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

Draft Reimbursement Review

Review Report

DIMETHYL FUMARATE (TECFIDERA)

(Non-Sponsored Review)

Therapeutic area: Multiple Sclerosis (MS), Radiologically Isolated Syndrome

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Key Messages

What Is Radiologically Isolated Syndrome?

- Radiologically isolated syndrome is considered the earliest detectable pre-clinical phase of multiple sclerosis that is characterized by incidental brain or spinal cord magnetic resonance imaging findings in individuals without typical multiple sclerosis symptoms. While radiologically isolated syndrome is defined as asymptomatic, patients may present with non-specific symptoms and require increased health care resources prior to the diagnosis of multiple sclerosis.
- In 2024, there are approximately 18,000 to 210,000 patients with radiologically isolated syndrome in Canada.

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

- Delaying disease onset and slowing disability progression with increased tolerability and safety were identified as important outcomes of treatments 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 radiologically isolated syndrome in Canada. Patients with radiologically isolated syndrome are often untreated. Treatment options may include off-label drugs that are used for multiple sclerosis (e.g., interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide) or for other indications (e.g., minocycline).

What Is Dimethyl Fumarate and Why Did We Conduct This Review?

- Dimethyl fumarate is a drug that is available as an oral delayed-release capsule. Health Canada has approved dimethyl fumarate, 120 mg and 240 mg, for relapsing remitting multiple sclerosis.
- We previously reviewed dimethyl fumarate for relapsing remitting multiple sclerosis and issued a recommendation for reimbursement. At the request of the participating drug programs, we reviewed dimethyl fumarate to inform a recommendation on whether it should be reimbursed for adults with radiologically isolated syndrome.

How Did We Evaluate Dimethyl Fumarate?

- We reviewed the clinical evidence on the beneficial and harmful effects and compared costs of dimethyl fumarate versus other treatments used in Canada for radiologically isolated syndrome:
- The clinical evidence was identified through systematic searches for available studies. We consulted 2 clinical specialists with expertise in the diagnosis and management of multiple sclerosis, as part of the review process. 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 around issues that may impact their ability to implement a recommendation.

What Did We Find?

Clinical Evidence

We reviewed the following clinical evidence:

- 1 trial (ARISE) comparing dimethyl fumarate with placebo in patients with radiologically isolated syndrome

For the comparison of dimethyl fumarate 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. Treatment with dimethyl fumarate may reduce the number of

new lesions detected through imaging. 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 no evidence to inform how dimethyl fumarate compares with interferon beta, glatiramer acetate, or teriflunomide.
- The safety profile of dimethyl fumarate was as expected with no new safety signals.
- The effects of dimethyl fumarate on important outcomes such as functional status and health-related quality of life are unknown.

Economic Evidence

- The reimbursement of dimethyl fumarate 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 dimethyl fumarate will result in increased drug acquisition costs. Given that dimethyl fumarate 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 dimethyl fumarate relative to no active intervention.

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Abbreviations

AE	adverse event
CI	confidence interval
CNS	central nervous system
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
HR	hazard ratio
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention to treat
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
RCT	randomized controlled trial
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)	Dimethyl fumarate, 120 mg and 240 mg, oral delayed-release capsules
Relevant Health Canada indication	Not applicable
Mechanism of action	Activation of the Nrf2 pathway involved in the cellular response to oxidative stress, leading to the upregulation of antioxidant response genes, thereby inducing anti-inflammatory responses and reducing aberrant immune cell activation
Data protection status	October 3, 2021
Status of generic drugs or biosimilars	Several generics 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], and teriflunomide[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), and HRQoL Harms: AE, SAE, withdrawal due to AE, death due to AE, and adverse events of special interest (i.e., lymphopenia, gastrointestinal events)

AE = adverse event; 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 dimethyl fumarate, 120 mg and 240 mg, oral delayed-release capsules in the treatment of adults with radiologically isolated syndrome (RIS). The focus will be placed on comparing dimethyl fumarate to relevant comparators and identifying gaps in the current evidence. The economic review consists of a cost comparison for dimethyl fumarate compared with relevant comparators for RIS in adults. The comparators considered relevant to the reviews were interferon beta, glatiramer acetate, and teriflunomide.

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 <insert hyperlink or citation>. Input from patient and clinician groups is considered throughout the review, including in 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 a separate document.

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 (number of respondents was not reported), as no patient was identified to have been diagnosed with RIS and treated with dimethyl fumarate.

