Canada's Drug Agency
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Drugs Health Technologies Health Systems

Reimbursement Review

Teriflunomide: Supplemental Material

Requester: Public drug programs

Therapeutic area: Multiple sclerosis (MS), radiologically isolated syndrome (RIS)

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Abbreviations

AE	adverse event
CSCT	Computerised Speed Cognitive Test
DMT	disease-modifying therapy
MID	meaningful important difference
MRI	magnetic resonance imaging
MS	multiple sclerosis
MusiQoL	Multiple Sclerosis International Quality of Life
PASAT	Paced Auditory Serial Addition Test
RIS	radiologically isolated syndrome

Background Appendices

Appendix 1: Background

Please note that this appendix has not been copy-edited.

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 Teriflunomide, Dimethyl Fumarate, Interferon Beta, and Glatiramer Acetate

Treatment	Mechanism of action	Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
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.
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.
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, and	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
		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 hour apart (relapsing remitting MS)	Contraindicated in patients who are hypersensitive to this drug or any ingredient in the formulation.

CNS = central nervous system; MRI = MRI; MS = multiple sclerosis.

[a]Health Canada–approved indication.

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

Clinical Review Appendices

Appendix 2: Methods of the Systematic Review

Please note that this appendix has not been copy-edited.

Systematic Review Eligibility Criteria

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Adults with radiologically isolated syndrome
Intervention	Teriflunomide Dosage: oral tablet, 14 mg once daily
Comparator	• Placebo • Interferon beta • Glatiramer acetate • Dimethyl fumarate

Outcomes	Efficacy outcomes:
	• Time to first neurologic 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:
	  ◦ Hepatotoxicity
	  ◦ Teratogenicity

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 comprised 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 teriflunomide and radiologically isolated syndrome. The following clinical trials registries were searched: the US National Institutes of

Health's clinicaltrials.gov, WHO'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.

The initial search was completed on July 31, 2024. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee 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 FDA and European Medicines Agency). Google was used to search for additional internet-based materials.

A focused literature search for indirect treatment comparisons 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)
- Cochrane Central Register of Controlled Trials (CCTR)

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

Date of search: August 30, 2021

Alerts: Biweekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits:

- Publication date limit: none
- Language limit: none
- 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)
.rn	Registry number
.nm	Name of substance word (MEDLINE)

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. (teriflunomid* or aubagio* or leflunomide impurity B* or leflunomide related compound B* or flunisol* or flunitram* or funomid* or libinis* or loderix* or tenomid* or terflimida* or terebyo* or pharmacor teriflunomid* or teriflagio* or terimid* or klamy* or ryfluna* or denopsy* or merosya* or scleteri* or terigen* or teru ms* or teriem* or asclero* or femorix* or axyla* or teflimes* or terigio* or aubamide* or A771726 or A77-1726 or A-77-1726 or A-771726 or A-1726 or A1726 or HMR-1726 or HMR1726 or ave-1726 or ave1726 or rs-61980 or rs61980 or su-0020 or su0020 or 1C058IKG3B).ti,ab,kf,ot,hw,rn,nm.
13. (ACH-Teriflunomid* or APO-Teriflunomid* or JAMP-Teriflunomid* or M-Teriflunomid* or MAR-Teriflunomid* or NAT-Teriflunomid* or PMS-Teriflunomid* or SANDOZ Teriflunomid* or TEVA-Teriflunomid*).ti,ab,kf,ot,hw,rn,nm.
14. (ACHTeriflunomid* or APOteriflunomid* or JAMPTeriflunomid* or MTeriflunomid* or MARTeriflunomid* or NATTeriflunomid* or PMSTeriflunomid* or SANDOZTeriflunomid* or TEVATeriflunomid*).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* and (isolat* or asymptom* or possible inflammatory* or demyelinat*) and (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. *teriflunomide/
30. (teriflunomid* or aubagio* or leflunomide impurity B* or leflunomide related compound B* or flunisol* or flunitram* or funomid* or libinis* or loderix* or tenomid* or terflimida* or terebyo* or pharmacor teriflunomid* or teriflagio* or terimid* or klamy* or ryfluna* or denopsy* or merosya* or scleteri* or terigen* or teru ms* or teriem* or asclero* or femorix* or axyla* or teflimes* or terigio* or aubamide* or A771726 or A77-1726 or A-77-1726 or A-771726 or A-1726 or A1726 or HMR-1726 or HMR1726 or ave-1726 or ave1726 or rs-61980 or rs61980 or su-0020 or su0020).ti,ab,kf,dq.
31. (ACH-Teriflunomid* or APO-Teriflunomid* or JAMP-Teriflunomid* or M-Teriflunomid* or MAR-Teriflunomid* or NAT-Teriflunomid* or PMS-Teriflunomid* or SANDOZ Teriflunomid* or TEVA-Teriflunomid*).ti,ab,kf,dq.
32. (ACHTeriflunomid* or APOteriflunomid* or JAMPTeriflunomid* or MTeriflunomid* or MARTeriflunomid* or NATTeriflunomid* or PMSTeriflunomid* or SANDOZTeriflunomid* or TEVATeriflunomid*).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 US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | radiologically Isolated syndrome AND teriflunomide]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- radiologically Isolated syndrome AND teriflunomide]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- radiologically Isolated syndrome AND teriflunomide]

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 AND teriflunomide]

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 AND teriflunomide]

Grey Literature

Search dates: July 11 to 16, 2024

Keywords: radiologically Isolated syndrome OR teriflunomide

Limits: none

Updated: Search updated before 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)
- Internet Search

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

Please note that this appendix has not been copy-edited.

