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

Draft Reimbursement Review

Working Papers

DIMETHYL FUMARATE (TECFIDERA)

(Non-Sponsored Review)

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

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Abbreviations

AE	adverse event
CI	confidence interval
CNS	central nervous system
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
FMEC	Formulary Management Expert Committee
ITT	intention to treat
MRI	magnetic resonance imaging
MS	multiple sclerosis
RCT	randomized controlled trial
RIS	radiologically isolated syndrome
SD	standard deviation

Background Appendices

Appendix 1: Drug Program Input and Treatment Characteristics

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 and provided to the expert committee in a separate document.

Table 1: Key Characteristics of ~~dimethyl~~ Dimethyl fumarate, ~~teriflunomide~~Teriflunomide, ~~interferon~~ Interferon beta, and ~~glatiramer~~ Glatiramer acetate

Treatment	Mechanism of action	Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
Dimethyl fumarate	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	None Health Canada: As monotherapy for the treatment of relapsing remitting MS to reduce the frequency of clinical exacerbations and to delay the progression of disability	Initial dose: 120 mg twice daily orally, for a total of 240 mg per day Usual dose: After 7 days, increase to recommended dose of 240 mg twice daily orally, for a total of 480 mg per day	Lymphopenia and gastrointestinal events Contraindicated in patients with hypersensitivity to dimethyl fumarate or to any ingredient in the formulation.
Teriflunomide	Blocks the proliferation of stimulated lymphocytes, diminishing the numbers of activated lymphocytes in peripheral blood, which may reduce numbers of active lymphocytes available for migration into the CNS	None Health Canada: As monotherapy for the treatment of patients with relapsing remitting MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability	14 mg orally once daily	Hepatotoxicity and risk of teratogenicity Contraindicated in patients with severe hepatic impairment.
Interferon beta	Immunomodulatory drug	None Health Canada: For the treatment of relapsing forms of MS, to reduce the number and severity of clinical exacerbations, slow the progression of physical disability, reduce the requirement for steroids,	44 mcg given 3 times a week by subcutaneous injection. The dose can be reduced to 22 mcg 3 times a week if the patient is not able to tolerate the higher dose.	Contraindicated in pregnant individuals and patients with a known hypersensitivity to natural or recombinant interferon beta, albumin (human), or any other component of the formulation.

Treatment	Mechanism of action	Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
		and reduce the number of hospitalizations for treatment of MS and reduction of T1-gadolinium enhanced and T2 (burden of disease) as seen on MRI		
Glatiramer acetate	Immunomodulatory drug	None Health Canada: Treatment of ambulatory patients with relapsing remitting MS, including patients who have experienced a single demyelinating event and have lesions typical of MS on brain MRI: to decrease the frequency of clinical exacerbations, and to reduce the number and volume of active brain lesions identified on MRI scans	20 mg/mL once daily (relapsing remitting MS, including patients who have experienced a single demyelinating event and have lesions typical of MS on brain MRI) 40 mg/mL 3 times a week and at least 48 hours apart (relapsing remitting MS)	Contraindicated in patients who are hypersensitive to this drug or any ingredient in the formulation.

CNS = central nervous system; MRI = magnetic resonance imaging; MS = multiple sclerosis.

[a] Health Canada–approved indication.

Source: Health Canada product monographs for dimethyl fumarate (Tecfidera),[1] teriflunomide (Aubagio),[2] interferon beta-1a (Rebif),[3] and glatiramer acetate (Copaxone).[4]

Clinical Review Appendices

Appendix 2: Methods of the Systematic Review

Systematic Review Eligibility Criteria

Table 2. Systematic Review Eligibility Criteria

Criteria	Description
Population	Adults with radiologically isolated syndrome
Intervention	Dimethyl fumarate Dosage: oral delayed-release capsule, 120 mg twice daily; after 7 days, increase to 240 mg twice daily
Comparator	Placebo Interferon beta Glatiramer acetate Teriflunomide

Outcomes	Efficacy outcomes:
	• 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., EDSS)
	• HRQoL (with preference for disease-specific measures)
	
	Safety:
	• AE, SAE, withdrawal due to AE, death due to AE
	• Adverse events of special interest:
	  ○ Lymphopenia
	  ○ Gastrointestinal events

Study design	Published phase III and IV RCTs

AE = adverse event; CNS = central nervous system; EDSS = Expanded Disability Status Scale; HRQoL= health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event.

