Technology Guidance

Disease-modifying therapies

for treating multiple sclerosis

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Fingolimod 0.25 mg and 0.5 mg capsules for treating adults and children with relapsing-remitting multiple sclerosis, and
- ✓ Siponimod 0.25 mg and 2 mg tablets for treating adults with secondary progressive multiple sclerosis with active disease evidenced by relapses or imaging features of inflammatory activity.

Subsidy status

Fingolimod 0.25 mg and 0.5 mg capsules and siponimod 0.25 mg and 2 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indications.

MAF assistance **does not** apply to any formulations or strengths of alemtuzumab, cladribine, dimethyl fumarate, interferon beta-1a, natalizumab, ofatumumab or teriflunomide for treating adults or children with any form of multiple sclerosis.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of disease-modifying therapies (DMTs; alemtuzumab, cladribine, dimethyl fumarate, fingolimod, interferon beta-1a, natalizumab, ofatumumab, siponimod and teriflunomide) for treating adults and children with multiple sclerosis (MS). The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for all DMTs was considered in line with their registered indications. Evidence for rituximab (off-label) was also considered in line with local clinical practice; however, it was not considered for subsidy as rituximab biosimilar is already included on the Standard Drug List (SDL).

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1. The Committee noted that about 261 adults and 3 children have been diagnosed with MS in Singapore based on data from the public healthcare institutions in 2020. Local clinical experts estimated that among adults with MS, approximately 80% have relapsing-remitting multiple sclerosis (RRMS), 5% have clinically isolated syndrome (CIS), 10% have primary progressive multiple sclerosis (PPMS), and 5% have secondary progressive multiple sclerosis (SPMS). Among children, RRMS is most common, but a few cases of CIS have been previously recorded. There are no known cases of PPMS or SPMS.

2.2. The Committee heard that patients with RRMS have episodes of symptom exacerbation or relapses, which are followed by partial or complete remission. Some patients who initially present with RRMS go on to develop SPMS; this occurs when relapses become less frequent or stop completely, but there is a gradual accumulation of disability. PPMS is characterised by disability progression from onset, without relapses and remissions. Patients are diagnosed with CIS if they do

not meet the criteria for a confirmed diagnosis of MS but they have had a single clinical episode with symptoms and objective findings that reflect an inflammatory demyelinating event in the central nervous system.

2.3. In line with local expert advice, the Committee reviewed the drug treatments for CIS in adults, RRMS in adults and children, and SPMS in adults. Of note, treatments for CIS in children and PPMS for adults and children were not reviewed as these conditions are not routinely treated in local practice.

2.4. The Committee noted that rituximab is used off-label in local practice for treating RRMS in adults and children and SPMS in adults. Given that none of the HSA-approved DMTs for MS are subsidised, the Committee acknowledged the clinical need to consider these drugs for subsidy to ensure appropriate patient care and improve treatment affordability.

2.5. CIS in adults

The Committee acknowledged that subcutaneous (SC) interferon (IFN) beta-1a is the only HSA-approved DMT for CIS. In local practice, SC IFN beta-1a is used to treat adults with CIS who are at high risk of conversion to MS. Adults with CIS who are at low risk of conversion are usually observed without starting a DMT.

2.6. RRMS in adults

There are currently eight HSA-approved DMTs for treating RRMS in adults– alemtuzumab, cladribine, dimethyl fumarate, fingolimod, SC IFN beta-1a, natalizumab, ofatumumab and teriflunomide. In addition, rituximab is used as an off-label treatment in local practice.

2.7. The Committee noted that local clinical experts do not follow a fixed algorithm for treating adults with RRMS. Instead, the choice of treatment is typically patient-specific depending on multiple factors including disease activity, patient characteristics, preference and risk tolerance.