Clinician group input was submitted by the representative on behalf of Canadian Network of MS Clinics (number of clinicians was not reported) which 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] and symptoms including vision loss, motor weakness, and paresthesia.[1] Incidental brain or spinal cord magnetic resonance imaging (MRI) findings suggestive of MS in individuals without typical MS symptoms is defined as RIS.[3,4]

While RIS is asymptomatic by definition, increased health care resource utilization prior to the diagnosis of MS suggests a prodromal phase or non-specific symptoms preceding classical experiences among people with MS; in those with RIS, common reasons for an initial MRI scan included headache and trauma.[1,5] Patients with RIS have presented with cognitive impairment, with a similar profile to patients with relapsing remitting MS.[4]

Based on accumulating evidence about the natural history of RIS, the original 2009 RIS criteria[6] was revised in 2023 to incorporate observed CNS anomalies, risk factors, and earlier treatment; the revised criteria had better sensitivity and maintained specificity, was aligned with the existing 2017 McDonald Criteria, and provided clinicians with a broadly applicable framework.[1,7] Note that the official publication of the 2024 McDonald Criteria was not yet released at the time of writing this report; some patients who were previously diagnosed with RIS would be diagnosed with MS according to the proposed revised criteria.

The prevalence of RIS has been estimated to range from 0.06% to 0.7%,[4] approximately 18,000 to 210,000 patients in Canada in 2024. Studies that used the Okuda criteria reported that the incidence of RIS ranged from 0.05% to 0.1% per year.[8,9] Data are limited on the proportion of patients with RIS at risk of developing MS, with an estimated 30% of patients who converted to symptomatic MS.[5]

Current Management

Treatment Goals

Input from the patient group indicated that there is a need for treatments to delay disease onset and slow disability progression with increased 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 HRQoL.

Current Treatment Options

Currently, there are no publicly funded treatments for RIS in Canada. As such, the clinical experts have expressed that patients with RIS can sometimes be treated off-label with drugs that are approved by Health Canada for patients with relapsing remitting MS (e.g., interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide, ocrelizumab, ofatumumab, natalizumab), or drugs 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. Since RIS is recognized as being a subclinical precursor to clinical MS, including a prodromal phase (i.e., non-specific symptoms such as cognitive impairment, motor or dexterity impairments, fatigue), there is emerging consensus among MS clinicians that treatment with disease-modifying agents may be appropriate among certain patients with RIS.

Key characteristics of dimethyl fumarate are summarized with other treatments available for RIS in the Working Papers, Table 2.

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 generics), 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 to disease-modifying therapies (DMTs) on behalf of patients with RIS which can significantly delay disease onset and slow disability progression, including dimethyl fumarate

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 pre-clinical, early phase of MS, and the goals of treatment are to prevent future relapses and disability progression. Given that early treatment of a potentially disabling condition is critical, and that current guidelines recommend off-label treatments, the experts expressed that there is a clear gap in approved treatments for patients with RIS.

Clinical Review

Methods

Eligibility Criteria

We included studies that adhered to the a priori eligibility criteria, detailed in Working Papers, Table 3. Eligible studies included published phase III and IV randomized controlled trials (RCTs) that included adults with RIS being treated with dimethyl fumarate. Relevant comparators included drugs used in clinical practice in Canada to treat patients described in the indication under review and those included in the Pharmacoeconomic Review. These included: interferon beta, glatiramer acetate, and teriflunomide. Because no comparative trials were expected, placebo was also considered to be a relevant comparator. Long term extension studies of included RCTs 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 are 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 (ITCs) 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 peer reviewed literature search of key bibliographic databases, trial registries, and grey literature sources. The initial search was completed on August 8, 2024, with alerts maintained until the Formulary Management Expert Committee meeting on November 21, 2024. The Working Papers document 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 texts. 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 study 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 115 unique records via the searches of databases and registers, of which we excluded 113 by title and abstract. We screened 2 records by full text and included 1 report of 1 study.

From a supplemental search for ITCs, we identified 24 unique records via the searches of databases and registers, of which none met eligibility by title and abstract.

A list of excluded studies, including reasons for exclusion, is in the Working Papers, Table 4.

No long term extension studies nor studies addressing gaps were identified.

Systematic Review

Description of Studies

The ARISE study[11] was a multicentre (12 sites in the US), phase IV, double-blinded, placebo-controlled, RCT that enrolled 87 patients with RIS from March 9, 2016, to October 31, 2019. The primary end point was time to development of a first acute, adjudicated, clinical event or a progressive neurologic symptom suggestive of CNS demyelination. An acute neurological event was defined as a clinical symptom localized to the optic nerve, brainstem, cerebellum, spinal cord, or long sensory or motor tracts, lasting greater than 24 hours and followed by a period of symptom improvement. The onset of a nonacute primary demyelinating event was defined as gradual worsening of a neurologic symptom over a minimum of 12 months, fulfilling criteria for primary progressive MS. Secondary end points included the number of new and/or newly enlarging T2-weighted hyperintense lesions, and the number of gadolinium-enhancing lesions. The Expanded Disability Status Scale (EDSS) was an additional prespecified end point. Adverse events (AEs) were recorded throughout the study. A detailed description of the outcome measures is in the Working Files, Appendix 3.