Search Strategy

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[5]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were dimethyl fumarate and radiologically isolated syndrome. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See below for the detailed search strategies.

The initial search was completed on August 8, 2024. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee (FMEC) meeting on November 21, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials. See below for more information on the grey literature search strategy.

A focused literature search for indirect treatment comparisons ~~(ITCs)~~ dealing with radiologically isolated syndrome was run in MEDLINE on September 12, 2024. Retrieval was not limited by publication date or by language.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts.

Clinical Literature Search

Overview

Interface: Ovid
Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: August 8, 2024
Alerts: Bi-weekly search updates until FMEC meeting
Search filters applied: None
Limits

- Conference abstracts: excluded

Table 3. Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*****	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily

oemezd	Ovid database code; Embase, 1974 to present, updated daily

Warning

To conduct a comprehensive search, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multi-Database Strategy

1 (radiologic* and (isolat* or asymptom* or possible inflammatory* or demyelinat*) and (syndrome* or disease*)).ti,kf.
2 (radiologic* adj5 (isolat* or asymptom* or possible inflammatory* or demyelinat*) adj5 (syndrome* or disease*)).ab.
3 (RIS and (ms or multiple scleros* or demyelinat*)).ti,ab,kf.
4 RAPIDD.ti,ab,kf.
5 (lack* adj5 (history or sign* or symptom*) adj5 (ms or multiple scleros* or demyelinat*)).ti,ab,kf.
6 or/1-5
7 (demyelinating autoimmune diseases, cns/ or exp multiple sclerosis/) and (pre-clinical* or preclinical* or subclinical* or sub-clinical* or suggested or suggestive* or asymptom* or pre-symptom* or presymptom* or prodromal*).ti,ab,kf.
8 (demyelinating autoimmune diseases, cns/ or exp multiple sclerosis/) and (lack* and (history or sign* or symptom*)).ti,ab,kf.
9 ((pre-clinical* or preclinical* or subclinical* or sub-clinical* or suggested or suggestive* or asymptom* or pre-symptom* or presymptom* or prodromal*) adj5 (ms or multiple scleros* or demyelinat*)).ti,ab,kf.
10 or/7-9
11 6 or 10
12 (dimethyl fumarate* or dimethylfumarate* or skilarence* or tecfidera* or panaclar* or psorinovo* or verum* or azl-0211089 or azl0211089 or bg-0012 or bg0012 or bg-12 or bg12 or fag-201 or fag201 or fp-187 or fp187 or tl-353 or tl353 or azl-o-211089 or azlo211089 or las-41088 or las41008 or FO2303MNI2).ti,ab,kf,ot,hw,rn,nm.
13 (ACH-dimethyl fumarate* or APO-dimethyl fumarate* or AURO-dimethyl fumarate* or GLN-dimethyl fumarate* or JAMP-dimethyl fumarate* or MAR-dimethyl fumarate* or PMS-dimethyl fumarate* or SANDOZ-dimethyl fumarate* or TEVA-dimethyl fumarate*).ti,ab,kf,ot,hw,rn,nm.
14 (ACHdimethyl fumarate* or APOdimethyl fumarate* or AUROdimethyl fumarate* or GLNdimethyl fumarate* or JAMPdimethyl fumarate* or MARdimethyl fumarate* or PMSdimethyl fumarate* or SANDOZdimethyl fumarate* or TEVAdimethyl fumarate*).ti,ab,kf,ot,hw,rn,nm.
15 or/12-14
16 11 and 15
17 16 use medall
18 (radiologic* and (isolat* or asymptom* or possible inflammatory* or demyelinat*) and (syndrome* or disease*)).ti,kf,dq.
19 (radiologic* adj5 (isolat* or asymptom* or possible inflammatory* or demyelinat*) adj5 (syndrome* or disease*)).ab.
20 (RIS and (ms or multiple scleros* or demyelinat*)).ti,ab,kf,dq.
21 RAPIDD.ti,ab,kf,dq.
22 (lack* adj5 (history or sign* or symptom*) adj5 (ms or multiple scleros* or demyelinat*)).ti,ab,kf,dq.
23 or/18-22
24 (demyelinating disease/ or exp multiple sclerosis/) and (pre-clinical* or preclinical* or subclinical* or sub-clinical* or suggested or suggestive* or asymptom* or pre-symptom* or presymptom* or prodromal*).ti,ab,kf,dq.
25 (demyelinating disease/ or exp multiple sclerosis/) and (lack* and (history or sign* or symptom*)).ti,ab,kf,dq.
26 ((pre-clinical* or preclinical* or subclinical* or sub-clinical* or suggested or suggestive* or asymptom* or pre-symptom* or presymptom* or prodromal*) adj5 (ms or multiple scleros* or demyelinat*)).ti,ab,kf,dq.
27 or/24-26
28 23 or 27
29 *dimethyl fumarate/
30 (dimethyl fumarate* or dimethylfumarate* or skilarence* or tecfidera* or panaclar* or psorinovo* or verum* or azl-0211089 or azl0211089 or bg-0012 or bg0012 or bg-12 or bg12 or fag-201 or fag201 or fp-187 or fp187 or tl-353 or tl353 or azl-o-211089 or azlo211089 or las-41088 or las41008).ti,ab,kf,dq.
31 (ACH-dimethyl fumarate* or APO-dimethyl fumarate* or AURO-dimethyl fumarate* or GLN-dimethyl fumarate* or JAMP-dimethyl fumarate* or MAR-dimethyl fumarate* or PMS-dimethyl fumarate* or SANDOZ-dimethyl fumarate* or TEVA-dimethyl fumarate*).ti,ab,kf,dq.