2.8. RRMS in children

The Committee noted that fingolimod, dimethyl fumarate (off-label) and teriflunomide (off-label) are the preferred initial treatment options for children with RRMS in local practice. While the HSA package insert for SC IFN beta-1a injection indicates that it could be used in adolescents ≥12 years old, it is seldom used due to lower patient compliance. The Committee acknowledged that for the purpose of the evaluation, only HSA-approved DMTs, fingolimod and SC IFN beta-1a, were evaluated for subsidy listing.

2.9. For patients who require a subsequent line of treatment, the Committee noted that off-label use of rituximab could be considered, though local clinical experts indicated that most children with RRMS are well-controlled on initial therapy.

2.10. SPMS in adults

The Committee acknowledged that clinical experts may use siponimod, ofatumumab or rituximab (off-label) for treating adults with SPMS in local practice.

Clinical effectiveness and safety

3.1. CIS in adults

The Committee reviewed the available clinical evidence for SC IFN beta-1a from a randomised controlled trial (RCT) (REFLEX) and its 3-year extension study (REFLEXION). The studies included adults who had CIS but did not meet the 2005 McDonald criteria for a diagnosis of MS. The results showed that SC IFN beta-1a delayed conversion from CIS to MS and reduced the number of magnetic resonance imaging (MRI) lesions compared with placebo.

3.2. However, the trials did not show a reduction in long-term disability progression with SC IFN beta-1a. The Committee heard that local experts considered the study duration was too short to show any long-term benefits, since patients with CIS are at an early stage of the disease. Nonetheless, the Committee considered that the clinical benefit of SC IFN beta-1a for treating CIS was uncertain based on the available evidence.

3.3. The Committee also considered that it was uncertain whether the results were generalisable to patients diagnosed with CIS based on current 2017 McDonald criteria. While there were post-hoc analyses which suggested that the treatment effect of SC IFN beta-1a may be similar between the overall trial population and a subgroup of patients who would be diagnosed with CIS based on 2010 criteria, the Committee noted that these analyses were exploratory and should be interpreted with caution.

3.4. In terms of safety, SC IFN beta-1a resulted in a higher incidence of injection site reactions, influenza-like illnesses, increased liver enzyme levels, and cytopenia compared with placebo.

3.5. RRMS in adults

For the eight HSA-approved DMTs, the Committee reviewed the clinical evidence from 10 placebo-controlled RCTs for six DMTs (cladribine, dimethyl fumarate, fingolimod, SC IFN beta-1a, natalizumab and teriflunomide), seven head-to-head RCTs for six DMTs (alemtuzumab, fingolimod, SC IFN beta-1a, natalizumab, ofatumumab and teriflunomide), and indirect treatment comparisons. The Committee also reviewed the available clinical evidence for rituximab from a placebo-controlled RCT and observational studies.

3.6. *Clinical evidence for HSA-approved DMTs:*

Results from the placebo-controlled RCTs showed that all six DMTs were effective compared to placebo in reducing annualised relapse rates and MRI lesion counts,

although there were varying effects reported on disability progression. Cladribine and natalizumab consistently delayed the time to confirmed disability progression (CDP) that was determined over 3 and 6 months. The other four DMTs either led to a delay in the time to 3-month CDP but not 6-month CDP, or statistical significance was not consistently shown in the trials.

3.7. Results from the head-to-head RCTs showed that teriflunomide was similar in effectiveness to SC IFN beta-1a; alemtuzumab was more effective than SC IFN beta-1a; and ofatumumab was more effective than teriflunomide. The REVEAL RCT that compared natalizumab and fingolimod was terminated early due to enrolment issues, hence the results could not be meaningfully interpreted.

3.8. Given the paucity of head-to-head evidence, the Committee considered the results of indirect comparisons of DMTs that were reviewed by NICE (UK) and PBAC (Australia). While acknowledging the uncertainty associated with indirect comparisons due to heterogeneity of trial populations, the Committee noted from the results that SC IFN beta-1a and dimethyl fumarate were likely to be comparable in effectiveness, while alemtuzumab, cladribine, fingolimod, natalizumab and ofatumumab were likely to be comparable in effectiveness.

