7.08 SIPONIMOD
Tablet 0.25mg, 2mg,
Mayzent®,
Novartis Pharmaceuticals Pty Ltd.

1 Purpose of resubmission

1.1 The resubmission requested a General Schedule, Authority Required (STREAMLINED) listing for siponimod for the treatment of relapse-onset phenotypes of multiple sclerosis (MS).

1.2 Listing was requested on the basis of a cost minimisation analysis versus fingolimod.

1.3 Table 1 presents key components of the clinical issues addressed by the resubmission.

Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

Component	Description
Population	Patients with relapse-onset multiple sclerosis, including those with EDSS 6.0/6.5[a]
Intervention	Siponimod 1 mg or 2 mg daily
Comparator	Fingolimod, as the reference therapy for other DMTs[b]
Outcomes	Annualised relapse rate; proportion (%) free from relapse; 3- and 6-month confirmed disability progression; and safety
Clinical claim	In patients with relapse-onset multiple sclerosis, including those with EDSS 6.0/6.5, siponimod is non-inferior to fingolimod with respect to efficacy and safety[c]

Source: Table 1.1, p3 of the resubmission

DMT = disease modifying treatment; EDSS = Expanded Disability Status Scale

[a] The previous submission described the population as patients with SPMS

[b] The previous submission nominated placebo and multiple RRMS DMTs as the comparator

[c] The previous submission made two claims. 1) In the SPMS untreated population - Superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo and 2) in the SPMS treated population - Superior in terms of comparative effectiveness and with comparable but different safety profiles compared with interferon-beta/glatiramer acetate and natalizumab.

2 Background

Registration status

2.1 Siponimod was TGA registered on 1 November 2019 for secondary progressive multiple sclerosis (SPMS).

2.2 The TGA registration differs from the EMA and FDA, which require evidence of relapses (EMA), or, limits use of siponimod to relapsing forms of MS such as RRMS (FDA), despite the regulatory dossier submitted to each jurisdiction requesting registration for the treatment of patients with SPMS.

Previous PBAC consideration

2.3 A summary of the key matters of concern in the resubmission is presented in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical place in therapy	It may be appropriate to include siponimod within the existing treatment algorithm for RMS DMTs (para 7.15, Nov 2019 PSD). Any future resubmission should include consultation with clinicians about the role of genetic testing (para 7.6, Nov 2019 PSD).	Restriction amended to align more closely with existing RRMS listings. Amended restriction may be broader than existing evidence, and TGA indication. Addressed. Genetic testing included in prescriber notes. Sponsor expressed willingness to include in clinical criteria if so advised.
Comparator	Mixed comparator of an untreated population (placebo) and treated population (interferon beta, glatiramer acetate, natalizumab, fingolimod and ocrelizumab) was not appropriate. Placebo was the most appropriate comparator (para 7.7, Nov 2019 PSD).	The resubmission nominated fingolimod as the main comparator.
Clinical effectiveness	Indirect comparisons against DMTs were not presented, though comparisons would be limited by the quality of the available evidence for RRMS.	Indirect comparison against fingolimod presented. As noted by PBAC, the comparisons were limited by the exchangeability issues between the trials.
Clinical Safety	The PBAC considered siponimod was of inferior comparative safety to placebo (para 7.10, Nov 2019 PSD).	Resubmission claims non-inferior safety to fingolimod.
Cost-effectiveness	Resubmission should assess cost-effectiveness of siponimod versus placebo among people with SPMS (para 7.15, Nov 2019 PSD). Alternatively, cost-effectiveness could be informed by a comparison with DMTs among people with RRMS.	Not addressed. No economic evaluation presented. Partially addressed. No economic model was presented. A cost minimisation to fingolimod was presented based on an indirect comparison with transitivity issues. To account for the uncertainty in the cost-effectiveness of fingolimod in patients with EDSS ≥ 6 who are currently untreated, the pre-PBAC response offered a lower price in this population, which was equivalent to the cost of interferon beta.
Financial estimates	Likely utilisation of siponimod to be highly uncertain given the potential RRMS patients who are experiencing progressive disease but have not been diagnosed with SPMS, and the level of clinical judgment often required in making an SPMS diagnosis (para 7.14, Nov 2019 PSD).	Market share approach for RRMS population and an epidemiological approach for SPMS patients who would not otherwise have been treated with a PBS-listed DMT.

Source: Table P1, Sections D and E of the resubmission.
DMT = disease modifying treatment; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis
Paragraph references are to the siponimod PBAC Public Summary Document, November 2019.