32 (ACHdimethyl fumarate* or APOdimethyl fumarate* or AURODimethyl fumarate* or GLNdimethyl fumarate* or JAMPdimethyl fumarate* or MARdimethyl fumarate* or PMSdimethyl fumarate* or SANDOZdimethyl fumarate* or TEVAdimethyl fumarate*).ti,ab,kf,dq.
33 or/29-32
34 28 and 33
35 34 use oemezd
36 35 not (conference abstract or conference review).pt.
37 17 or 36
38 remove duplicates from 37

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.
[Search -- Studies with results | radiologically isolated syndrome OR dimethyl fumarate]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.
[Search terms -- radiologically isolated syndrome OR dimethyl fumarate]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.
[Search terms -- radiologically isolated syndrome OR dimethyl fumarate]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.
[Search terms -- radiologically isolated syndrome OR dimethyl fumarate]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.
[Search terms -- radiologically isolated syndrome OR dimethyl fumarate]

Grey Literature

Search dates: July 10-14, 2024
Keywords: radiologically isolated syndrome OR dimethyl fumarate
Limits: None
Updated: Search updated prior to the completion of stakeholder feedback period
Relevant websites from the following sections of the grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Excluded Studies

Table 4. Excluded Studies

Study	Reason for exclusion

Studies excluded from the systematic review	
Okuda DT, Azevedo CJ, Pelletier D, Moog TM, Moazami S, Rezvani S, et al; ARISE Study Investigators. Dimethyl fumarate preserves brainstem and cervical spinal cord integrity in radiologically isolated syndrome. Journal of Neurology. 2024 Jul 9.	Outcome

Appendix 3: Methods of the Studies Included in the Systematic Review

Characteristics of the Included Study

Statistical Analysis

In the ARISE trial,[6] sample size calculations were estimated using a Cox proportional hazards regression for 80 patients per arm to have 80% power to detect a 50% reduction in the risk of the first clinical event, assuming that 25% of patients experience a first clinical event at 96 weeks with a trial duration of 240 weeks. Due to slow patient recruitment, the protocol was amended to include a secondary analysis using a Bayesian approach combining prior distribution (from trials of patients in relapsing remitting multiple sclerosis [MS]) for treatment effect with results observed in the ARISE trial (representing likelihood). The scenario used for the analysis was in the subgroup with 'early MS' defined as individuals with no previous treatment, less than 240 weeks since clinical disease onset, and an Expanded Disability Status Scale (EDSS) score of up to 1.5, based on the treatment effect (hazard ratio of 0.24; 95% confidence interval, 0.13 to 0.43), resulting in 40 patients per arm needed to have 90% power to detect a 50% treatment effect.

