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

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Drugs Health Technologies Health Systems

Reimbursement Review

Dimethyl Fumarate (Tecfidera)

Requester: Public drug programs
Therapeutic area: Multiple sclerosis, radiologically isolated syndrome

Key Messages

What Is Radiologically Isolated Syndrome?

- Radiologically isolated syndrome (RIS) is considered the earliest detectable preclinical phase of multiple sclerosis (MS). It is characterized by brain or spinal cord MRI anomalies found incidentally in individuals without typical MS symptoms. RIS is defined as asymptomatic; however, patients may present with nonspecific symptoms and require increased health care resources before a potential diagnosis of MS.
- In 2024, there were approximately 18,000 to 210,000 patients with RIS in Canada.

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

- Delaying disease onset, slowing disability progression with improved tolerability and safety were identified as important treatment outcomes 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 RIS in Canada. Patients with RIS are often untreated. Treatment options may include off-label drugs used for MS (e.g., interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide) or 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 MS.
- We previously reviewed dimethyl fumarate for relapsing-remitting MS 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 RIS.

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 RIS.
- The clinical evidence was identified through systematic searches for available studies. As part of the review process, we consulted 2 clinical

Key Messages

specialists with expertise in the diagnosis and management of MS. 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 regarding 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) that compared dimethyl fumarate with placebo in patients with RIS.
- 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 in the treatment of RIS.
  - The safety profile of dimethyl fumarate in the treatment of RIS was as expected with no new safety signals.
  - The effects of dimethyl fumarate on important outcomes in RIS, 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. Because 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
CDA-AMC	Canada’s Drug Agency
CNS	central nervous system
EDSS	Expanded Disability Status Scale
HRQoL	health-related quality of life
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
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 generic drugs 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 — AEs, SAEs, withdrawals due to AEs, deaths due to AEs, and AEs of special interest (i.e., lymphopenia, gastrointestinal events)

AE = adverse event; CDA-AMC = Canada's Drug Agency; 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 is on comparing dimethyl fumarate with relevant comparators and identifying gaps in the current evidence. The Economic Review consists of a cost comparison for dimethyl fumarate 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. Input from patient and clinician groups is considered throughout the review, including 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 the Response Summary.

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 (the number of respondents was not reported) because no patients were identified who were diagnosed with RIS and treated with dimethyl fumarate.

Clinician group input was submitted by the representative on behalf of Canadian Network of MS Clinics (the number of clinicians was not reported) that 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] symptoms include vision loss, motor weakness, and paresthesia.[1] RIS is diagnosed when brain or spinal cord MRI anomalies suggestive of MS are found incidentally in individuals who do not have symptoms of MS[3,4]

Although RIS is asymptomatic by definition, increased health care resource utilization is common among people with RIS and suggests a prodromal phase or nonspecific symptoms preceding classical experiences among people with MS. In those with RIS, common reasons for an initial MRI scan include headache and

trauma.[1,5] Patients with RIS can present 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 (Okuda diagnostic criteria)[6] were revised in 2023 to incorporate observed CNS anomalies, risk factors, and earlier treatment. The revised criteria have better sensitivity and maintains specificity, align with the existing 2017 McDonald diagnostic criteria, and provide clinicians with a broadly applicable framework.[1,7] Note the 2024 McDonald diagnostic criteria were not yet officially released at the time of writing this report; some patients previously diagnosed with RIS would now be diagnosed with MS according to the proposed revised criteria.

The prevalence of RIS is estimated to range from 0.06% (Australia, Germany, Japan, the Netherlands, Taiwan, and the US) to 0.7% (Pakistan),[4] and to have affected approximately 18,000 to 210,000 people in Canada in 2024. Studies that used the Okuda diagnostic criteria reported that the incidence of RIS ranged from 0.05% to 0.1% per year (Sweden).[8,9] Data are limited on the proportion of patients with RIS who are at risk of developing MS; 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 that delay disease onset and slow disability progression with improved 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 health-related quality of life (HRQoL).