3.9. *Clinical evidence for rituximab:*
The Committee noted evidence on the use of rituximab in adults with RRMS from a placebo-controlled RCT (HERMES; where 2 infusions were administered on days 1 and 15 without any 6-monthly maintenance dose) and observational studies. The RCT showed that rituximab led to lower annualised relapse rates and MRI lesion counts at 24 weeks compared to placebo. The observational studies suggested that rituximab may be more effective than SC IFN beta-1a, dimethyl fumarate and fingolimod, but have comparable effectiveness to natalizumab.

3.10. *Comparative clinical effectiveness and safety:*
Taking into consideration direct and indirect evidence as well as local expert input, the Committee agreed that DMTs may be broadly categorised into 2 groups:

- Group 1: dimethyl fumarate, SC IFN beta-1a and teriflunomide
- Group 2: alemtuzumab, cladribine, fingolimod, natalizumab, ofatumumab, and rituximab

where the DMTs within each group were considered to be comparable in clinical effectiveness, and the DMTs in Group 2 were considered to be more effective than those in Group 1.

3.11. In terms of safety, the adverse event profiles of the DMTs were noted to vary considerably. Within each group, there was insufficient evidence to show that any DMT had a substantially better or worse safety profile compared to the others.

3.12. RRMS in children
The Committee noted that fingolimod has not been investigated in a placebo-controlled trial in children with RRMS. However, it has been compared against

intramuscular (IM) IFN beta-1a in an RCT (PARADIGMS). The results showed that fingolimod was more effective in reducing annualised relapse rates and MRI lesions, and delaying the time to 3-month CDP compared with IM IFN beta-1a. The use of SC IFN beta-1a in children has not been studied in an RCT.

3.13. No published indirect comparisons between SC IFN beta-1a and fingolimod in children with RRMS were identified. However, a network meta-analysis (NMA) conducted by NICE's Evidence Review Group (UK) showed that the SC and IM preparations of IFN beta-1a were similarly effective for treating patients with RRMS. In view of these findings and the results of the PARADIGMS RCT, the Committee considered that fingolimod was likely to be more effective than SC IFN beta-1a for treating children with RRMS.

3.14. In terms of safety, the PARADIGMS RCT showed that adverse events occurred in a lower proportion of patients in the fingolimod group compared to IM IFN beta-1a group (89% vs 95%). However, serious adverse events occurred in a higher proportion of patients in the fingolimod group compared to IM IFN beta-1a group (17% vs 7%). Fingolimod resulted in more adverse events of leukopenia, upper respiratory tract infections and influenza, while IM IFN beta-1a resulted in more influenza-like illness, pyrexia and chills.

3.15. <u>SPMS in adults</u>
The Committee reviewed the clinical evidence from an RCT (EXPAND), which showed that siponimod was effective compared with placebo in reducing annualised relapse rates and number of MRI lesions, and delaying the time to 3-month and 6-month CDP in adults with SPMS. According to subgroup analyses, the treatment effect of siponimod in delaying disability progression was driven by the subgroup of patients with active disease. In terms of safety, siponimod resulted in a higher incidence of bradycardia at treatment initiation, hypertension and elevated liver enzymes compared with placebo.

3.16. Although the EXPAND trial excluded patients who previously received fingolimod for more than 6 months, local clinical experts opined that patients who receive fingolimod for RRMS can still be treated with siponimod if they develop SPMS. While both fingolimod and siponimod belong to the same drug class (sphingosine 1-phosphate [S1P] receptor modulators), they differ in target receptor selectivity. The Committee heard that in overseas reference countries, the reimbursement criteria for siponimod do not preclude prior use of fingolimod.

