companies have provided MS Canada with sponsorship over the past two years. No company has expressed interest in the drug review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
EMD Serono				X
Hoffmann La Roche				X
Biogen				X
Novartis				X
Sanofi-Genzyme			X	
Pendopharm (Pharmascience)			X	
Bristol-Myers Squibb	X			
Sandoz	X			
Alexion			X	
JAMP		X		
AbbVie			X	
AstraZeneca			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Jennifer McDonell
Position: Director, Information and Resources
Patient Group: MS Canada
Date: August 21, 2024

[i] Accessing Disease-Modifying Therapies for Multiple Sclerosis: A Pan-Canadian Analysis. The Conference Board of Canada, 48 pages, December 3, 2020 Primer by Junyi Feng , Isabelle Gagnon-Arpin , Nicholas Moroz , Monika Slovinec D'Angelo.
[ii] De Stefano N, Giorgio A, Tintore M, Pia Amato M, Kappos L, Palace J et al (2018) Radiologically isolated syndrome or subclinical multiple sclerosis: MAGNIMS consensus recommendations. Mult Scler 24(2):214–221.
[iii] Preziosa, P., Rocca, M.A. & Filippi, M. Radiologically isolated syndromes: to treat or not to treat?. J Neurol 271, 2370–2378 (2024).
[iv] Magyari, M., Koechlin, A., Duclos, A., Kopp, T. I., Allaoui, E. M., Polazzi, S., Seeldrayers, P., & Autier, P. (2024). Long-Term Safety of Teriflunomide in Multiple Sclerosis Patients: Results of Prospective Comparative Studies in Three European Countries. Pharmacoepidemiology and Drug Safety, 33(7), e5866.

CDA-AMC Open Calls for Input and Feedback: Proposed Project Scope for Teriflunomide in RIS

Project number: SX0752-000

Brand Name: Aubagio

Generic Name: Teriflunomide

Indication(s): radiologically isolated syndrome (RIS)

Group Name: Canadian Network of MS Clinics (CNMSC)

Primary contact: Dr. Sarah Morrow

E-mail: [redacted]

Telephone: [redacted]

Comments from CNMSC

a) Table 1: Policy Question

- CDA should consider clarifying the policy question to read as follows: "Should teriflunomide be publicly reimbursed for radiologically isolated syndrome (RIS) in patients who meet the 2023[1] RIS diagnostic criteria?"
- Note: it is expected that these RIS criteria will be integrated in some manner into the 2024 McDonald criteria for MS (release expected in Fall 2024).

b) Table II: Products available in Canada

- CNMSC has no additional comments related to this table.

c) Table III: Project Scope

CNMSC has reviewed the PICOs outlined for the project scope. Comments and proposed changes are outlined below regarding the population, comparators, and outcomes.

- Population:
  - should be clarified, as follows: Patients with radiologically isolated syndrome (RIS) who meet the 2023 RIS diagnostic criteria.
- Comparators:
  - The only relevant comparator for RIS is placebo or no treatment.
  - Neither interferon nor glatiramer acetate are relevant comparators as there are no randomized controlled studies specific to their use in RIS based on the 2023 diagnostic criteria.

[1] Lebrun-Frénay C, Okuda DT, Siva A, Landes-Chateau C, Azevedo CJ, Mondot L, Carra-Dallière C, Zephir H, Louapre C, Durand-Dubief F, Le Page E, Bensa C, Ruet A, Ciron J, Laplaud DA, Casez O, Mathey G, de Seze J, Zeydan B, Makhani N, Tutuncu M, Levraut M, Cohen M, Thouvenot E, Pelletier D, Kantarci OH. The radiologically isolated syndrome: revised diagnostic criteria. Brain. 2023 Aug 1;146(8):3431-3443. doi: 10.1093/brain/awad073. PMID: 36864688; PMCID: PMC11004931.