Current Treatment Options

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

Key characteristics of dimethyl fumarate are summarized with those of other treatments available for RIS in Table 2 in the Supplemental Material.

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

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 preclinical, early phase of MS, and the goals of treatment are to prevent future relapses and disability progression. Because early treatment of a potentially disabling condition is critical and current guidelines recommend off-label treatments due to no publicly funded treatments for RIS, the experts expressed there is a clear gap in available treatments for patients with RIS.

Clinical Review

Methods

Eligibility Criteria

We included studies that adhered to the a priori eligibility criteria, which are detailed in Table 3 in the Supplemental Material. Eligible studies included published phase III and IV randomized controlled trials that included adults with RIS treated with dimethyl fumarate. Relevant comparators included drugs used in clinical practice in Canada to treat RIS and those included in the Economic Review. These included interferon beta, glatiramer acetate, and teriflunomide. Because no comparative trials were expected, placebo was also considered a relevant comparator. Long-term extension studies of the included randomized controlled trials 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 were 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 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 literature search of key bibliographic databases, trial registries, and grey literature sources, using a peer-reviewed search strategy. The initial search was completed on August 8, 2024, with alerts maintained until the Formulary Management Expert Committee meeting on November 21, 2024. The Supplemental Material 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 text. 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, registries, and grey literature, 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 indirect treatment comparisons, we identified 24 unique records via the searches of databases and registries; none met eligibility by title and abstract.

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

No long-term extension studies or 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, randomized controlled trial 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 neurological 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 neurological 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 Appendix 3 in the Supplemental Material.

Key inclusion criteria in the ARISE study included adults 18 years and older who met the 2009 RIS diagnostic criteria,[6] with an index MRI date of 2009 or later, had incidental anomalies identified on MRI of the brain or spinal cord resulting from an evaluation unrelated to MS, and had no clinically apparent neurological 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: 9 or more T2-weighted hyperintense lesions or 1 or more gadolinium-enhancing lesions, 3 or more periventricular lesions, 1 or more juxtacortical lesions, and 1 or more infratentorial lesions. Key exclusion criteria included exposure to a disease-modifying therapy (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) (starting dose of 120 mg twice daily for 7 days and then 240 mg twice daily thereafter) or placebo until week 96. MRI scans were conducted at baseline and at 96 weeks. An independent clinical committee blinded to randomization 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 (experienced a first acute clinical event or progressive neurological symptom suggestive of CNS demyelination) or experienced continuing intolerance to study treatment were withdrawn from the study and invited for open-label treatment with dimethyl fumarate or peginterferon beta-1a (Plegridy); individuals with intolerance who did not meet the primary end point criteria were encouraged to be followed for MRI and study assessments until the end of the study.

All randomized patients were included in the intention-to-treat 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 the dimethyl fumarate (n = 44) and placebo (n = 43) groups received the randomized treatment. Twelve patients (27.3%) and 13 patients (30.2%) discontinued study treatment in the dimethyl fumarate and placebo groups, respectively. Reasons for study discontinuation in the dimethyl fumarate and placebo groups, 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 in the dimethyl fumarate group and 1 patient in the placebo group 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 years in the dimethyl fumarate group; mean = 45 years; SD = 14 years in the placebo group), females (70%) and males (30%), EDSS (median = 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

