Teriflunomide (SX0752)
FMEC Responses to Questions from the Drug Programs

Response Summary

Drug Program Implementation Questions	Clinical Expert Response	FMEC response
Relevant comparators		
No comparator was included in the TERIS (Teriflunomide in Radiologically Isolated Syndrome) multicentre, placebo-controlled, double-blind, RCT. The primary outcome was the time to a first acute or progressive neurological event resulting from CNS demyelination. Secondary outcomes were brain MRI metrics. The study concluded that treatment with teriflunomide extends the time to symptomatic MS in patients with RIS compared to placebo. Note: a very similar study (ARISE RCT) demonstrated a risk reduction of over 90% of a first clinical event when patients with RIS were treated with dimethyl fumarate compared with placebo. None of the comparator drugs (interferon beta, glatiramer acetate, dimethyl fumarate) are indicated for the treatment of RIS; treatment with teriflunomide and comparators would be considered off-label use. This is potentially an issue in jurisdictions where these drugs are listed as special authorization. There are no head-to-head trials, therefore, the comparative efficacy of disease-modifying therapies is unknown.	The clinical experts agreed that there is no evidence comparing different DMTs in patients with RIS to determine efficacy of any 1 DMT over 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 inclusion criteria in the TERIS trial included age older than 18 years, fulfillment of the 2009 RIS criteria with structural neuroimaging abnormalities not explained by another disease process, and no historical accounts of remitting clinical symptoms consistent with neurological dysfunction.	a) The clinical experts expressed no concerns with adjusting the eligibility criteria of the TERIS trial to use the updated 2023 RIS criteria as long as a neurologist with experience in managing patients with MS was making the diagnosis.	a) FMEC agrees with the experts. Refer to the initiation criteria as outlined in Table 2 of the recommendation report.

a) The exclusion criteria comprised severe hepatic, kidney, and immune system impairments, lactating or pregnant individuals, or previous exposure to immunosuppressive or disease modifying treatments. The trial used the 2009 RIS criteria whereas the clinical experts consulted for the review indicated that the updated 2023 RIS criteria are used in clinical practice. Would it be reasonable to use the inclusion criteria from the TERIS trial to determine eligibility for treatment with teriflunomide, with the exception of using the 2023 RIS criteria instead of the 2009 RIS criteria? b) Are there any specific baseline scores that should be considered (e.g., EDSS)?	b) According to the clinical experts, once a patient has been identified as having RIS, the Expanded Disability Status Scale (EDSS) is typically assessed with or without the Multiple Sclerosis Functional Composite (MSFC) (or its components) depending on local resources and practice patterns, and no additional evaluations are required (aside from bloodwork or other tests to exclude other diagnoses).	b) FMEC agrees with the experts.
a) Is there a way to identify patients with RIS who are at an increased risk of progressing to MS? b) If teriflunomide is recommended for listing by the drug plans, would all patients with RIS be treated with DMT? If not, under what circumstances or considering which 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 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 and with clinical and MRI stability, the experts recommended a watch-and-wait approach to treatment initiation.	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.
Considerations for continuation or renewal of therapy		
a) How often should follow-up occur for patients with RIS (e.g., every 6 months, annually)?	a) The experts indicated that patients with RIS would be followed annually, or more frequently if needed (e.g., AEs).	FMEC agrees with the experts.

b) What should be monitored at follow-up (e.g., bloodwork, MRI, EDSS)?	b) 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, including bloodwork. The EDSS is typically assessed with or without the MSFC (or its components) depending on local resources and practice patterns.	
Considerations for discontinuation of therapy		
In the TERIS trial, the primary outcome was time to a first acute or progressive neurologic event resulting from CNS demyelination and secondary outcomes were brain MRI metrics. a) How would loss of response to therapy be defined in clinical practice? b) How would therapy be discontinued with loss of response?	a) 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 MRI lesions, according to the clinical experts. b) A patient who converts to active MS during treatment with teriflunomide 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 patient's disease activity level.	FMEC agrees with the experts.
If treatment was interrupted (e.g., due to adverse events, pregnancy), would it be reasonable to retreat with teriflunomide at a later time?	According to the clinical experts, if treatment with teriflunomide was interrupted for any reason unrelated to neurological symptoms suggestive of CNS demyelination, the option of restarting teriflunomide 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	FMEC agrees with the experts.

	resume treatment with teriflunomide if the interruption was due to an AE.	
If there is no disease progression, how long should treatment with teriflunomide be continued for?	According to the clinical experts, patients with RIS would be treated similarly to those with definitive MS, for as long as they are clinically and radiologically stable and without intolerable AEs. The experts noted that given the absence of evidence to indicate optimal duration of treatment or to support de-escalation of treatment, the risks (e.g., AEs) and benefits (e.g., reduced risk of conversion to MS) of treatment with teriflunomide must be weighed in shared decision-making with patients to determine if and when treatment discontinuation may be warranted.	FMEC agrees with the experts. FMEC acknowledges clinical data for long-term use is lacking
Considerations for prescribing of therapy		
The indicated dosage of teriflunomide is 14 mg, oral, once daily.	The experts confirmed that the dosage of teriflunomide per indication is the dosage that would be used for patients with RIS.	FMEC agrees with the experts and notes that this was the dosage used in the TERIS trial.
There is a risk of misdiagnosing patients with nonspecific MRI anomalies as having RIS. Should teriflunomide be prescribed by a neurologist with experience in the management of MS, or should it be restricted to prescribers at MS clinics or centres?	The experts expressed that teriflunomide may be prescribed outside of MS clinics or centres, by neurologists with experience in management of patients with MS, as restricting to neurologists at MS clinics or centres would unduly limit access by patients who reside in geographic locations that may not have a MS clinic.	Refer to the prescribing condition as outlined in Table 2 of the recommendation report. Note that the use of teriflunomide is contraindicated in pregnant individuals and those of childbearing age due to its risk of teratogenicity.
Would this be used in combination with other drugs used in the treatment of MS?	The experts noted that combination therapies are not indicated for any form of MS and no patients are currently treated with multiple DMTs at the same time.	FMEC agrees with the experts. Additionally, please refer to the prescribing condition as outlined in Table 2 of the recommendation report that teriflunomide should not be used concurrently with other DMTs.

Care provision issues		
Should bloodwork be scheduled regularly to monitor patients for adverse events (e.g., hepatotoxicity, hematologic toxicity)?	The experts agreed that bloodwork, per product monograph, is routine in clinical practice to monitor for AEs.	FMEC agrees with the experts.
System and economic issues		
Provision of teriflunomide in the first line setting may translate into substantial 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.
Generics for teriflunomide are available, so product listing agreement is not applicable, but generic pricing agreements are 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; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; FMEC = Formulary Management Expert Committee; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; RCT = randomized controlled study; RIS = radiologically isolated syndrome.