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

Dimethyl Fumarate

FMEC Responses to Questions From the Drug Programs

Table 1: Response Summary

Drug program implementation questions	Clinical expert response	FMEC response
Relevant comparators		
The ARISE trial published in 2022 was a multicentre, double-blind, placebo-controlled study in patients with RIS. Patients were randomly assigned 1:1 with either dimethyl fumarate or placebo. There are no head-to-head trials comparing 1 DMT to another for treatment in RIS, so it's unknown if 1 drug is more effective than another.	The clinical experts agreed that there is no evidence comparing different DMTs in patients with RIS to determine efficacy of any 1 DMT versus another.	FMEC agrees with the experts and acknowledges the lack of head-to-head comparison trials for this indication.
Considerations for initiation of therapy		
The study enrolled patients who had been identified as having RIS based on meeting 2009 RIS criteria. CNS anomalies were required to be inconsistent with a vascular pattern and to not account for clinically apparent neurological impairments. There have since been revisions to the RIS criteria, updated in 2023. Of note, the study acknowledges that sometimes the accurate classification of RIS subjects has been challenged by the high sensitivity of MRI as nonspecific white matter anomalies resulting from chronic migraine, microvascular disease, normal aging, and so on. The accurate classification may also be hindered by reduced patient memory of medical information, and there may be misdiagnoses in centres that are not highly specialized. At baseline, 37 of the 87 participants (42%) had EDSS scores higher than	a) The clinical experts indicated that documentation of clinical history for the absence of clinical features consistent with MS, symptoms suggesting a condition other than MS, and MRI findings would be necessary to identify a patient as having RIS. b) The clinical experts expressed no concerns with adjusting the eligibility criteria of the ARISE trial to use the updated 2023 RIS criteria if a neurologist with experience in managing patients with MS was making the diagnosis. c) According to the clinical experts, once a patient has been identified as having RIS, the EDSS is typically assessed with or without the MSFC (or its components) depending on local resources	a) FMEC agrees with the experts. Refer to the initiation criteria as outlined in Table 2 of the recommendation report. b) FMEC agrees with the experts. Refer to the initiation criteria as outlined in Table 2 of the recommendation report. c) FMEC agrees with the experts.

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1.0; however, these were due to blinded examinations that captured physical impairments resulting from trauma, recent surgical procedures, and other well-documented non–CNS-based existing medical conditions. An EDSS of 1.0 refers to there being no disability with minimal signs in 1 functional system. a) What documentation would be necessary to have a confident classification of RIS in a patient? b) Are there any concerns with adjusting the eligibility criteria to utilize the updated 2023 RIS criteria? c) Once deemed to have RIS, which, if any, baseline scores or characteristics are appropriate to document, such as EDSS, MSFC, blood work, or other?	and practice patterns, and no additional evaluations are required (aside from blood work or other tests to exclude other diagnoses).	
The trial enrolled patients who were 18 years of age and older. It is noted that a meaningful proportion of people classified as having RIS, but not all, are at risk for developing active MS. a) Is there a way to identify those patients with RIS who are at an increased risk of progressing to MS? b) If recommended for listing, would all patients with RIS be treated with DMT? If not, under what circumstances or patient characteristics would you choose to not treat?	a) The clinical experts reported that patients with CSF findings (e.g., CSF-restricted oligoclonal bands), MRI evolution (e.g., MRI showing new and/or enhancing lesions), and/or spinal cord lesions are likely at increased risk of progressing to MS. b) The clinical experts felt that while all patients fulfilling diagnostic criteria for RIS should ideally be offered DMT, those at higher risk of developing MS may be more likely to be offered treatment with DMT. Among older patients with low lesion load deemed to be stable (e.g., as defined by clinical and MRI imaging findings) , the experts recommended a watch-and-	a) FMEC agrees with the experts. b) FMEC agrees with the experts. Refer to the initiation criteria as outlined in Table 2 of the recommendation report.