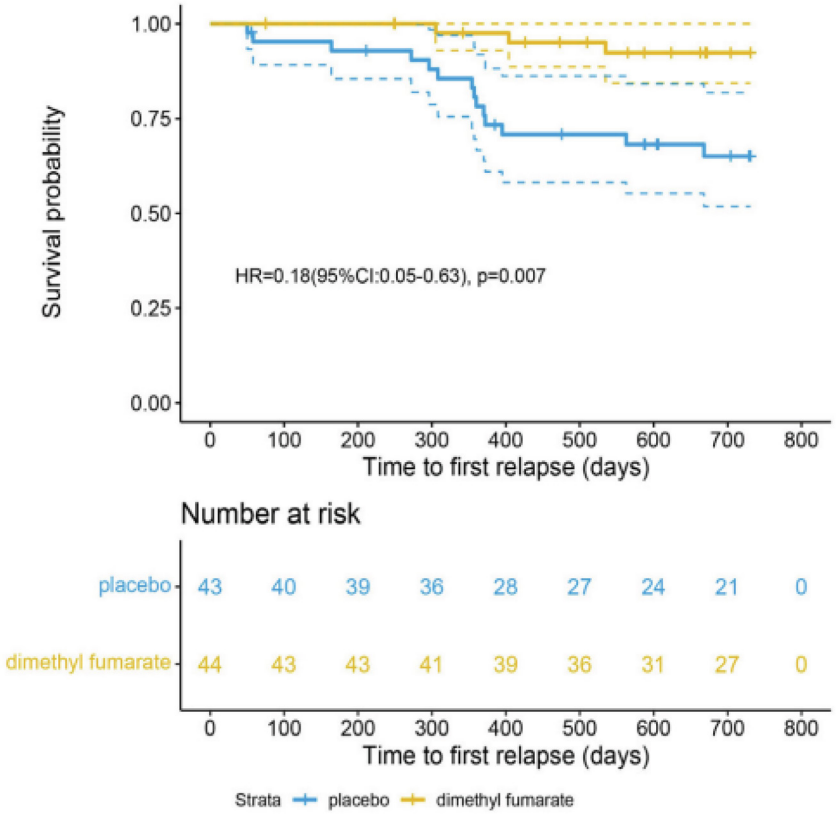
Treatment exposure, adherence, and concomitant medications were not reported in the ARISE trial.
Nine patients (21%) who were randomized to treatment with placebo experienced a clinical relapse and subsequently received treatment with dimethyl fumarate.

Efficacy

Results for outcomes important to this review are presented in Table 2. The Kaplan-Meier plot for the time to first acute or progressive neurological symptom associated with CNS demyelinating event is presented 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 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 the placebo group. The number of patients with at least 1 new and/or a newly enlarging T2-weighted hyperintense lesion was similar between treatment groups. The cumulative number of new and/or newly enlarging T2-weighted hyperintense lesions had an adjusted rate ratio of 0.20 (95% CI, 0.04 to 0.94; P value = 0.042), favouring dimethyl fumarate.
- Data for the EDSS were 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)



CI = confidence interval; HR = hazard ratio.

Source: Reproduced with permission from Okuda et al. (2023).[11] Copyright © 2022 American Neurological Association.

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]		
Patients with a first acute or progressive neurological symptom associated with a CNS demyelinating event, n (%)	3 (6.8)	14 (32.6)
First acute clinical event	3 (6.8)	14 (32.6)
First progressive neurological symptom	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

Variable	Dimethyl fumarate N = 44	Placebo N = 43
P value[c]	0.005	Reference
Secondary end points		
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)
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		
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: EDSS (0 [no disability] to 10 [death from MS])		
Patients with data at baseline, n	87	
Patients with EDSS > 1 at baseline, n (%)	37 (42)	
Patients with data at week 96, n	57	
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 of RIS diagnosis, family history of MS, 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 the dimethyl fumarate and placebo

groups, respectively, were infections (7% and 5%), nervous system disorders (9% and 7%), and musculoskeletal and connective tissue disorders (5% and 9%).

- Serious adverse events (SAEs) occurred in 2 patients (5%) in the dimethyl fumarate group and in 4 patients (9%) in the placebo group. A patient could experience more than 1 SAE. SAEs in the dimethyl fumarate group included breast cancer, prostate cancer, invasive ductal breast carcinoma, and spontaneous cerebrospinal fluid leak syndrome; SAEs in the placebo group included cholelithiasis, procedural headache, spondylolysis, and migraine.
- Study discontinuations due to AEs were not reported.
- No deaths due to an 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 patients 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 patients), abdominal discomfort (0 patients versus 1 patient), and food poisoning (1 patient versus 0 patients).

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 the presence of gadolinium-enhancing lesions at baseline (both higher in the dimethyl fumarate group) as well as a family history of MS (higher in the placebo group). These were likely due to chance, due to 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 or subsequent treatments. Although unlikely to be of concern before crossover (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 the placebo were able to cross over to the dimethyl fumarate arm. The potential bias is likely to be directed toward 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), both of which had statistically significant findings.