Key inclusion criteria in the ARISE study included adults 18 years and older who met the 2009 RIS criteria,[6] of whom had an index MRI date of 2009 or later, incidental anomalies identified on MRI of the brain or spinal cord resulting from an evaluation unrelated to

MS, and no clinically apparent neurologic impairments that could be accounted for by the MRI anomalies. Incidentally observed MRI anomalies highly suggestive of CNS demyelination were required to fulfill at least 3 of the following 4 criteria: 1) 9 or more T2-weighted hyperintense lesions or 1 or more gadolinium-enhancing lesion, 2) 3 or more periventricular lesions, 3) 1 or more juxtacortical lesion, and 4) 1 or more infratentorial lesion. Key exclusion criteria included exposure to a DMT (past 3 months) or high dose glucocorticoid (past 30 days).

Patients were randomized (block sizes of 4) in a 1:1 ratio to receive oral dimethyl fumarate (Tecfidera) 120 mg twice daily for 7 days followed by 240 mg twice daily, or placebo, until until week 96. MRI scans were conducted at baseline and 96 weeks. An independent clinical committee that was blinded to randomized assignments reviewed patients' medical information for study eligibility and adjudicated clinical relapses related to inflammatory demyelination based on independent reviews of MRI data. The MRI Committee performed independent reviews of MRI data (appropriate size, shape, number, and distribution pattern of lesions) and confirmed imaging criteria for study inclusion. The EDSS was assessed at baseline, week 48, and week 96; it was also evaluated at time of first clinical relapse, early withdrawal, or an unscheduled visit. An independent external safety committee monitored and reviewed all reported AEs. Patients who experienced intolerable flushing and/or gastrointestinal events were permitted to undergo dose reduction (1 capsule once daily) for 1 month before resuming the initial dose. Patients who met the primary end point or experienced continuing intolerance to study treatment were withdrawn from the study and invited for open-label treatment with dimethyl fumarate or peg-interferon beta-1a (Plegridy); individuals with intolerance but who did not meet the primary end point were encouraged to be followed for MRI and study assessments.

All randomized patients were included in the intention to treat (ITT) 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. A data cut off date for analyses was not specified.

Results

Patient Disposition

A total of 87 patients were screened and enrolled into the ARISE trial. All patients who were allocated to dimethyl fumarate (n = 44) and placebo (n = 43) received the randomized treatment. Twelve patients (27.3%) and 13 patients (30.2%) discontinued study treatment in the dimethyl fumarate and placebo group, respectively. Reasons for study discontinuation in the dimethyl fumarate and placebo group, respectively, were due to the study being terminated by the sponsor (9% and 14%), patient withdrawal (5% and 9%), physician decision (0 and 7%), pregnancy (2% and 0), protocol violation (2% and 0), and other reasons not specified (9% versus 0). Two patients and 1 patient in the dimethyl fumarate and placebo group, respectively, were lost to follow-up. Overall, 30 patients (68.2%) in the dimethyl fumarate group and 29 patients (67.4%) in the placebo group completed the study.

Baseline Characteristics

Baseline characteristics of patients were overall similar between treatment groups in age at RIS diagnosis (mean 44 years [standard deviation (SD), 13] and mean 45 years [SD, 14] in the dimethyl fumarate and placebo group, respectively), females (70%) and males (30%), EDSS (median of 1 [range, 0 to 3]), and T2-weighted hyperintense lesion volume (mean 7.31 [SD, 0.97]). Reasons for the index MRI scan were similar between groups except for a higher proportion of patients with headache in the dimethyl fumarate group (36%) versus the placebo group (30%). A difference greater than 5% in the proportion of patients in the dimethyl fumarate group versus placebo group, respectively, was noted for family history of MS (7% versus 14%), prior exposure to glatiramer acetate (9% versus 0) and presence of gadolinium-enhancing lesions at baseline (16% versus 5%).