3 Requested listing

3.1 The requested listing is presented below. The underlined text indicates the difference between the current DMT restrictions and the proposed siponimod restrictions.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SIPONIMOD				
Tablet, 0.25mg,	12	0	$[redacted] published price $[redacted] effective price	
Tablet, 0.25mg	120	5	$[redacted] published price $[redacted] effective price	Mayzent® Novartis Pharmaceuticals Pty Ltd
Tablet, 2mg	28	5	$[redacted] published price $[redacted] effective price	

Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Severity:	Nil
Condition:	Multiple Sclerosis
PBS Indication:	Multiple Sclerosis
Treatment phase:	Initial
Restriction:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone, Electronic ☒Streamlined
Clinical criteria:	The condition must be, or have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR The condition must be, or have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient, AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND Patient must be ambulatory (with or without assistance or support). Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical record.
Prescriber Instructions:	Patient must have a genotype test to determine their metaboliser status for the CYP2C9 metabolising enzyme, as per the TGA-approved Product Information.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply
Treatment phase:	Continuing
Restriction:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone, Electronic ☒Streamlined

Clinical criteria:	The condition must be, or have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis, AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not show continuing progression of disability while on treatment with this drug, AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Prescriber Instructions:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply
Treatment phase:	Grandfathering
Restriction:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone, Electronic ☒Streamlined
Clinical criteria:	The condition must be, or have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR The condition must be, or have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient, AND Patient must have received treatment with this drug for this condition prior to [PBS listing date], AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND Patient must be ambulatory (with or without assistance or support). AND Patient must not show continuing progression of disability while on treatment with this drug, AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Prescriber Instructions:	Patient must have a genotype test to determine their metaboliser status for the CYP2C9 metabolising enzyme, as per the TGA-approved Product Information.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

3.2 The requested effective price was [redacted]% lower than that in the previous submission.

3.3 The requested restriction was modified in the resubmission to align with the restriction for RRMS disease modifying treatments (DMTs). Specifically, the resubmission made the following changes to the original submission's restriction:

- amended the condition/indication to Multiple Sclerosis to align with other DMTs on the PBS, as recommended by the PBAC Secretariat;
- broadly aligned the listing with other DMTs listed on the PBS;
- allowed current diagnosis of RRMS;
- removed criterion on disability progression and mild/moderate disability from the initial restriction;

- added a prescriber instruction related to genotype testing;
- retained the criterion 'ambulatory (with or without assistance or support)'; and
- removed the 'sustained progression' text from the continuation criteria (to make the criteria the same as existing DMTs).

3.4 The requested listing permits use in patients with RRMS or SPMS (given only a historical RRMS diagnosis is required). The PBAC noted that siponimod is only TGA registered for SPMS (not RRMS) but considered that it may not be appropriate for the restriction to specifically exclude patients with RRMS given that it can be clinically difficult to determine when patients transition from RRMS to SPMS (as outlined further in paragraph 4.3).

3.5 The commentary and the ESC noted that the definition of SPMS would generally not include patients with low or minimal accumulated disability. The Pre-Sub-Committee Response (PSCR) indicated the Sponsor's willingness to include the criterion from the original submission of, 'patient must have mild disability in at least 3 functional systems or moderate disability in at least 1 functional system' if requested by the PBAC. This would mean that only patients with a disability equivalent to an Expanded Disability Status Score (EDSS) of at least 3.0 would be eligible for treatment with siponimod. The pre-PBAC response stated that it considered that use in patients with EDSS < 3 was unlikely to occur as most clinicians would chose an existing DMT as initial therapy. The PBAC considered that the restriction should exclude use of siponimod in patients with EDSS < 3 given the limited clinical evidence for siponimod in this patient population.

3.6 In contrast to other DMT restrictions, the requested restriction allows initiation in:

- patients with a previous diagnosis of RRMS (SPMS); and
- ambulatory patients who require assistance to initiate treatment (EDSS equivalent of 6.0 to 6.5), noting that the current RRMS DMT restrictions limit initiation of therapy to patients who are ambulant without the need for assistance or support only, which is equivalent to a maximum EDSS of 5.5.

3.7 For clarity, the definitions of an EDSS score of 6.0 and 6.5 are:

- EDSS 6.0 – Intermittent or unilateral constant assistance required to walk 100 metres, with/without resting; and
- EDSS 6.5 – Constant bilateral assistance (canes, crutches, braces) required to walk 20 metres without resting.