- Outcomes:
    - Should be clarified as follows:
        - Time to first acute or progressive (non-acute) neurological event from CNS demyelination
        - Time to progression
        - Development of new MRI changes: new and/or enlarging lesions (T2-weighted hyperintense, gadolinium-enhancing (Gd+), changes in lesion volumes, brain atrophy etc.)
        - Number of new and/or enlarging lesions (T2-weighted hyperintense, gadolinium-enhancing (Gd+), changes in lesion volumes, brain atrophy etc.)
        - Health Related Quality of Life (HRQoL)
        - Harms (i.e., adverse events)

d) Table IV: Research Questions

- The first two research questions proposed (i.e., clinical effectiveness and harms) are relevant.
- The third research question (i.e., expected cost) cannot be addressed unless the key policy questions of precision around the definition of the population (see above) and, therefore, the number of patients expected are addressed.

CADTH Reimbursement Review
Drug Program Input on Implementation Issues

Section 1: General Information

1.1 Drug Product Information:	
Drug name (generic): teriflunomide	**Sponsor: FMEC review**
Indication: monotherapy for the treatment of patients with relapsing remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.	
Reimbursement Request: for the indication of radiologically isolated syndrome (RIS)	

1.2 Lead Jurisdiction
Jurisdiction: VAC

Section 2: Jurisdictional Implementation Issues

Table 1: Jurisdictional Context

2.1 RELEVANT COMPARATORS Check (type "X") whether you have identified potential or current **issues** and provide brief details	
X	**a) Issues with the choice of comparator in the submitted trial(s)** No comparator in the trial; the TERIS trial (Teriflunomide in Radiologically Isolated Syndrome) was a multicenter, placebo-controlled, double-blind, randomized clinical trial. The primary outcome was the time to a first acute or progressive neurologic event resulting from CNS demyelination. Secondary outcomes were brain MRI metrics. The study concluded that treatment with teriflunomide extends the time to symptomatic MS in patients with RIS compared to placebo. No head-to-head trials, therefore, cannot say if one disease modifying therapy is better than another.
X	**b) Other implementation issues regarding relevant comparators (e.g., access/funding, covered population)** None of the comparator drugs (interferon beta, glatiramer, dimethyl fumarate) are indicated for the treatment of RIS; treatment with teriflunomide and comparators would be considered off-label use. Potentially an issue in jurisdictions where these drugs are listed as SA.

Table 2: Policy Considerations for Reimbursing the Drug

2.2 CONSIDERATIONS FOR INITIATION OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
X	**a) Disease diagnosis, scoring or staging for eligibility** Inclusion criteria for the TERIS trial was as follows: 1) Age older than 18 years; 2) Fulfillment of the 2009 RIS criteria with structural neuroimaging abnormalities not explained by another disease process;

	3) No historical accounts of remitting clinical symptoms consistent with neurologic dysfunction Exclusion criteria: severe hepatic, kidney, and immune system impairments, lactating or pregnant women, or previous exposure to immunosuppressive or disease modifying treatments. NOTE: The trial used 2009 RIS criteria; however, during the first teleconference the clinical experts noted that the updated 2023 RIS criteria are used in clinical practice. Questions for the expert: Would it be reasonable to use the inclusion criteria from the TERIS trial to determine eligibility for treatment with teriflunomide, with the exception of using the 2023 RIS criteria instead of the 2009 RIS criteria? Any specific baseline scores that should be considered (i.e. EDSS)?
X	**b) Other patient characteristics for eligibility (e.g., age restrictions, comorbidities)** Question for the expert: Is there a way to identify patients with RIS who are at an increased risk of progressing to MS? If recommended for listing, would all patients with RIS be treated with DMT? If not, under what circumstances/patient characteristics would you choose to not treat?
☐	**c) Prior therapies required for eligibility** Example: Should patients having experienced a drug of the same class be eligible for the drug under review?
☐	**d) Eligibility to re-treatment**
☐	**e) Special subtypes (not explicitly mentioned in the indication) to consider separately for eligibility** Example: Would patients with CNS metastases equally benefit from this oncology drug and would they be considered eligible?
☐	**f) Consistency with initiation criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with reimbursement criteria for drug B.
2.3 CONSIDERATIONS FOR CONTINUATION OR RENEWAL OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
X	**a) Challenges related to assessment and monitoring of therapeutic response** Question for the expert: How often should follow up occur (eg: every 6 months, annually)? What should be monitored at follow up (i.e. bloodwork, MRI, EDSS, etc)?
☐	**b) Consistency with renewal criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with renewal criteria for drug B.
2.4 CONSIDERATIONS FOR DISCONTINUATION OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
X	**a) Definition of loss of response, absence of clinical benefit, or disease progression** In the study, the primary outcome was time to a first acute or progressive neurologic event resulting from CNS demyelination and secondary outcomes were brain MRI metrics.