Treatment Exposure and Concomitant Medications

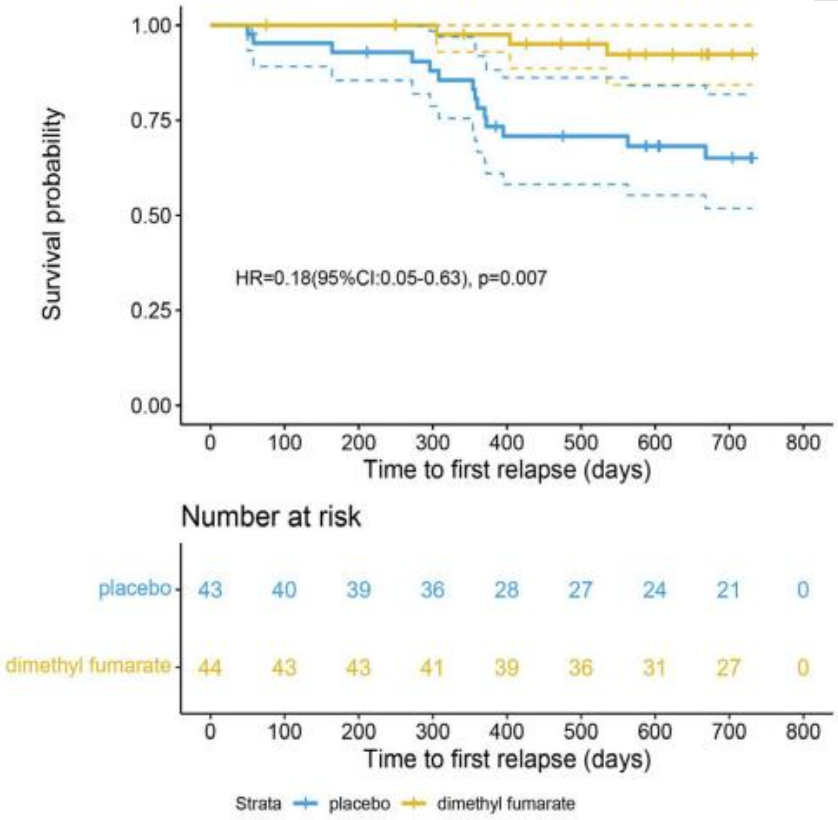
Treatment exposure, adherence, and concomitant medications were not reported in the ARISE trial. Nine patients (21%) who were randomized to treatment with placebo experienced a clinical relapse and subsequently received treatment with dimethyl fumarate.

Efficacy

- Results for outcomes important to this review are presented in

Figure 1: Kaplan-Meier Estimate of Time from Randomization to the First Demyelinating Event (Unadjusted Analysis)

Alt Text: The Kaplan-Meier curves of time to first demyelinating event in the dimethyl fumarate group (N = 44) versus the placebo group (N = 43), showing clear separation at about 50 days, dropping at about 300 days in the dimethyl fumarate group (number of patients at risk was 41) but was lower in the placebo group (number of patients at risk was 36), and trending the same for teriflunomide but notably lowered for the placebo group through 700 days (number of patients at risk was 27 versus 21 in the dimethyl fumarate versus placebo group, respectively).



CI = confidence interval; HR = hazard ratio.
Source: Reproduced with permission from Okuda et al. (2023).[11]

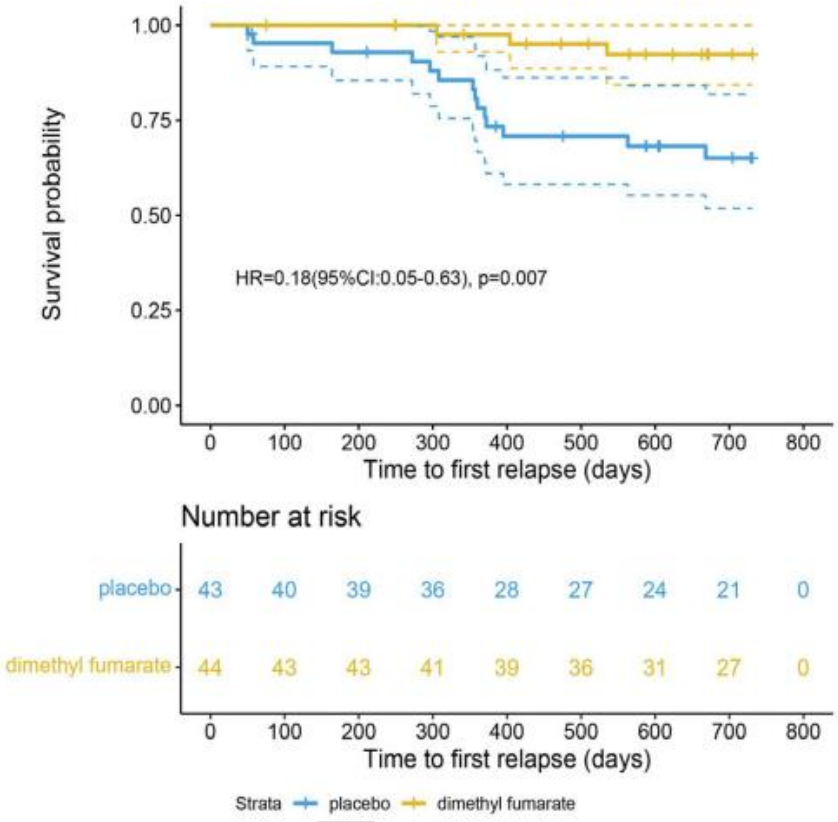
Table 2. The Kaplan-Meier plot for the time to first acute or progressive neurological symptom associated with CNS demyelinating event is in Figure 1. Key results include the following:

- Length of follow-up (e.g., median weeks or months [range]) was not reported.
- The median time to event (first acute or progressive neurological symptom associated with CNS demyelinating event) in each treatment group was not reported. The adjusted hazard ratio (HR) was 0.07 (95% CI, 0.01 to 0.45; P value = 0.005), favouring dimethyl fumarate.
- Sensitivity analyses of the primary end point were similar across 4 scenarios of different prior distribution parameters.

