DRAFT Reimbursement Recommendation

Dimethyl Fumarate

> Reimbursement request: Radiologically Isolated Syndrome (RIS)
>
> Requester: Public drug programs
>
> Draft Recommendation: Reimburse with conditions

Summary of Recommendation

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

FMEC reviewed the ARISE trial identified by CDA-MAC's systematic review of literature, where dimethyl fumarate 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 that there may be a clinically important delayed time to first acute or progressive neurological symptom 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 this setting of radiologically isolated syndrome.

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

Therapeutic Landscape

What Is Radiologically Isolated Syndrome?

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 Based on historical references, approximately 30% to 50% of patients with RIS progress to MS. However, based on input from the clinical experts consulted, these historical references likely underrepresent the proportion of patients that will develop MS later in life..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

What Are The Current Treatment Options?

Currently, there are no publicly funded treatments for RIS in Canada. Treatment options may include off-label drugs that are used for MS (e.g., interferon beta, glatiramer acetate).

Why Did We Conduct This Review?

Given the emergence of evidence of therapeutics in the benefits to delay MS and its associated disability, public drug programs requested a review of the available evidence on the efficacy and safety of dimethyl fumaratein the treatment of adults with RIS. Dimethyl fumarate was eligible for a nonsponsored reimbursement review given that generics 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** (CNMSC) submitted input on the proposed scope for this review.
- No input was provided by **industry** groups.
- **Public drug plans** inquired about the evidence for dimethyl fumarate 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 working papers 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 started dimethyl fumarate in February 2019 to slow disease progression. Treatment was paused due to chest pains but later resumed successfully with lifestyle adjustments such as eating heartier meals. She explained several aspects of treatment such as monitoring progress, the frequency of MRIs and the financial challenges in treatment access. The presentation helped the committee understand how the initial diagnosis and subsequent progression from RIS to RRMS in November 2021, impacted her, and how it continues to be a "learning curve" for her and other RIS patients.

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 non-clinical 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 point(s)
Clinical Value	• **Given limitations in the evidence, FMEC noted the clinical value is uncertain.** • Based on the ARISE trial, 7% of patients on dimethyl fumarate compared with 33% on placebo experienced a first acute or progressive neurological symptom associated with CNS demyelinating event. Time to first demyelinating event was delayed, representing approximately 90% relative hazard reduction[a] with dimethyl fumarate when compared with placebo. FMEC noted this is a clinically valuable endpoint as delaying disease onset and to slowing disability have meaningful impacts to patients. • However, FMEC highlighted that there are limitations to the evidence supporting dimethyl fumarate for RIS. These include the lack of subgroup analysis, comparative data on impact to functional status or HRQoL, and comparative efficacy and safety when compared with currently available treatments used in MS. There was uncertainty in the findings due to internal validity issues, wide confidence intervals and small sample size. • FMEC noted that patients who are currently receiving off-label injectable therapies 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 that there is an unmet need to offer evidence-informed treatment for RIS to delay symptoms of MS and associated disability.** • FMEC highlighted that 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. • Given 30-50% 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. These options are not adequately supported by evidence. 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 this setting of radiologically isolated syndrome. • 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 which 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 symptoms and future disability may not be realized or be needed.
Economic Considerations	• FMEC noted that in several jurisdictions where no therapies are currently funded for the treatment of RIS, the reimbursement of dimethyl fumarate will result in increased drug acquisition costs and incremental benefits. No evidence was identified regarding the cost-effectiveness of dimethyl fumarate relative to no active intervention for the treatment of RIS, and therefore, estimates of cost-effectiveness were not available to the committee. However, FMEC discussed that since several generics of dimethyl fumarate are currently marketed and available in Canada, prices are set by the generic pricing framework as opposed to value. • FMEC also noted that 2 participating drug plans (Canadian Armed Forces and Veterans Affairs Canada) currently fund glatiramer acetate and interferon beta for the treatment of RIS, however the guest clinical experts indicated that these treatments are not used frequently. FMEC noted that, using publicly available pricing information, dimethyl fumarate is less costly than glatiramer acetate and interferon beta. Given that dimethyl fumarate is associated with decreased drug acquisition costs and unknown clinical benefit, the reimbursement of dimethyl fumarate may result in cost savings with uncertain benefit in jurisdictions that currently fund therapies for the treatment of RIS. • FMEC noted that CDA-AMC conducted a concurrent review of teriflunomide for RIS also being considered through the non-sponsored review pathway, estimating an annual per-patient drug acquisition cost of $5,449.
Impacts on Health Systems	• FMEC discussed that there are limitations to the clinical evidence supporting the treatments in RIS. For example, RIS patients may not be currently identified through routine screening. Rather, they may be detected through incidental findings on MRI imaging ordered for other investigations. The requirement for routine MRI imaging may impact trial enrollment and feasibility of adoption.