3.8 The requested listing included the clinical criterion 'patient must not show continuing progression of disability while on treatment with this drug' which aligns with that for existing RRMS DMT listings. This means that for a patient commencing siponimod with EDSS 6.5, treatment must cease when patients progress to no longer being ambulant (i.e. EDSS score of ≥ 7).

3.9 The standard dose of siponimod is 2 mg once daily or 1 mg once daily for patients who are intermediate metabolisers of siponimod, based on the results of CYP2C9 genetic testing. The latter is administered as 4x250 mcg tablets; the Sponsor stated it is not

currently manufacturing a 1 mg tablet form, but foreshadowed registration at a later date. The resubmission also requested listing of a titration pack (comprising 12x250 mcg tablets) to allow for a titration period of five days (one tablet on days 1 and 2, two on day 3, three on day 4 and five on day 5). While it is not usual for starter/titration packs that are of the same strength as a regular continuing strength to be PBS listed, the PSCR stated that siponimod requires refrigeration and thus it will not be possible to provide sample/starter packs to all prescribers. As such, the PBAC considered it would be reasonable to list the titration pack, while acknowledging that PBS reimbursement claiming rules currently do not permit claiming of two PBS benefits of the same pharmaceutical item prescribed on the same day (colloquially referred to as 'same day prescribing'.

3.10 Before treatment with siponimod, the Product Information recommends that patients have a genotype test to determine their metaboliser status for the CYP2C9 metabolising enzyme. The PBAC considered that it would be reasonable to have words to this effect appear in the listing. However, additional words would need to clarify (1) the reimbursement status of the enzyme test, and (2) how responsibility for reimbursement could be contained to the sponsor within a PBS listing, given that the resubmission stated that the sponsor would incur the cost of testing, but had not explained how this would be practically implemented.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Multiple sclerosis (MS) is a "chronic, immune-mediated disease of the central nervous system (CNS) characterised by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability" (p.3 of the resubmission). MS symptoms are heterogeneous between patients, but can manifest in any of five major health problems (motor control; fatigue; continence problems; neuropsychological symptoms (such as depression, cognitive difficulties and memory loss); other neurological symptoms (such as vertigo, neuralgia and visual disturbances)). Inflammation and neurodegeneration are considered to be the underlying processes of MS. Inflammation and neurodegeneration can be seen as a spectrum in MS patients, whereby RRMS patients generally suffer from intense focal inflammatory symptoms before transitioning to SPMS which is characterised by neurodegeneration and axon loss.

4.2 SPMS is a phenotype of MS, which transitions from an RRMS phenotype. The pathology of progression from RRMS to SPMS is also considered to include meningeal inflammation, vascular dysfunction, microglial activation, chronic oxidative injury, age-related iron accumulation in the brain and the accumulation of axon mitochondrial damage. As MS progresses, impairment of the five major health problems (noted above) increases. Patients with SPMS see a progressive increase in

neurological disability and T2 lesions, and a progressive decrease in brain volume, relapse rate and Gd-enhancing lesions.

4.3 The 2013 International Advisory Committee on Clinical Trials of MS (Lublin et al 2014) noted that 'in most clinical contexts, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course. To date, there are no clear clinical, imaging, immunologic, or pathologic criteria to determine the transition point when RRMS converts to SPMS; the transition is usually gradual'.