- The number of newly enlarging T2 lesions and the number of new T2 lesions were numerically lower in the dimethyl fumarate group compared with placebo. The number of patients with at least 1 new and/or newly enlarging T2-weighted hyperintense lesion were similar between treatment groups. The cumulative number of new and/or newly enlarging T2-weighted hyperintense lesions was adjusted rate ratio of 0.20 (95% CI, 0.04 to 0.94; P value = 0.042), favouring dimethyl fumarate.
- Data for the EDSS was not reported by treatment group. Although HRQoL was considered important to this review, it was not assessed in the included study.

Figure 1: Kaplan-Meier Estimate of Time from Randomization to the First Demyelinating Event (Unadjusted Analysis)

Alt Text: The Kaplan-Meier curves of time to first demyelinating event in the dimethyl fumarate group (N = 44) versus the placebo group (N = 43), showing clear separation at about 50 days, dropping at about 300 days in the dimethyl fumarate group (number of patients at risk was 41) but was lower in the placebo group (number of patients at risk was 36), and trending the same for teriflunomide but notably lowered for the placebo group through 700 days (number of patients at risk was 27 versus 21 in the dimethyl fumarate versus placebo group, respectively).



CI = confidence interval; HR = hazard ratio.
Source: Reproduced with permission from Okuda et al. (2023).[11]

Table 2: Summary of Key Efficacy Results in the ARISE Trial (ITT Population)

Variable	Dimethyl fumarate N = 44	Placebo N = 43
Primary End Point: Time to first CNS demyelinating event[a]		
Number of patients with a first acute or progressive neurological symptom associated with CNS demyelinating event, n (%)	3 (6.8)	14 (32.6)
First acute clinical event, n (%)	3 (6.8)	14 (32.6)
First progressive neurological symptom, n (%)	0 (0)	0 (0)
Time to first clinical demyelinating event (weeks), median (95% CI)	NR	NR
Unadjusted HR (95% CI)	0.18 (0.05 to 0.63)	Reference
P value	0.007	Reference
Adjusted HR[b] (95% CI)	0.07 (0.01 to 0.45)	Reference
P value[c]	0.005	Reference
Secondary End Points:		
Number of patients contributing to the analysis, n (%)	27 (61.4)	26 (60.5)
New and/or newly enlarging lesions at week 96		
Number of newly enlarging T2 lesions, mean (SD)	0.03 (0.003)	0.10 (0.07)
Number of new T2 lesions, mean (SD)	0.09 (0.06)	0.54 (0.28)
Number of patients with ≥ 1 new and/or newly enlarging T2-weighted hyperintense lesion(s), n (%)	7 (25.9)	8 (30.8)
Cumulative number of new and/or newly enlarging T2-weighted hyperintense lesions, mean (SD)	0.12 (0.07)	0.62 (0.30)
Adjusted rate ratio[d] (95% CI)	0.20 (0.04 to 0.94)	Reference
P value	0.042	Reference
New gadolinium-enhancing lesions at week 96		
Number of patients with new gadolinium-enhancing lesions, n (%)	1 (3.7)	0 (0)
Cumulative number of new gadolinium-enhancing lesions, mean (SD)	0.07 (0.38)	0 (0)
Adjusted rate ratio[d] (95% CI)	Not estimable	Reference
P value	Not estimable	Reference
Functional Status: Expanded Disability Status Scale (0 [no disability] to 10 [death from MS])		
Number of patients with data at baseline, n	87	
Number of patients with EDSS > 1 at baseline, n (%)	37 (42)	
Number of patients with data at week 96, n	57	
Number of patients with EDSS > 1 at week 96, n (%)	35 (61)	

CI = confidence interval; CNS = central nervous system; EDSS = Expanded Disability Status Scale; HR = hazard ratio; ITT = intention to treat; MS = multiple sclerosis; NR = not reported; SD = standard deviation.

[a] The primary end point was time from randomization to first acute or progressive neurological event resulting from CNS demyelination.

[b] Based on a Cox proportional hazards regression model that adjusted for sex, age at time or RIS diagnosis, MS family history, EDSS score at baseline, brain T2-weighted hyperintense lesion volume at baseline (log-transformed), and presence of gadolinium-enhancing lesions at baseline.