Unadjusted and adjusted Cox proportional hazards regression models estimated impact of treatment on the primary end point (time to first clinical event); baseline variables used in the adjusted model included sex, age at time of radiologically isolated syndrome (RIS) diagnosis, MS family history, EDSS, brain T2-weighted hyperintense lesion volume (log-transformed), and the presence of gadolinium-enhancing lesions. Survival curves of treatment effect were displayed using the Kaplan-Meier method, with treatment effect for the primary end point estimated using hazard ratios and 95% confidence intervals.

Secondary magnetic resonance imaging (MRI) outcomes (cumulative mean number of new and/or newly enlarging lesions on T2-weighted MRI, and cumulative mean number of new gadolinium-enhancing lesions over 96 weeks) were compared between treatment groups using a negative binomial regression model, with adjusted analyses that included the number of gadolinium-enhancing lesions on MRI at baseline.

Description of Outcomes

Functional Status

The EDSS is a clinician-administered scale to assess disease progression and has been validated in patients with MS.[7,8] The scale comprises 8 independent functional systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual or optic, cerebral or mental, and other), scored in 0.5 increments representing higher levels of disability from 0 (normal neurologic exam) to 10 (death due to MS).[9] In the EDSS, a change score that is recognized as a clinical increase in disability is dependent on the score at baseline (i.e., a 1.0-point change for a baseline score ≤ 5.5, and a 0.5-point change for a baseline score > 5.5), although disability change has been acknowledged to be more accurately defined as a sustained change for 12 to 24 weeks.[8] While limitations of the EDSS have been identified (e.g., weak inter- and intra-rater reliability, poor correlation with MRI measures, non-linearity with health-related quality of life outcomes, lack capture of upper limb function or cognitive skills), it is a well-known instrument that is widely used in clinical trials to assess disease progression in MS.[8]

Harms

Treatment-emergent adverse events ~~AEs~~ (TEAEs) were defined as an untoward medical occurrence in a patient who received a study drug after the first dose of study treatment through to week 96, at the end of study visit, or at the early withdrawal or

discontinuation visit. Signs and symptoms present at baseline were considered as adverse events (AEs) if they worsened during study treatment.

Appendix 4: Place in Therapy

Contents within this section have been informed by input from the clinical expert(s) consulted for the purpose of this review and from clinician groups. The following has been summarized by the review team.

Potential Place in Therapy

RIS is considered to be encompassed within the spectrum of MS, as an early form of the disease. The clinical experts consulted for this review recognize that RIS has the same pathophysiology as MS, with cerebrospinal fluid findings and highly sensitive MRI characteristics (e.g., central vein sign, paramagnetic rim lesions). Similarly to the prodromal phase of MS, patients with RIS can have evidence of clinical findings (e.g., cognitive impairment) prior to the development of primary progressive MS or conventional MS relapses. The clinical experts indicated that disease-modifying therapies (DMTs) reduce symptoms in patients with MS by addressing the underlying disease process. Prior to clinical trials of patients with RIS, clinicians have opted to treat RIS when there was evidence of radiological progression using off-label treatments (increasingly DMTs); the option to offer treatment has been previously noted in practice patterns and treatment optimization recommendations.[10-12] The experts indicated that historically, interferon beta and glatiramer acetate were the first approved DMTs for MS. While these injectable treatments continue to be used in MS despite not being preferred by most patients due to their mode of administration, patients with RIS may also be offered interferon beta or glatiramer acetate. Both clinical experts expressed that while they have not directly offered treatment with interferon beta or glatiramer acetate, they were aware of patients with RIS being treated with either drug.

Since dimethyl fumarate has been approved in the first line setting for patients with relapsing remitting MS, the experts expressed that it would neither be appropriate to recommend that patients with RIS (considered an earlier phase of MS) try other drugs before offering either approved treatment nor to offer combination DMT as this is not currently being used. According to the clinical experts, current treatments for MS are prescribed off-label, but available only to patients with insurance coverage or compassionate program access, indicating a clear gap in availability of approved treatments for patients with RIS. The clinical experts outlined that dimethyl fumarate has been associated with lower risk of serious AEs than other standard DMTs currently used (e.g., monoclonal antibodies, oral induction therapies) or first-generation injectable DMTs used less frequently (e.g., glatiramer acetate and interferon betas) to support its use as first line treatment in RIS. The clinical experts noted that they are aware of patients with RIS who are currently being treated with dimethyl fumarate, teriflunomide, or monoclonal antibody therapies. Overall, the experts felt that patients with RIS would benefit from DMT as first line treatment for preventing future relapses and disability progression (as in MS), including those who have contraindications to or are intolerant of other treatments.