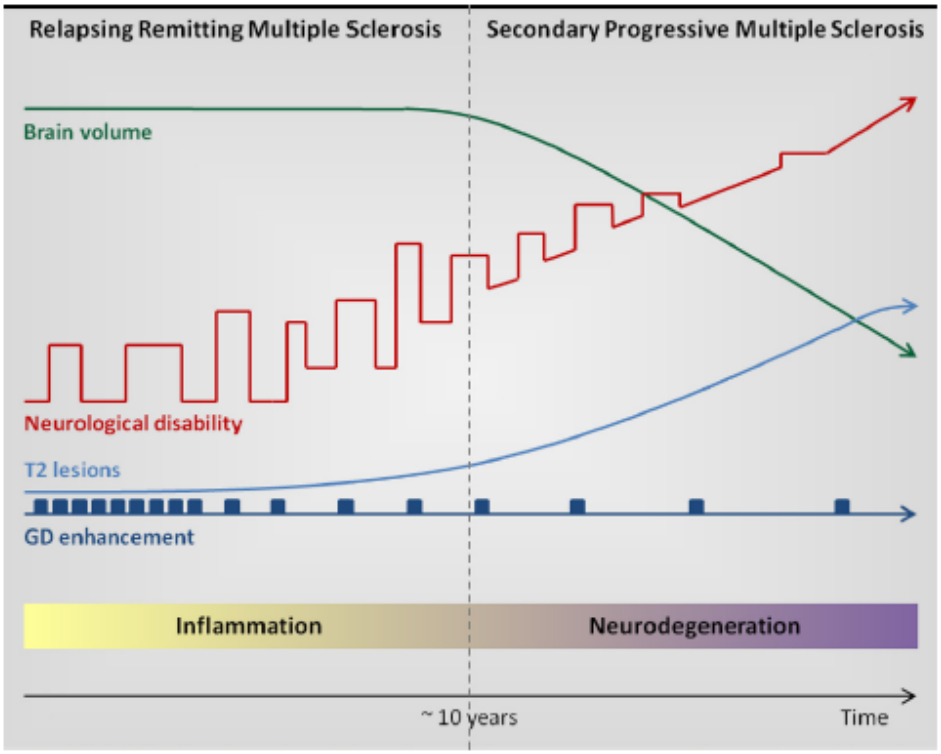
4.4 In the clinical evidence (EXPAND, BOLD, FREEDOMS I & II) disability is defined by the Kurtzke Expanded Disability Status Scale (EDSS). The resubmission noted that while the EDSS is used by MS Centres and neurologists enrolling patients in clinical trials and registries, it is not often used by general neurologists. The resubmission considered that transition to SPMS can be identified by reviewing a patient's history of ability/disability. In the pivotal trial for siponimod included in this resubmission (EXPAND), a physician's summary of the clinical evidence of a patient having disability progression of at least 6 months duration, could be provided if an EDSS score was not available at study screening. Patients were also required to have a prior history of RRMS.

4.5 There are 12 DMTs listed on the PBS for patients with RRMS that may be commenced in RRMS and can be used until continuing progression of disability or until the patient requires assistance to walk (i.e. the DMTs must be ceased if EDSS equivalent of >5.5). However, there is no listed therapy specifically for SPMS.

4.6 The resubmission proposed siponimod for use in RRMS patients (aligned with the existing DMT restrictions) as well as SPMS patients.

4.7 Figure 1 illustrates factors associated with progression from RRMS to SPMS.

Figure 1: Disease course from RRMS to SPMS



Source: Figure 1.2, p6 of the resubmission.
T2= time taken between magnetic pulses and image capture using magnetic resonance imaging; Gd = Gadolinium
Note: The graph shows neurological disability, brain atrophy, frequency of inflammatory events [T1 lesions with gadolinium (GD) contrast enhancement showing blood–brain barrier breakdown] and global level of tissue damage (T2 lesions)."

5 Comparator

5.1 The resubmission nominated fingolimod as the main comparator as a point of reference for PBS-listed DMTs. The main arguments provided in support of this nomination were as follows:

- The PBAC considered that the cost-effectiveness of siponimod could alternatively be informed by a comparison with the DMTs among people with RRMS (paragraph 7.15, siponimod, PBAC PSD, November 2019).
- Cladribine, ocrelizumab and alemtuzumab were all listed on the basis of similar efficacy and safety compared with fingolimod.
- Fingolimod is a pharmacological analogue of siponimod.

5.2 Given that cladribine, ocrelizumab and alemtuzumab were all listed on the basis of similar efficacy and safety compared to fingolimod, the commentary, ESC and PBAC considered that fingolimod may be considered an appropriate reference for other RRMS DMTs, among patients who are ambulatory and do not require assistance to walk (broadly consistent with an EDSS ≤5.5).

5.3 The requested listing for siponimod additionally includes ambulatory patients who require assistance to walk, while fingolimod (and other DMTs) are not PBS-subsidised

in patients who require assistance to walk. Patients with EDSS 6.0 and 6.5 (defined as patients who require assistance to walk but do not require a wheelchair) i.e. patients who are not eligible for PBS-subsidised DMTs make up the majority of the resubmission's estimated incremental financial impact to the PBS/RPBS. For these patients, the commentary and the ESC considered that best supportive care would be the more appropriate comparator. The commentary, ESC and PBAC considered that accepting non-inferiority of siponimod to fingolimod in this population would not necessarily support the cost-effectiveness of siponimod in this population as the cost-effectiveness of fingolimod in this population has not been established.

5.4 The ESC noted that although DMTs may be an appropriate comparator for patients with an EDSS score of 3.5-5.5, a comparison with best supportive care may also be relevant given that the cost-effectiveness of DMTs in SPMS has not previously been assessed.