[c] P value has not been adjusted for multiple testing so there is risk of type I error.

[d] Based on a negative binomial regression model that adjusted for the number of gadolinium-enhancing lesions on MRI at baseline.

Source: Okuda et al. (2023).[11]

Harms

Detailed results for harms for the included study are in the following publication: Okuda 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 14 of 44 patients (32%) in the dimethyl fumarate group and in 9 of 43 patients (21%) in the placebo group. Common moderate AEs (> 5% of patients) that occurred in either the dimethyl fumarate or placebo group, respectively, were infections (7% versus 5%), nervous system disorders (9% versus 7%), and musculoskeletal and connective tissue disorders (5% versus 9%).
- Serious adverse events (SAEs) occurred in 2 patients (5%) in the dimethyl fumarate group and in 4 patients (9%) in the placebo group. SAEs in the dimethyl fumarate group occurred in 1 patient each for breast cancer, prostate cancer, invasive ductal breast carcinoma, and spontaneous cerebrospinal fluid leak syndrome; SAEs in the placebo group occurred in 1 patient each for cholelithiasis, procedural headache, spondylolysis, and migraine.
- Study discontinuations due to AEs were not reported.
- No deaths due to AE were reported.
- Notable harms identified for this review (lymphopenia and gastrointestinal events) were not prespecified in the included study. One patient (2%) in the dimethyl fumarate group and 0 patient in the placebo group had decreased lymphocyte counts. A total of 2 patients (5%) in the dimethyl fumarate group versus 2 patients (5%) in the placebo group experienced gastrointestinal disorders, including nausea (1 patient in each group), dyspepsia (1 patient versus 0 patient), abdominal discomfort (0 versus 1 patient), and food poisoning (1 patient versus 0 patient).

Critical Appraisal

Internal Validity

Risk of bias in the randomization process was low based on centralized allocation and there were few between-group imbalances in baseline characteristics. There were some imbalances on exposure to glatiramer acetate and presence of gadolinium-enhancing lesions at baseline (both higher in the dimethyl fumarate group), and family history of MS (higher in the placebo group). These were likely due to chance, given the small sample size.

Study personnel and patients were blinded to allocated treatment (identical packaging and capsules of dimethyl fumarate and placebo) to reduce potential bias related to knowledge of assigned intervention. Patients in the placebo group were able to start treatment with dimethyl fumarate 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 dimethyl fumarate. No information was reported on concomitant nor subsequent treatments. While unlikely to be of concern prior to cross-over (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 placebo were able to cross over to the dimethyl fumarate arm. The potential bias is likely to be directed towards the null, but no information was provided to enable the review team to appraise the presence or extent of potential bias. Importantly, unblinding due to an AE occurred in the dimethyl fumarate group (18.2%) and placebo group (25.6%), increasing concerns for risk of bias due to knowledge of randomized treatment for patient-reported outcomes.

Sample size calculations using a Cox proportional hazards regression were initially based on 80 patients per arm to achieve 80% power to detect a 50% reduction in the risk of the first clinical event. Due to slow patient recruitment, analyses were revised to a Bayesian approach as a secondary analysis to achieve 90% power to detect a 50% treatment effect. This secondary analysis was not described sufficiently which limits the ability of the review team in interpreting and appraising the results. Survival curves for the

primary end point were plotted using the Kaplan-Meier method without detailing the proportional hazards assumption and how this was tested although visual inspection indicates clear separation of the treatment groups at about 50 days that was maintained thereafter. The mean time to event was not reported so it is unclear how long patients were followed, including those who remained in follow-up without an event. There was no adjustment for multiple comparisons, resulting in increased risk of type I error for the primary end point and the secondary end point (cumulative number of new and/or newly enlarging T2-weighted hyperintense lesions) which had statistically significant findings.

MRI analysis was performed centrally to evaluate screening eligibility and follow-up of clinical events using a standardized protocol at scheduled visits in addition to unscheduled visits (e.g., neurological events). Although no details were provided on procedures to ensure within- and inter-rater reliability, there was likely low risk of bias in evaluations of MRI data. As previously mentioned, blinding of study personnel and patients would have mitigated any potential risk of bias in the outcome measurement. However, 9 patients (21%) in the placebo group experienced a clinical relapse and were allowed to switch to dimethyl fumarate, becoming unblinded. This would result in a risk of bias in subjective outcomes (notably HRQoL), likely toward the null. However, no data were reported for the Multiple Sclerosis Functional Composite (MSFC) and patient-reported outcomes, so the presence and extent of this potential bias is unknown.