Given the emphasis on early diagnosis and potential benefits of early treatment, the clinical experts anticipate a greater number of clinicians will start to offer earlier treatment to patients with RIS. From the perspective of the clinical experts, if both dimethyl fumarate and teriflunomide were approved for patients with RIS, the choice of which treatment would be based mainly on possible harms and patient preference (e.g., patient-specific circumstances, mode of administration [twice daily with dimethyl fumarate; once daily with teriflunomide]), in the absence of comparative efficacy from clinical trials. The experts' experience with MS noted that no drug has demonstrated 100% effectiveness, with some patients experiencing breakthrough disease and the consideration of escalating treatment; the decision to switch therapy (to a different DMT) is at the discretion of the treating clinician and individualized to the patient (e.g., severity of disease, extent of change in disease status). The experts further added that duration of treatment with a DMT, without progression to clinically definite MS, may be ongoing for a patient with RIS until possible reduced risk of progression (e.g., age limit of 55 or 60 years); the de-escalation of treatment is an area of ongoing research and debate in a disease entity that is not routinely being treated. Given that some individuals with RIS may not progress to MS, there is some controversy about the management of RIS.[13] Overall, any approach to treatment should be based on shared decision making between clinicians and patients' individual circumstances and preferences.

Patient Population

The clinical experts expressed that the diagnosis of MS is complex. The detection of nonspecific white matter lesions on MRI have sometimes been erroneously attributed to demyelinating disease rather than an alternative cause (e.g., migraine, microvascular changes, high blood pressure), resulting in errors in diagnosis (e.g., misdiagnosis or overdiagnosis of MS). There is literature on the phenomenon of overdiagnosis in MS, resulting from inaccurate interpretations of brain MRIs by radiologists who do not specialize in MS, an issue which has become less common with revised MRI criteria to refine and streamline diagnosis. Further, the experts noted that a MS prodrome prior to a MS diagnosis is increasingly recognized given that not all patients are entirely asymptomatic; patients who do not display overt clinical dysfunction or 'classic' symptoms of MS (e.g., optic neuritis and myelitis) but who present with nonspecific symptoms (e.g., headache, cognitive dysfunction, motor coordination impairment, bimanual dexterity impairment), signal the need for further evaluations (e.g., neurological examination) to rule out or confirm a diagnosis of RIS. Overall, the clinical experts emphasized the importance of applying updated diagnostic criteria for RIS to accurately determine which patients may be candidates for DMT.

There is emerging consensus among clinicians that current treatments for MS may be appropriate in select RIS patients (based on risk factors, including paraclinical, clinical, and MRI characteristics), despite formal approval of DMTs in RIS. Literature and clinical observations support the identification of patients who may be at higher risk for developing MS, including factors that have been associated with developing a clinical event (e.g., lesions involving the spinal cord, presence of oligoclonal bands in the cerebrospinal fluid, findings suggestive of central nervous system~~CNS~~ inflammation), for whom treatment would be warranted albeit with an unclear contribution to treatment response in RIS, according to the clinical experts. According to the experts, the selection of patients with RIS who may be eligible for treatment with a DMT including dimethyl fumarate would be individualized. A patient with RIS who is clinically well or stable (e.g., no sign of MRI evolving over time) may not be considered by the experts to benefit from treatment given the potential for AEs. However, a patient with RIS who exhibits clinical indicators (e.g., prodromal symptoms) but do not meet criteria for MS, would likely be offered treatment given the weighing of potential risk versus benefit. The experts acknowledged that there is a subgroup of patients with younger age, highly active MRI lesions, and nonspecific symptoms, for whom neurologists may consider higher efficacy therapies (e.g., B-cell depleting drugs). Anecdotally, the expert shared that in practice, about 50% of patients with RIS who were offered DMT declined treatment, as their wellbeing was sufficiently satisfactory.