Characteristics of the Included Study

Description of Outcomes

Functional Status

The Paced Auditory Serial Addition Test (PASAT) is a measure of information processing speed and both auditory and verbal working memory, taking into account calculation ability.[6] In the PASAT-3 (a subtest of cognitive function of the Multiple Sclerosis Functional Composite), consecutive numbers are presented at a rate of 3-second inter-stimulus interval, where each number is added to the 1 that immediately precedes it.[6] The total score (range, 0 to 60) is the total number of correct sums verbally reported by the participant.[6] A meaningful importance difference (MID) in the PASAT-3 has not been identified.

The Computerised Speed Cognitive Test (CSCT) is a measure of attention and information processing speed that has been validated in patients with multiple sclerosis (MS).[7] The CSCT is a proposed computerized version of the digits/symbols substitution test that displays a key list on the upper part with a list of 9 symbols with a row beneath displaying a list of 9 digits.[7,8] The lower main portion of the screen displays symbols on consecutive lines, where blinking vertical line indicates which symbol to be taken into consideration;[7] the participant enters the digit on the computer keypad (or the examiner enters the response based on the participant's verbal answer) and the blinking signal progresses to the next symbol.[7] The total score (range not reported) is the number of correct answers out of the total number of displayed symbols within the allotted time (approximately 90 seconds).[7,8] The CSCT is performed at the beginning and at the end of the neuropsychological evaluation.[7] An MID in the CSCT has not been identified.

Health-Related Quality of Life

The Multiple Sclerosis International Quality of Life (MusiQoL) is a patient-reported outcome measure of 31 items (each rated on a scale of 1 [never/not at all] to 5 [always/very much]) capturing 9 dimensions (activities of daily living [8 items], psychological wellbeing [4 items], symptoms [4 items], relationships with friends [3 items], relationships with family [3 items], relationships with health care system [3 items], sentimental and sexual life [2 items], coping [2 items], and rejection [2 items]) of health-related quality of life.[9,10] The MusiQoL index score is computed as the mean of the dimension scores, and are linearly transformed and standardized on a 0 (worst possible quality of life) to 100 (best possible quality of life) scale,[9] with a global score computed as the mean of the dimension scores.[10] An MID in the MusiQoL has not been identified.

Harms

An adverse event (AE) was defined as any untoward medical occurrence in a patient who was administered a study treatment whether or not it was considered related to the treatment, and included signs and symptoms that worsened during the study. Serious AEs were defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization,

resulted in persistent or significant disability or incapacity, or consisted of a congenital anomaly or birth defect. Withdrawals due to AEs and deaths due to AEs were not defined in the TERIS trial.[11]

Appendix 4: Place in Therapy

Please note that this appendix has not been copy-edited.

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

Radiologically isolated syndrome (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 (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) before 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.[12-14] 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 teriflunomide 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 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 [once daily with teriflunomide; twice daily with dimethyl fumarate]), 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.[15] 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 before 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., neurologic 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 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.

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 5: Cost Comparison Table

Please note that this appendix has not been copy-edited.

The comparators presented in Table 4 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were sourced from the TERIS trial for teriflunomide and based on clinical expert input for the off-label use of glatiramer acetate and interferon beta.[16] Pricing for all treatments were based on publicly available list prices.

The recommended dose of teriflunomide is 14 mg once daily (Table 4). At $14.93 per 14 mg tablet, the treatment acquisition cost of teriflunomide is $14.93 daily, or $5,449 per patient per year. In jurisdictions that currently fund therapies for the treatment of RIS, the incremental cost savings of teriflunomide compared to glatiramer acetate, per patient per year, are $4,719. In addition, the incremental cost savings of teriflunomide compared to interferon beta ranged from $14,626 to $43,552 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 teriflunomide will result in increased drug acquisition costs. Results may differ by jurisdiction depending on individual list prices for the drugs presented in Table 4.

Table 4: CDA-AMC Cost Comparison Table for Radiologically Isolated Syndrome

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost ($)	Annual cost ($)
Teriflunomide (generics)	14 mg	Tablet	14.9300	14 mg once daily[a]	14.93	5,449
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),[17] unless otherwise indicated, and do not include dispensing fees.

[a]Recommended dosage, per the TERIS trial.[11]

[b]Price retrieved from Ontario Exceptional Access program (accessed September 2024).[18]

References

1. Aubagio (teriflunomide): 14 mg oral tablets [product monograph]. Toronto (ON): Sanofi-Aventis Canada Inc.; 2024 Apr 17: https://pdf.hres.ca/dpd_pm/00075282.PDF. Accessed 2024 Oct 18.
2. Tecfidera (dimethyl fumarate): 120 mg and 240 mg, delayed-release, oral capsules [product monograph]. Toronto (ON): Biogen Canada Inc.; 2023 Mar 16: https://pdf.hres.ca/dpd_pm/00070736.PDF. Accessed 2024 Oct 18.
3. Rebif (interferon beta-1a): 22 mcg/0.5 mL and 44 mcg/0.5 mL, solution for injection in pre-filled syringes; Rebif (interferon beta-1a): multidose 66 mcg/1.5 mL and 132 mcg/1.5 mL, solution for injection in pre-filled cartridges [product monograph]. Mississauga (ON): EMD Serono, A Division of EMG Inc., Canada; 2020 Feb 06: https://pdf.hres.ca/dpd_pm/00054920.PDF. Accessed 2024 Oct 18.
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Canada's Drug Agency
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