A complete case analysis was conducted without imputation for missing outcome data (only observed values were included in analyses). The lack of information on the number of patients censored and censoring reasons for the primary end point, and absence of imputation for outcome data combined with a high rate of treatment and/or study discontinuations (29%) and missing follow-up MRIs for secondary end points (39%) result in a risk of bias related to missing outcome data, although the direction of the potential bias cannot be predicted. 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 neither supported by ambiguous reasons for dropouts that differed in frequency across groups, nor lack of sensitivity analyses to verify the robustness of the findings. In contrast, there was low risk of bias for few patients who were lost to follow-up in the dimethyl fumarate group (2 patients) and placebo group (1 patient). Finally, there was a risk of bias for selective outcome reporting based on EDSS data not presented by treatment group, and no results for the MSFC and patient-reported outcomes.

External Validity

According to the clinical experts consulted for the review, the eligibility criteria in the ARISE trial appeared to be reasonable for capturing patients with RIS and aligned with patients who would be considered eligible for treatment with dimethyl fumarate in clinical practice. No sites recruiting patients were in Canada and the majority of enrolled patients were designated racially as White (90%) with a minority as Black (approximately 5%) and 'Other' (5%) which may not be fully representative of patients in Canada. The experts had no concerns with the documented baseline. Patients were evaluated for study eligibility based on meeting the 2009 RIS criteria which was 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 otherwise be diagnosed as having RIS and therefore, eligible for treatment with dimethyl fumarate. No information was provided for efficacy in the expanded population of patients with RIS (those with fewer lesions but at high risk of conversion to MS due to positive cerebrospinal fluid, presence of spinal cord lesions, and new T2 lesions on follow-up scans). Overall, the experts considered the eligibility criteria of the ARISE trial to be reasonable for capturing patients with RIS and aligned with patients who would be considered eligible for treatment with dimethyl fumarate in clinical practice. No details were specified for prior DMT use (e.g., number of patients, reason, duration) that was reported in the discussion of the study publication, indicating the potential that these patients may differ from the overall population in their disease spectrum and/or prognosis.

In addition to the brand version (TECFIDERA) of dimethyl fumarate that was used in the trial, the experts noted that the generic version is mostly applicable in clinical practice with a minority of patients using the brand name drug. Placebo used as a comparator in the ARISE trial was appropriate according to the experts based on a lack of approved treatments for RIS in Canada. Given that there are currently no approved treatments for RIS in Canada, the experts acknowledged placebo to be an appropriate comparator in the ARISE trial but expressed uncertainty on the comparative efficacy or harms of dimethyl fumarate versus available treatments for MS, including emerging evidence on teriflunomide.

The primary end point of time to first CNS demyelinating event captured the key outcome of interest among patients with RIS, and was overall aligned with how relapse is defined in clinical practice according to the experts. While 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 used as part of routine clinical practice. Acknowledging the EDSS to be an imperfect but widely used and understood measure of disability in MS, the experts reported it to be used universally in clinical practice as an indicator of disease progression, with a 0.5-change as being clinically meaningful; however, data for the EDSS were reported wholly for all patients and not by study arm to inform potential treatment effects. Since the experts indicated that patients may undergo treatment for many years, 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 dimethyl fumarate for adults with RIS is available in the Working Papers, in the Place in Therapy section.

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. In the ARISE trial, time to first acute or progressive neurological symptom associated with CNS demyelinating event was the primary end point, with new and/or newly enlarging T2 lesions, and new gadolinium-enhancing lesions as secondary end points.

Findings from the ARISE trial demonstrated that dimethyl fumarate may increase time to a clinical event when compared to placebo among a relatively small sample of patients with RIS, although there is some uncertainty in the results based on potential risk of bias and a relatively small sample size. The clinical experts agreed that findings for time to first acute or progressive neurological symptom associated with CNS demyelinating event was considered clinically meaningful in demonstrating benefit with dimethyl fumarate when compared with placebo, and aligned with observations of patients with MS in practice. All secondary end points (new and/or newly enlarging T2 lesions, and new gadolinium-enhancing lesions) were considered supportive of the primary efficacy findings but limited in interpretability given the number of patients who had MRI findings (approximately 60%) were notably smaller than the randomized population. Relative to placebo, the point estimate suggested a direction of effect to favour dimethyl fumarate in the number of patients with new and/or newly enlarging T2-weighted hyperintense lesions. Interpretation of the findings for the secondary end points was challenging due to a small sample size and missing MRI data.

There was 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 the most from treatment; the relatively small number of patients in the ARISE trial likely precluded any subgroup analyses, and this remains a gap in the evidence for prognosis and long-term follow-up of patients with RIS according to the clinical experts.