5.5 The PSCR stated that PBS-listed DMTs are used in SPMS patients with EDSS of 6 and above ([redacted]%) as indicated in the MSBase analysis. The ESC noted that the MSBase analysis indicated that [redacted] ([redacted]%) of Australian SPMS patients were currently using a DMT, which may be PBS-supplied, but the proportion of SPMS patients with an EDSS 6 and above using DMTs was not provided. The ESC considered these data would be informative, however the pre-PBAC response stated that the sponsor does not have access to DMT usage data split by EDSS.

5.6 The ESC acknowledged that [redacted] ([redacted]%) of the Australian SPMS patients had an EDSS of 6 and above and thus there may be use of DMTs in SPMS patients with an EDSS of 6 and above, but there were also some who were not using a DMT, where the ESC considered BSC would be the appropriate comparator.

5.7 The ESC further considered that the cost-effectiveness of DMTs, including siponimod, in patients with an EDSS score of 3.5-5.5 was not likely to be transferable to patients with higher EDSS scores.

5.8 In the context of the cost minimisation approach taken by the resubmission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy.

5.9 For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: interferon beta[s], glatiramer acetate, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, ocrelizumab and cladribine.

5.10 Fingolimod and natalizumab were recommended on a cost-effectiveness basis compared with interferon beta-1a and interferon beta-1b, respectively. Ocrelizumab and cladribine were listed on a cost minimisation basis with fingolimod and

alemtuzumab was listed on a cost minimisation basis with both fingolimod and natalizumab. The PBAC was satisfied that siponimod provides, for some patients, a significant improvement in effectiveness and safety over interferon beta for the purposes of Section 101 (3B) of the *National Health Act 1953.* The PBAC noted that, based on the pricing approach proposed in the resubmission and pre-PBAC response, the cost of siponimod would be less than that of fingolimod and treatments that have been listed on a cost-minimisation basis versus fingolimod.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), and the Australian and New Zealand Association of Neurologists (ANZAN) via the Consumer Comments facility on the PBS website. The comments from ANZAN supported the listing of siponimod for patients with relapsing forms of MS with an EDSS of up to 6.5. ANZAN also noted that, while the safety profile of siponimod appears similar to that of fingolimod, the titrated starting dose with siponimod avoids the bradycardia (and consequent first dose monitoring) seen with fingolimod. Comments from patients described the importance of having effective treatments for SPMS for when their condition progresses.

Clinical trials

6.3 The resubmission was based on the following trials:

- EXPAND (N=1,651), a multicentre, randomised, double-blind, parallel-group, placebo controlled variable treatment duration study evaluating the efficacy and safety of siponimod in patients with SPMS. In the Core part of the trial, eligible patients were randomised (2:1) to receive either siponimod 2 mg or placebo. The duration of the Core part was event-driven and terminated when a pre-defined number of confirmed disability progression (CDP) events had occurred. If patients had CDP confirmed over a 6 month period (6-month CDP) they could elect to stay on blinded treatment, or switch to open-label siponimod or another DMT. This trial was considered by the PBAC as part of the previous siponimod submission.
- BOLD, a randomised, double-blind, placebo controlled, multicentre, adaptive dose-ranging study (N=275) in patients with RRMS. This trial has not been previously considered by the PBAC.
- FREEDOMS I (N=1,272), a 24-month randomised, multicentre, placebo-controlled, parallel group study designed to evaluate the efficacy, safety, and tolerability of two doses of fingolimod (1.25 mg and 0.5 mg) compared with placebo.

- FREEDOMS II (N=1,083), similarly designed to FREEDOMS I except it was conducted predominantly in the USA (101 of 117 centres), incorporating FDA requirements that were not included in FREEDOMS I, such as Holter monitoring.

Although not considered in the previous siponimod submission, FREEDOMS I and/or II have previously been considered in submissions for fingolimod (March 2011), alemtuzumab (July 2014) and cladribine (July 2018).

6.4 Details of the trials presented in the resubmission are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
STUDY 2304 (EXPAND)	CBAF312A2304. A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of Siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312.	21 February 2018
	Kappos L, Bar-Or A, Cree B, Fox R, Giovannoni G, Gold R, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study.	*Lancet* 2018; 391: 1263-1273
STUDY 2201 (BOLD)	CBAF312A2201. A phase II, double-blind, randomized, multi-center, adaptive dose-ranging, placebo-controlled, parallel-group study evaluating safety, tolerability and efficacy on MRI lesion parameters and determining the dose response curve of BAF312 given orally once daily in patients with relapsing remitting multiple sclerosis.	*CSR* 2012
	Selmaj, K., et al.) Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study.	*The Lancet Neurology* 2013; 12(8): 756-767
FREEDOMS I	FTY720D2301. A 24-month double-blind, randomized, multicenter, placebo controlled, parallel-group study comparing the efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis.	*CSR*
	Kappos, L., et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis.	*NEJM* 2010; 362(5): 387-401.
FREEDOMS II	FTY720D2309. A 24-month double-blind, randomized, multicenter, placebo controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis.	January 2012
	Calabresi, P. A., et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial.	*The Lancet Neurology* 2014; 13 (6): 545-556

Source: Table 2.7, p52-57 and Table 2.8, pp 58-59 of the resubmission.