3.17. The Committee noted that no RCT has been specifically conducted to investigate the use of ofatumumab for treating SPMS. In 2 RCTs (ASCLEPIOS I and II) that compared ofatumumab with teriflunomide, the majority of patients (94%) had RRMS, and only a small proportion (6%) had active SPMS. Given the small sample size, the Committee agreed that there was insufficient evidence to assess the clinical effectiveness and safety of ofatumumab in patients with SPMS.

3.18. The Committee noted the results of an RCT which showed that rituximab was similar to glatiramer in reducing annualised relapse rates in patients with SPMS. However, the results were not applicable to the local setting as glatiramer is not approved for use in Singapore or used in local practice.

Cost effectiveness

4.1. The manufacturers of all HSA-approved DMTs were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration. Price reductions were offered for alemtuzumab, dimethyl fumarate, fingolimod, natalizumab and teriflunomide, contingent on MAF listing. No price reduction was offered for cladribine and SC IFN beta-1a. New prices were proposed for ofatumumab and siponimod, which were not previously available in public healthcare institutions.

4.2. CIS in adults

No local cost-effectiveness analysis for SC IFN beta-1a in patients with CIS was identified. The Committee noted that an economic analysis reviewed by CADTH (Canada) which compared SC IFN beta-1a with best supportive care (BSC) resulted in a base-case incremental cost-effectiveness ratio (ICER) of CA$78,716 per quality-adjusted life year (QALY) gained. CADTH also highlighted that the ICER could be significantly higher as there was uncertainty whether a reduction in the risk of progression from CIS to MS would translate to clinically important differences in quality of life and survival over time. The Committee also noted that the proposed price for SC IFN beta-1a was higher than in all overseas reference jurisdictions, thus it was unlikely to represent a cost-effective treatment for CIS in the local context.

4.3. RRMS in adults

Given that DMTs in Groups 1 and 2 were considered to be comparable within their respective groups in clinical effectiveness and have different safety profiles, the Committee agreed that a cost-minimisation approach was appropriate to identify the DMT with the lowest treatment cost within each group for subsidy consideration. The Committee agreed that drug costs should be compared over the first 2 years of treatment, in line with the duration of DMT use in most of the pivotal trials, and given that cladribine is usually given for a fixed duration of 2 years.

4.4. Results of the cost-minimisation analysis (CMA) showed that among Group 1 DMTs, dimethyl fumarate had the lowest treatment cost. Among Group 2 DMTs, rituximab had the lowest treatment cost, followed by fingolimod. Of note, fingolimod was also the lowest cost option among all the HSA-approved DMTs. Hence, while dimethyl fumarate had the lowest cost in Group 1, it was not considered cost-effective in view of lower clinical effectiveness and higher cost compared to fingolimod.

4.5. The Committee considered a request from the manufacturer of cladribine for the CMA to be conducted over a 4-year duration, using 2 years' cost of cladribine treatment. The request was submitted on the basis that cladribine had shown durable treatment

effect over 4 years in the extension study of the pivotal CLARITY trial. However, the Committee noted the methodological limitations of the extension study and agreed that the results had to be interpreted with caution. Moreover, an observational study (CLARINET-MS) showed that 20-30% of patients who completed 2 years of cladribine treatment required another DMT in the 3rd or 4th year, thereby incurring additional treatment costs. Hence, the Committee concluded that the manufacturer's request was not supported. Nonetheless, a scenario analysis confirmed that even if a 4-year duration was used for the CMA, the cost of cladribine treatment for 2 years remained higher compared with 4 years of fingolimod treatment.

4.6. For fingolimod, no local cost-effectiveness analysis in adults with RRMS was identified. The Committee noted that an economic analysis reviewed by CADTH showed unfavourable cost-effectiveness when fingolimod was compared with beta-IFNs, glatiramer and BSC. However, the results were unlikely to be generalisable to the local setting, given that the treatment cost of fingolimod in the economic analysis was higher than that in Singapore based on the prices proposed by the manufacturer.