	• FMEC noted there are no specific concerns related to impacts on health systems. Dimethyl fumarate treatment can be monitored with appropriate assessment scales, imaging with MRI and other relevant lab investigations. Common adverse events for dimethyl fumarate are not expected to require hospitalization or costly utilization of health care resources. • FMEC also discussed that treatment for RIS can potentially delay disability and the burden on the health care system for caring 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. • FMEC also raised the importance of informed consent as a patient is offered a treatment for RIS with known risks with the goal to prevent or delay symptoms of MS, which may or may not occur in the future. The clinical guest specialist also highlighted that RIS and MS should be perceived as a spectrum of the same physiological disease process, where RIS is an earlier presentation of the disease of MS.

FMEC = Formulary Management Expert Committee; HRQoL = health related quality of life; MRI = magnetic resonance imaging; MS = multiple sclerosis; RIS = radiologically isolated syndrome.

[a] Note that the information about the absolute risk reduction (or the absolute effect) was not reported or available.

Full Recommendation

With a vote of 8 of 0, the FMEC recommends that dimethyl fumarate for radiologically isolated syndrome be reimbursed if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Dimethyl fumarate should be reimbursed in patients with RIS who meet all of the following criteria: 1.1. Age 18 years or older 1.2. Diagnosed with RIS by neurologist based on the most current RIS criteria	Evidence from the ARISE trial demonstrated a benefit of treatment with dimethyl fumarate in adult patients who met the 2009 RIS criteria. Although current clinical practice follows the 2023 RIS Criteria, the clinical experts and FMEC noted that revised RIS criteria are anticipated to be published imminently.	At the time of the FMEC review, the 2023 RIS Diagnostic Criteria include: • Fulfilment of 2009 RIS dissemination in space criteria: Incidentally identified CNS white matter lesions that appear typical for inflammatory demyelination with ≥ 3 of the following: 1. > 9 T2-weighted hyperintense lesions or ≥ 1 gadolinium-enhancing lesion 2. ≥ 1 juxtacortical lesion 3. ≥ 1 infratentorial lesion 4. ≥ 3 periventricular lesions OR • The presence of at least one lesion in a location typical for MS and two of the three following factors: 1. Spinal cord lesion 2. CSF restricted oligoclonal bands 3. New asymptomatic T2 or gadolinium-enhancing lesion demonstration dissemination in time
Discontinuation and Renewal		

Reimbursement condition	Reason	Implementation guidance
2. Dimethyl fumarate should be discontinued if the patient has any of the following: 2.1. Disease that is consistent with the current diagnostic criteria for MS 2.2. Significant intolerance or toxicity to dimethyl fumarate	Consistent with clinical practice, patients in the ARISE trial discontinued treatment upon experiencing a first acute or progressive neurological symptom associated with a CNS demyelination event 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 or MS.	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.
4. Dimethyl fumarate should not be used concurrently with other DMTs.	There is no evidence to support the use of dimethyl fumarate concurrently with other DMTs.	DMT is a disease modifying therapy that is typically used for treatment of MS and related conditions.
Cost		
5. Dimethyl fumarate must represent good value to the drug plans.	In jurisdictions where no therapies are funded for RIS, reimbursing dimethyl fumarate will increase drug acquisition costs. A cost-effectiveness analysis would be needed to determine whether dimethyl fumarate is cost-effective. Additionally, in the absence of comparative clinical evidence against other therapies for RIS, dimethyl fumarate 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 pCPA generic pricing framework.

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

Feedback on Draft Recommendation

<to be updated after the feedback period>

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, as well as two guest specialists from Alberta and Ontario.

Meeting date: November 21, 2024

Conflicts of interest: None

Special thanks: CDA-AMC extends our 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 & 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 use 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 the FMEC committee.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.