6.5 The key features of the included evidence are summarised in Table 4.

Table 4: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Siponimod versus placebo					
EXPAND	1651	R, MC, DB 36 months	Unknown	SPMS	CDP-24; CDP 12; ARR; % relapse free
BOLD	275	R, DB, MC AD, 6 months	Low	RRMS	CUAL-3 months: ARR; % relapse free
Fingolimod vs placebo					
FREEDOMS I	1250	R, MC 24 months	High	RRMS	CDP-24; CDP 12; ARR; % relapse free
FREEDOMS II	1083	R, MC 24 months	High	RRMS	CDP-24; CDP 12; ARR; % relapse free

Source: pp61-114 of the resubmission.
AD = Adaptive dosing; ARR = annualised relapse rate. DB = double blind; CDP = confirmed disability progression CUAL = combined unique active lesions; MC = multi-centre; R = randomised; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

6.6 Enrolment in the EXPAND trial was predicated on investigator attestation that a patient had at least 6 months of progressive increase in disability in the absence of, or independent of, relapses; these attestations were not collected at several study sites. Clinical experts and the FDA noted that this left open the possibility for misclassification of some patients.

6.7 The FDA's evaluation of siponimod noted a "dual database access issue" that may have resulted in the unblinding of several participants. The PSCR acknowledged this issue, and presented a sensitivity analysis which examined the impact of excluding all data from affected participants, which increased the hazard ratio for the 3-month CDP outcome from 0.79 (95% CI 0.65, 0.95) to 0.80 (95% CI 0.66, 0.97). The ESC was satisfied this 'dual database access issue' was unlikely to affect the validity of the outcomes of the EXPAND trial.

6.8 Table 5 presents a brief summary of the trial populations.

Table 5: Summary of trial populations

	EXPAND	BOLD	FREEDOMS	
			I	II
Key inclusion criteria				
Age	Aged 18 to 60 years (inclusive)	Aged 18 to 55 years (inclusive)		
Disease diagnosis	Prior history of relapsing-remitting MS (RRMS) (2010 Revised McDonald criteria, Polman et al 2011). Secondary progressive course[a]	A diagnosis of MS as defined by Revised McDonald criteria (Polman et al 2011) A relapse remitting disease course[c]	A diagnosis of MS as defined by McDonald criteria (2005) A relapse remitting disease course[d]	
EDSS	EDSS score of 3.0 to 6.5 (inclusive).[b]	EDSS score of 0 to 5.0 (inclusive).	EDSS score of 0 to 5.5 (inclusive).	
Key baseline characteristics[e]				
Mean Age, years	48.0	36.3	36.9	40.4
Mean time since MS diagnosis, years	12.6	4.4	5.0	6.1
Mean relapses in last 2 years	0.7	2.0	2.1	2.2
Mean EDSS	5.4	2.4	2.4	2.4
Trial duration				
Max follow-up, months for outcomes included in indirect comparison	36	6	24	24

Tables 2.13 - 2.20, pp77-91 of the resubmission. EDSS = expanded disability status scale; MS = multiple sclerosis

[a] defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of, relapses (confirmed by investigator at least 6 months prior to enrolment).

[b] in EXPANDS, EDSS inclusion criteria stated " Documented EDSS progression in the 2 years prior to study - ≥1 point for patients with EDSS <6.0, and ≥0.5 point for patients with EDSS ≥6.0 (If documented EDSS scores not available, a written summary of the clinical evidence of disability progression in the previous 2 years, and retrospective assessment of EDSS score from data up to 2 years prior to screening had to be submitted for central review)"

[c] with: At least 1 documented relapse during the previous year, or 2 documented relapses during the previous 2 years, or a positive Gd-enhanced MRI scan at screening (in case the first MRI scan obtained at screening was negative, a second scan could be obtained 1 month later)

[d] with at least 1 documented relapse during the previous year, or2 documented relapses during the previous 2 years

[e] means were calculated during evaluation by weighted average of mean the means of the trial arms.