Several gaps were identified in the evidence. Findings for the EDSS could not be appraised by the review team in the absence of data for each treatment group. Although prespecified, data for MSFC and patient-reported outcomes were not provided in the trial registry or publication. While patients' HRQoL was also important as part of assessing treatment response, according to the clinical experts, this was not evaluated in the ARISE trial. Based on the duration of the ARISE trial, the long term efficacy and harms of dimethyl fumarate in patients with RIS is unknown. The comparative efficacy and safety of dimethyl fumarate compared with currently available treatments used in MS is unknown in the absence of evidence. Finally, the concurrent emergence of trial evidence for teriflunomide as a treatment option for patients with RIS necessitates an evaluation of its efficacy and safety as a relevant comparator for dimethyl fumarate.[12]

Harms

The patient group input did not identify any individuals with RIS who had experience with dimethyl fumarate. Nevertheless, patients expressed a desire for treatments that were tolerable and safe. In the ARISE trial, the number of patients with moderate AEs were higher in the dimethyl fumarate group versus the placebo group whereas the number of patients with SAEs were similar between groups. No information was provided on overall AEs regardless of severity or study discontinuations or withdrawals due to AEs. The experts acknowledged that the AEs observed were unsurprising and manageable given what is known in patients with MS and that

there were no new safety signals. The experts outlined some observed AEs of treatment with dimethyl fumarate including frequent flushing and GI effects in approximately 10-20% of patients (e.g., abdominal pain, bloating, diarrhea). One expert noted that the patient population in their province appeared to favour treatment with dimethyl fumarate over teriflunomide due to a more tolerable side effect profile. SAEs with dimethyl fumarate, however, were noted to be rare among the 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. Overall, an oral medication is likely to be preferred over either glatiramer acetate or interferon beta, according to the experts.

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, with tolerable side effects and maintenance of quality of life. Evidence from a randomized, phase IV, double-blinded, trial (ARISE) that included 87 adult patients with RIS demonstrated that compared with placebo, treatment with dimethyl fumarate resulted in a statistically significant and clinically important delayed time to first acute or progressive neurological symptom associated with CNS demyelinating event. The evidence suggested that dimethyl fumarate may result in fewer new and/or newly enlarging T2 lesions when compared with placebo. There is some uncertainty in the findings based on potential risk of bias, small sample size, and relatively short duration of treatment. The comparative efficacy of dimethyl fumarate on functional status and HRQoL was not reported. The safety profile of dimethyl fumarate was as expected with no new safety signals. The comparative efficacy and safety of dimethyl fumarate 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 for dimethyl fumarate compared 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 CADTH indicated that glatiramer acetate and interferon beta are off-label treatments that are infrequently used for the treatment of RIS in clinical practice. Further, only 2 CADTH 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, dimethyl fumarate is expected to have a per patient cost of $6,283 in year 1 and $6,343 in subsequent years (Working files, Appendix 9). 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 dimethyl fumarate are $3,826 to $3,885 per patient per year compared to glatiramer acetate and $13,732 to $42,718 per patient per year compared to interferon beta. As such, the reimbursement of dimethyl fumarate 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 dimethyl fumarate will result in increased drug acquisition costs.

Additional items for consideration are provided in the following bullets:

- Evidence from ARISE,[11] a randomized, phase IV, double-blinded trial, demonstrated that treatment with dimethyl fumarate resulted in delayed time to first acute or progressive neurological symptom associated with CNS demyelinating event and may result in fewer new and/or newly enlarging T2 lesions compared with placebo.
- The comparative efficacy and safety of dimethyl fumarate compared with currently available treatments used in MS is unknown in the absence of evidence.
- Several generics of dimethyl fumarate 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 symptom associated with CNS demyelination could potentially lead to future healthcare savings by reducing the need for healthcare resources associated with the treatment of MS.
- A concurrent review is being conducted by CADTH for use of teriflunomide in the treatment of RIS based on the results of the TERIS clinical trial.[12] Teriflunomide is expected to have a per patient cost of $5,449 annually.
- No relevant Canadian cost-effectiveness studies were identified based on a literature search conducted on August 7, 2024.

Conclusion

In jurisdictions that currently fund therapies for the treatment of RIS, the reimbursement of dimethyl fumarate is expected to decrease drug acquisition costs, in comparison to glatiramer acetate and interferon beta. Based on the clinical review conclusions, the comparative efficacy and safety of dimethyl fumarate compared with currently available treatments used in MS is unknown in the absence of evidence. 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.

In the majority of jurisdictions where no therapies are currently funded for the treatment of RIS, the reimbursement of dimethyl fumarate will result in increased drug acquisition costs. Based on the clinical review conclusions, treatment with dimethyl fumarate delayed the onset of the first acute or progressive neurological symptom associated with CNS demyelination and may reduce the number of new and/or newly enlarging T2 lesions compared with placebo. Given that dimethyl fumarate 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 dimethyl fumarate relative to no active intervention. As this was not available, the cost-effectiveness of dimethyl fumarate relative to no active intervention for the treatment of RIS could not be determined.

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