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

## CDA-AMC REIMBURSEMENT REVIEW

# Patient/Clinician/Industry Input

**dimethyl fumarate**

(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: Dimethyl Fumarate
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 the 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 a letter to the Federal Minister of Health and all provincial/territorial Ministers of Health asking for improved access to all Health Canada-approved DMTs. This need for improved access to DMTs was reflected in research conducted by the Conference Board of Canada, which 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 dimethyl fumarate 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 dimethyl fumarate 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 Dimethyl Fumarate

Branded dimethyl fumarate was approved in Canada in 2013 and has since been joined by nine generic options, making dimethyl fumarate a cost-effective treatment for RIS. A long-term study found sustained safety and efficacy in people with relapsing MS treated with dimethyl fumarate for up to thirteen years[iv], suggesting it would be a safe, tolerable and efficacious 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 dimethyl fumarate.

## Final Thoughts

Dimethyl fumarate 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 an oral medication, offers 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. Dimethyl fumarate 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

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] Gold R, Arnold DL, Bar-Or A, Fox RJ, Kappos L, Mokliatchouk O, Jiang X, Lyons J, Kapadia S, Miller C. Long-term safety and efficacy of dimethyl fumarate for up to 13 years in patients with relapsing-remitting multiple sclerosis: Final ENDORSE study results. Mult Scler. 2022 Apr;28(5):801-816. doi: 10.1177/13524585211037909.

# CDA-AMC Open Calls for Input and Feedback: Proposed Project Scope for Dimethyl Fumarate in RIS

**Project number:** SX0751-000

**Brand Name:** Tecfidera

**Generic Name:** Dimethyl Fumarate

**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 dimethyl fumarate 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.