6.9 The EXPAND trial (of siponimod versus placebo) and the FREEDOMS trials (of fingolimod versus placebo) included patients with different baseline characteristics; both relapse and progression outcomes are likely to be substantially affected by these differences.

6.10 The BOLD trial was a dose finding trial with a small sample size, and only a six month maximum duration of double-blind placebo controlled treatment in patients with RRMS. The BOLD trial was not designed to adequately assess the effectiveness of siponimod.

6.11 The FREEDOMS I and II trials included patients on a different part of the MS disability spectrum compared with the EXPAND trial (baseline EDSS of 0-5.5 compared to 3-6.5). Though the inclusion criteria appear to have substantial overlap in the EDSS criteria, the following differences prevent a reliable indirect comparison:

- Patients in the EXPAND trial had substantially higher EDSS scores at baseline than patients in the other trials and the definition of disability progression may not

measure comparable effect at different EDSS scores. Since the fingolimod trials did not recruit patients with EDSS scores higher than 5.5 at baseline, there is a potential for imbalance in the EDSS increases required to qualify for progression. The EDSS scale is non-linear, meaning that there is no equivalence between 0.5 or 1.0 point increases at different levels of the scale. Consequently, when trials have different EDSS populations (i.e. EXPAND and FREEDOMS I and II), the basis for establishing an equivalence in progression related outcomes, even when using the same disability outcome, is questionable.

- The pivotal EXPAND trial had a substantially lower average number of relapses in the previous two years at baseline than in the other trials making a comparison of ARR ratios between EXPAND and the fingolimod trials challenging to interpret.

Comparative effectiveness

6.12 The resubmission presented the results of the EXPAND trial, unchanged from the previous submission, as well as results from the BOLD and the FREEDOMS I and II trials. The resubmission then conducted an indirect comparison of siponimod and fingolimod informed by the included trials.

6.13 Table 6 presents results of 3/6 month CDP in the included evidence. For the indirect comparisons, an odds ratio <1 favours siponimod.

Table 6: Results of 3-month and 6-month CDP in the included evidence

	DMT, n/N (%)	Placebo, n/N (%)	Odds ratio (95% CI)
3-month CDP			
EXPAND SIP vs PBO (SPMS; EDSS 3.0-6.5)	288/1096 (26.3)	173/545 (31.7)	**0.77 (0.61, 0.96)**
FREEDOMS I FIN vs PBO (RRMS, EDSS 0-5.5)	62/421 (14.7)	89/415 (21.4)	**0.63 (0.44, 0.90)**
FREEDOMS II FIN vs PBO (RRMS, EDSS 0-5.5)	71/357 (19.9)	84/353 (23.8)	0.79 (0.56, 01.14)
FREEDOMS I/II FIN vs PBO (RRMS, EDSS 0-5.5)	133/778 (17.1)	173/768 (22.5)	**0.71 (0.55, 0.91)**
Indirect[a], EXPAND vs FREEDOM I/II (36 vs 24 months)			1.085 (0.773, 1.522)
6-month CDP			
EXPAND SIP vs PBO (SPMS; EDSS 3.0-6.5)	218/1096 (19.9)	139/545 (25.5)	**0.73 (0.57, 0.92)**
FREEDOMS I FIN vs PBO (RRMS, EDSS 0-5.5)	42/421 (10.0)	69/415 (16.6)	**0.56 (0.37, 0.84)**
FREEDOMS II FIN vs PBO (RRMS, EDSS 0-5.5)	35/357 (9.8)	49/353 (13.9)	0.67 (0.43, 1.07)
FREEDOMS I/II FIN vs PBO (RRMS, EDSS 0-5.5)	77/778 (9.9)	118/768 (15.4)	**0.61 (0.45, 0.82)**
Indirect[a], EXPAND vs FREEDOM I/II (36 vs 24 months)			1.197 (0.815, 1.757)

Source: Table 2.32 and 2.33, p119 and p121, Table 2.56, p146 and Table 2.60, p150 of the resubmission.