4.7. Given that the proposed prices for fingolimod were comparable to overseas reference jurisdictions, the Committee agreed that fingolimod treatment was likely to be cost-effective versus BSC and dominant versus other HSA-approved DMTs in Singapore.

4.8. <u>RRMS in children</u>
The Committee heard that the cost of fingolimod over the first 2 years of treatment was lower than the cost for SC IFN beta-1a. Given that fingolimod was considered to be more clinically effective than SC IFN beta-1a for treating children with RRMS, the Committee agreed that fingolimod was the dominant treatment.

4.9. No local cost-effectiveness analysis for fingolimod in children with RRMS was identified. The Committee heard that reference HTA agencies had not specifically evaluated the cost-effectiveness of fingolimod versus BSC in children, though the reimbursement criteria of fingolimod in Australia, Canada and New Zealand did not preclude its use in children. The Committee noted that the PBAC (Australia) considered that the effectiveness and safety of fingolimod in children were non-inferior to adults on the basis of subgroup data from the PARADIGMS trial. Therefore, the Committee considered that the cost-effectiveness conclusions for fingolimod in adults with RRMS were also generalisable to children.

4.10. <u>SPMS in adults</u>
No local cost-effectiveness analysis of siponimod in adults with SPMS was identified. The Committee heard that NICE (UK) considered siponimod to be cost-effective versus BSC for treating active SPMS under confidential commercial arrangements. Given that the siponimod price used in the economic analysis was higher than the prices proposed by the manufacturer for MAF listing, the Committee considered that siponimod was likely to also be cost-effective in Singapore. The Committee also acknowledged that the prices proposed for siponimod were comparable to other overseas reference jurisdictions.

4.11. The Committee did not review the cost-effectiveness of ofatumumab and rituximab for treating SPMS in adults, given the uncertainties in clinical effectiveness and safety.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact in the first year of listing each treatment on MAF was estimated to be less than SG$1 million each for the following conditions:

- SC IFN beta-1a - for treating CIS in adults;
- Fingolimod - for treating RRMS in adults and children; and
- Siponimod - for treating SPMS in adults.

Additional considerations

6.1. As part of the deliberation, the Committee considered whether DMTs had an effect on COVID-19 vaccination response in patients with MS. According to a local consensus statement by the Chapter of Neurologists (College of Physicians, Singapore) and overseas guidances, some DMTs may reduce the effectiveness of COVID-19 vaccines, however, patients are advised not to stop DMTs but instead coordinate the timing of vaccine administration with the timing of their DMT dose, where possible. The Committee also reviewed clinical trial findings of the COVID-19 vaccination response in patients with MS.

6.2. After taking into consideration the available information and local expert opinion, the Committee acknowledged that until more evidence is available, the choice of DMT for MS should continue to be based on drug effectiveness and safety, rather than the effect on potential COVID-19 vaccination.

Recommendations

7.1. <u>CIS in adults</u>
Based on available evidence, the Committee recommended not listing SC IFN beta-1a on the MAF for treating adults with CIS due to uncertain clinical and cost-effectiveness.

7.2. <u>RRMS in adults and children</u>
Based on available evidence, the Committee recommended fingolimod 0.25 mg and 0.5 mg capsules be listed on the MAF for treating adults and children with RRMS, given the clinical need, favourable clinical and cost-effectiveness, and acceptable budget impact.

7.3. The Committee did not recommend alemtuzumab, cladribine, dimethyl fumarate, SC IFN beta-1a, natalizumab, ofatumumab and teriflunomide for listing on the MAF for treating adults or children with RRMS due to unacceptable cost effectiveness compared with fingolimod.

7.4. SPMS in adults

Based on available evidence, the Committee recommended siponimod 0.25 mg and 2 mg tablets be listed on the MAF for treating active SPMS, in view of clinical need, favourable clinical and cost-effectiveness, and acceptable budget impact.

7.5. The Committee did not recommend ofatumumab for listing on the MAF for treating adults with SPMS due to uncertain clinical effectiveness and safety.