MRI analysis, performed centrally using a standardized protocol, was used to evaluate screening eligibility and to follow up clinical events at scheduled visits in addition to unscheduled visits (e.g., neurological events). Although no details were provided on procedures to ensure within-rater and interrater 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 the censoring reasons for the primary end point, the 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 a 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 because EDSS data were not presented by treatment group and there were no results presented 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 selecting 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 in the study racially as white (90%) with a minority as Black (approximately 5%) or “other” (5%), which may not be fully representative of the ethnic and racial diversity of

patients in Canada. The experts had no concerns with the documented baseline characteristics of patients included in the ARISE trial. Patients were evaluated for study eligibility based on meeting the 2009 RIS diagnostic criteria, which were 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 now be diagnosed with 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 findings in 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 identifying patients with RIS and to align with patients who would be considered eligible for treatment with dimethyl fumarate in clinical practice. No details were specified about prior disease-modifying therapy (e.g., reason, duration), other than the number of patients who received interferon beta-1 alpha, interferon beta-1 beta, and glatiramer acetate that was reported in the baseline characteristics of the study publication, indicating the potential that these patients may differ from the overall population in their disease spectrum and/or prognosis.

The brand version (Tecfidera) of dimethyl fumarate was used in the ARISE trial. The experts noted that the generic version is used by most patients in clinical practice, with the brand-name drug used by a minority of patients. Because there are currently no approved treatments for RIS in Canada, the experts acknowledged that placebo is an appropriate comparator in the ARISE trial but expressed uncertainty about 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 aligned overall with how relapse is defined in clinical practice, according to the experts. Although 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 are used as part of routine clinical practice. The experts acknowledged the EDSS is an imperfect but widely used and understood measure of disability in MS, and reported it was used universally in clinical practice as an indicator of disease progression, with a 0.5-unit 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. The experts indicated that patients may undergo treatment for many years, but 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 Place in Therapy section in the Supplemental Material.

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 compared to placebo among patients with RIS, although there is some uncertainty in the results based on potential risk of bias and the relatively small sample size. The clinical experts agreed that findings for time to first acute or progressive neurological symptom associated with a CNS demyelinating event was considered clinically meaningful in demonstrating benefit with dimethyl fumarate 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 because MRI findings were available for a subset (approximately 60%) of 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 the small sample size and missing MRI data.

There was a 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 most from treatment. The relatively small number of patients in the ARISE trial likely precluded any subgroup analyses; there 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 the MSFC and patient-reported outcomes were not provided in the trial registry or publication. Although 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 was higher in the dimethyl fumarate group versus the placebo group, whereas the number of patients with SAEs was 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 about dimethyl fumarate use 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 gastrointestinal effects, in approximately 10% to 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. However, SAEs with dimethyl fumarate were noted to be rare among the few 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. According to the experts, an oral medication is likely to be preferred over either glatiramer acetate or interferon beta.

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 that have tolerable side effects and maintain 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 a CNS demyelinating event. The evidence suggested that dimethyl fumarate may result in fewer new and/or newly enlarging T2 lesions 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 of dimethyl fumarate 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 Canada's Drug Agency (CDA-AMC) indicated that glatiramer acetate and interferon beta are off-label treatments that are infrequently used for the treatment of RIS in clinical practice. Furthermore, only 2 CDA-AMC 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 (Appendix 9 in the Supplemental Material). 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 is $3,826 to $3,885 per patient per year compared with glatiramer acetate and $13,732 to $42,718 per patient per year compared with 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 include the following:

- 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 a 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 generic formulations 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 symptoms associated with CNS demyelination could potentially lead to future health care savings by reducing the need for health care resources associated with the treatment of MS.
- A concurrent review is being conducted by CDA-AMC 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 in 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 compared with 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. This

was not available; therefore, the cost-effectiveness of dimethyl fumarate relative to no active intervention for the treatment of RIS could not be determined.

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