	Question for the experts: How would the clinical experts define loss of response to therapy? Would therapy be discontinued with loss of response?
X	**b) Treatment interruptions** Question for the expert: If treatment was interrupted (due to adverse events, pregnancy, etc), can treatment be resumed at a later time?
X	**c) Definition of fixed-duration therapy** Question for the expert: If there is no disease progression, how long should therapy continue?
☐	**d) Consistency with discontinuation criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with stopping criteria for drug B.
2.5 CONSIDERATIONS FOR PRESCRIBING OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☐X	**a) Dosing, schedule/frequency, dose intensity** For information: Dose is 14mg PO once daily
☐	**b) Drug administration** Example: Intrathecal administration requires special training and facilities.
X	**c) Concerns related to accessing clinical specialists and/or special settings** There is a risk of misdiagnosing patients with nonspecific MRI anomalies as having RIS. Question for the expert: Should this be prescribed by a neurologist with experience in the management of MS? Should it be restricted to prescribers at MS Clinics/Centers?
X	**d) Concerns related to combination usage** Question for the expert: Would/could this be used in combination with other drugs used in the treatment of MS?
☐	**e) Consistency with prescribing criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with prescribing criteria for drug B.

Table 3: Special Implementation Issues

2.6 GENERALIZABILITY Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Populations of interest matching the indication but with insufficient data** Example: Patients with ECOG performance status >1 were excluded from the trial. Can they be considered eligible?
☐	**b) Populations outside the indication or reimbursement request but of interest to jurisdictions** Example: Can this RA drug also be given to patients with giant cell arteritis?
☐	**c) Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review** Example: Potential need to allow switching patients currently receiving a comparator, if the drug under review is recommended and deemed superior.
2.7 FUNDING ALGORITHM (ONCOLOGY ONLY) Check any aspect that may require the development of a provisional funding algorithm by CADTH	
☐	Drug may change place in therapy of comparator drugs
☐	Drug may change place in therapy of drugs reimbursed in previous lines

☐	Drug may change place in therapy of drugs reimbursed in subsequent lines
☐	Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products
☐	Other aspects:
2.8 CARE PROVISION ISSUES Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Drug preparation, storage, administration or dispensing** Example: Drug needs to be initiated in the hospital setting while maintenance therapy would be provided in the community setting.
X	**b) Management of adverse effects** Question for the clinical expert: Should bloodwork be scheduled regularly to monitor for adverse effects such as hepatotoxicity, hematologic toxicity?
☐	**c) Additional supportive medication or other health interventions** Example: Immunosuppressive drug requires co-administration of prophylactic antimicrobials.
☐	**d) Companion diagnostics (e.g., access issues, timing of testing)** Example: Need advice on optimal timing of biomarker testing (e.g., at time of diagnosis, as part of eligibility assessment prior to initiation).
☐	**e) Other care provision issues** Example: To manage toxicity, can one drug of the pair be stopped and the other continued until loss of clinical benefit?
2.9 SYSTEM AND ECONOMIC ISSUES Check any category where you have identified potential or current **issues** and provide brief details	
X	**a) Concerns regarding the anticipated budget impact and sustainability** Provision of this drug in the first line setting may translate into increased expenditure.
☐	**b) Additional costs to be considered (other than related to care provision as detailed above)** Example: This therapy requires facilities that are not available in all provinces. Drug plans may need to cover travel expenses for eligible patients.
☐	**c) Involvement of additional payers** Example: The implantable device component of this therapy will need to be funded by medical services departments within jurisdictional health care systems.
X	**d) Presence of confidential negotiated prices for comparators** Generics available, so no PLA but generic pricing agreements in place
☐	**e) Special programs or initiatives for the introduction and management of the drug(s) under review** Example: Due to their abuse potential, drugs of this class are usually subjected to a controlled distribution program.
☐	**f) Other system or economic issues** Example: High upfront cost of this gene therapy may require special payment arrangements.