Assessing the Response Treatment

The clinical experts reported that treatment response would be assessed using current standard clinical practice for relapsing remitting MS annually, with ongoing clinical and MRI evaluations per Canadian and international guidelines. Stability and delay in onset of clinical events and disease progression were considered by the experts to indicate a favourable treatment response, adding that frequency of assessments may vary depending on individual patient characteristics, specific neurologist practice patterns, and availability of local resources. The clinical experts reported that with dimethyl fumarate, it is standard to carry out blood work monitoring, particularly for potential hepatotoxicity and other AEs such as cytopenia; there may be a greater frequency of bloodwork due to the risk of lymphopenia with dimethyl fumarate.

Discontinuing Treatment

According to the clinical experts consulted, reasons for considering treatment discontinuation would be similar to those for relapsing remitting MS: breakthrough clinical or radiological (MRI) disease activity or disease progression, or development of AEs (per product monograph).

Prescribing Considerations

The clinical experts reiterated the importance of a neurologist with experience in diagnosing and managing MS to diagnose, treat, and monitor patients with RIS, adding that prescribing should not be limited to MS clinic-based neurologists which would unduly restrict access to treatment among patients who reside in geographical regions that have limited access to a MS clinic.

Economic Review Appendices

Appendix 9: Cost Comparison Table

The comparators presented in Table 5 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were sourced from the ARISE trial for dimethyl fumarate and based on clinical expert input for the off-label use of glatiramer acetate and interferon beta.[6] Pricing for all treatments were based on publicly available list prices.

The recommended dose of dimethyl fumarate is 120 mg twice daily for 7 days, and 240 mg twice daily thereafter (Table 1). At $4.43 per 120 mg capsule and $8.69 per 240 mg capsule, the treatment acquisition cost of dimethyl fumarate is $17.21 daily in year 1, and $17.38 in subsequent years or $6,283 per patient in year 1 and $6,343 in subsequent years. In jurisdictions that currently fund therapies for the treatment of RIS, the incremental cost savings of dimethyl fumarate compared to glatiramer acetate, per patient per year, are $3,885 in the first year and $3,826 thereafter. In addition, the incremental cost savings of dimethyl fumarate compared to interferon beta ranged from $13,732 to $42,718 per patient per year, dependent on the brand of interferon beta. However, 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. Results may differ by jurisdiction depending on individual list prices for the drugs presented in Table 5.

Table 5: CDA-AMC Cost Comparison Table for Radiologically Isolated Syndrome

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost ($)	Annual cost ($)
Dimethyl fumarate (generics)	120 mg 240 mg	Capsule	4.4266 8.6888	120 mg twice daily for 7 days; 240 mg twice daily thereafter[a]	Year 1: 17.21 Year 2+: 17.38	Year 1: 6,283 Year 2+: 6,343
Off-Label Treatments						
Glatiramer acetate (generics)	20 mg/mL	Pre-filled syringe	27.8587	20 mg daily	27.86	10,168
Interferon beta-1a (Avonex)	30 mcg/0.5 mL	Pre-filled syringe or pre-filled pen	491.2525[b]	30 mcg weekly	70.18	25,615
Interferon beta-1a (Plegridy)	125 mcg/0.5 mL	Pre-filled syringe or pre-filled pen	1,879.4900[b]	125 mcg every 2 weeks	134.25	49,001
Interferon beta-1a (Rebif)	22 mcg/0.5 mL 44 mcg/0.5 mL	Pre-filled syringe	170.6067[b] 207.7000[b]	22 mcg to 44 mcg, 3 times per week (every other day)	73.12 to 89.01	26,688 to 32,490
	66 mcg/1.5 mL 132 mcg/1.5 mL	Pre-filled Cartridges	511.8200[b] 623.0850[b]			
Interferon beta-1b (Betaseron)	300 mcg	Vial for SC injection	110.0000[b]	250 mcg every other day	55.00	20,075

SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed September, 2024),[14] unless otherwise indicated, and do not include dispensing fees.

[a] Recommended dosage, per the ARISE trial.[6]

[b] Price retrieved from Ontario Exceptional Access program (accessed September, 2024).[15]

References

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