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	wait approach to treatment initiation.	
Study participants were excluded if they had exposure to a DMT within the past 3 months or exposure to high-dose glucocorticoid treatment within the past 30 days and participation in other clinical trials involving treatment with a DMT. Looking at the baseline characteristics, 4% of patients in the dimethyl fumarate arm had prior exposure to glatiramer. Between 1% and 2% of patients in both arms had tried either interferon beta-1 alpha (Avonex) or interferon beta-1 beta (Betaseron) previously. It is unclear how this might impact study results. Given this is a preclinical phase, in patients with prior DMT, are there any circumstances or patient characteristics that would indicate inadequate response and necessitate a change to dimethyl fumarate?	The clinical experts indicated that a suboptimal response to treatment would be the conversion to MS or development of new and/or enhancing lesions shown on MRI while on therapy. For example, if a patient with RIS was receiving interferon and developed new lesion(s) shown on MRI and/or converted to MS (e.g., experienced relapse), this would be considered by the experts as experiencing treatment failure with off-label interferon. In the ARISE trial, there was a very small number of patients who received interferon beta to have a meaningful impact on study results, according to the experts.	FMEC agrees with the experts.
Considerations for continuation or renewal of therapy		
The study looked at a primary end point of time to development of first acute, adjudicated, clinical event, or progressive neurological symptom suggestive of CNS demyelination from study enrolment. Assessments of study participants including EDSS, MSFC, and patient-reported outcomes were done at weeks 0, 48, and 96. Brain MRI examinations were completed at weeks 0 and 96. Blood tests were done more frequently (week 0, year 1, year 2, year 4, year 6, and year 8). a) Which parameters would be most appropriate for monitoring therapeutic response in RIS? How often should each parameter be assessed?	a) The clinical experts outlined that patients with RIS would be monitored for therapeutic response at least once a year (or more frequently depending on patient needs) at clinic visits using clinical and MRI parameters. b) According to the experts, a patient with RIS would be classified as having active MS if there was a clinical event (e.g., clinical relapse) characterizing MS, or they developed new and/or enhancing and/or unequivocally enlarging lesions shown on MRI.	FMEC agrees with the experts.

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b) At what point would the patient be reclassified as having active MS?		
Considerations for discontinuation of therapy		
Upon conversion to active MS, would patients who had been treated with dimethyl fumarate be deemed to have experienced treatment failure, and require a switch to a different disease-modifying agent? How would you define loss of response to therapy?	A suboptimal response or loss of response to therapy is defined as having a clinical relapse or the development of new and/or enhancing and/or unequivocally enlarging lesions shown on MRI, according to the clinical experts. A patient who converts to active MS during treatment with dimethyl fumarate would be considered by the experts to experience suboptimal response or loss of response and no longer considered to have RIS. The experts noted that since no DMT has been demonstrated to completely prevent disease activity in MS, those who convert to MS during treatment may benefit by switching to another therapy, depending on the activity level of the patient's disease.	FMEC agrees with the experts.
If treatment is interrupted for any reason, not related to neurological symptoms suggestive of CNS demyelination, when, if at all, would it be appropriate to restart therapy with dimethyl fumarate?	According to the clinical experts, if treatment with dimethyl fumarate was interrupted for any reason unrelated to neurological symptoms suggestive of CNS demyelination, the option of restarting dimethyl fumarate would depend on the reason for the interruption, if the issue has been resolved (e.g., stopped due to a drug shortage), and other patient factors. The experts stated that it would not be appropriate to resume treatment with dimethyl fumarate if the interruption was due to an AE.	FMEC agrees with the experts. FMEC also noted that, in the ARISE trial, patients who experienced persistent, intolerable flushing and/or gastrointestinal disturbance were able to proceed with a dose-reduction treatment option for 1 month and restart at the full treatment dose as per the study protocol.

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When classified as having RIS and beginning treatment with DMT, is there a period in which you would expect conversion to MS? In other words, is there a duration of treatment, in which therapy would be discontinued pending the patient has not converted to MS?	The clinical experts were not aware of any duration of treatment after initiating therapy in which treatment would be discontinued if a patient had not converted to MS (and considering individual patient profiles), since it would be reasonable to assume that lack of disease progression was due to therapy. The experts noted that the age at which treatment discontinuation in MS is being considered has generally increased as clinicians gain familiarity with the AE profiles of DMTs.	FMEC agrees with the experts. FMEC acknowledges clinical data for long-term use is lacking.
Considerations for prescribing of therapy		
Access to neurologists can be challenging in some areas.	According to the clinical experts, limited access to neurologists may be additionally challenged by access to neurologists with experience in MS.	Refer to the prescribing condition as outlined in Table 2 of the recommendation report.
System and economic issues		
At this time, it is unknown what the potential budget impact would be. Given that the treated population would be in addition to the population currently being treated for this drug under provincial drug plans who have restricted coverage to dimethyl fumarate, the assumption would be an increased budget impact.	The clinical experts agreed that the potential budget impact is unknown.	FMEC acknowledges that reimbursement will result in increased drug acquisition costs in most jurisdictions.
There may be additional health costs in terms of testing, depending on how the progression of RIS is monitored.	The experts agreed that there may be additional costs related to testing but noted that patients with RIS are usually followed similarly as for patients with documented MS, with ongoing MRIs and clinic visits.	FMEC agrees with the experts.

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Dimethyl fumarate is generic and there are generic pricing agreements in place.	This is a comment from the drug plans to inform FMEC deliberations.	FMEC notes generic pricing was used for cost comparison assessment during this review.

AE = adverse event; CNS = central nervous system; CSF = cerebrospinal fluid; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; FMEC = Formulary Management Expert Committee; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; RIS = radiologically isolated syndrome.