CDP=confirmed disability progression; CI=confidence interval; EDSS = Expanded Disability Status Scale; FIN = fingolimod; n=number of subjects with events; N=number of subjects in the analysis; OR=odds ratio; RRMS = relapsing-remitting multiple sclerosis; SIP = siponimod; SPMS = secondary progressive multiple sclerosis

Bold typography indicates statistically significant differences between groups

[a] Indirect comparison via Bucher's method

6.14 The ARR results are shown in Table 7.

Table 7: Results of annualised relapse rate in the included evidence

	DMT, ARR (95% CI)	Placebo, ARR (95% CI)	ARR ratio (95% CI)
EXPAND SIP vs PBO (SPMS; EDSS 3.0-6.5)	0.071 (0.055, 0.092)	0.160 (0.123, 0.207)	**0.445 (0.337, 0.587)**
BOLD SIP vs PBO (RRMS; EDSS 0-5.0)	0.20 (0.081,0.478)	0.580 (0.337,1.002)	**0.340 (0.121, 0.956)**
FREEDOMS I FIN vs PBO (RRMS, EDSS 0-5.5)	0.211 (0.178, 0.250)	0.469 (0.412, 0.533)	**0.450 (0.365, 0.556)**
FREEDOMS II FIN vs PBO (RRMS, EDSS 0-5.5)	0.204 (0.168, 0.249)	0.394 (0.336, 0.462)	**0.519 (0.404, 0.667)**
FREEDOMS I/II FIN vs PBO (RRMS, EDSS 0-5.5)	0.209 (0.184, 0.2380	0.438 (0.396, 0.485)	**0.477 (0.406, 0.561)**
Indirect[a], EXPAND vs FREEDOM I/II (36 vs 24 months)			0.713 (0.250, 2.029)
Indirect[a], BOLD vs FREEDOM I/II (6 vs 24 months)			0.933 (0.677, 1.286)

Source: Table 2.26, p114 and Table 2.27, p115, Table 2.54, p144 and Table 2.58, p149 of the resubmission
ARR=annualised relapse rate; CI=confidence interval; EDSS = Expanded Disability Status Scale; FIN = fingolimod; n=overall number of relapses in the analysis period for all subjects; N=number of subjects in the analysis; OR=odds ratio; RRMS = relapsing-remitting multiple sclerosis; SIP = siponimod; SPMS = secondary progressive multiple sclerosis
[a] Indirect comparison via Bucher's method
Bold typography indicates statistically significant differences between groups

6.15 Table 8 presents pooled results for proportion of patients remaining relapse-free.

Table 8: Proportion relapse-free in the included evidence

	DMT, n/N (%)	Placebo, n/N (%)	Odds ratio (95% CI)
EXPAND SIP vs PBO (SPMS; EDSS 3.0-6.5), 36 months	986/1099 (89.7)	444/546 (81.3)	**2.00 (1.50, 2.68)**
BOLD SIP vs PBO (RRMS; EDSS 0-5.0), 6 months	45[a]/49 (92.0)	32[a]/45 (72.0)	**4.12 (1.33, 14.68)[b]**
FREEDOMS I FIN vs PBO (RRMS, EDSS 0-5.5), 24 months	299/425 (70.4)	191/418 (45.7)	**2.82 (2.12, 3.74)**
FREEDOMS II FIN vs PBO (RRMS, EDSS 0-5.5), 24 months	256/358 (71.5)	187/355 (52.7)	**2.25 (1.65, 3.07)**
FREEDOMS I/II FIN vs PBO (RRMS, EDSS 0-5.5)	555/783 (70.9)	373/773 (48.3)	**2.54 (2.05, 3.17)**
Indirect[c], EXPAND vs FREEDOM I/II (36 vs 24 months)			0.787 (0.548,1.132)
Indirect[c], BOLD vs FREEDOM I/II (6 vs 24 months)			1.622 (0.478, 5.500)

Source: Tables 2.30 and 2.31, p118, Table 2.55, p145 and Table 2.59, p149 of the resubmission
CI=confidence interval; EDSS = Expanded Disability Status Scale; FIN = fingolimod; n=overall number of relapses in the analysis period for all subjects; N=number of subjects in the analysis; OR=odds ratio; RRMS = relapsing-remitting multiple sclerosis; SIP = siponimod; SPMS = secondary progressive multiple sclerosis
[a] back calculated during the evaluation from the percentage and the sample size.
[b] For BOLD, pairwise comparison of treatments to placebo are based on odds ratios estimated from a logistic regression model adjusted for treatment group and using number of relapses in the previous 2 years as a covariate. Proportions estimated from the logistic regression model
[c] Indirect comparison via Bucher's method
Bold typography indicates statistically significant differences between groups.

6.16 The resubmission stated that the indirect comparison of siponimod and fingolimod was undertaken at the request of the PBAC in response to views from various stakeholders (PBAC, ESC, clinicians group [ANZAN] and health practitioners) that recognise MS as a single disease across a spectrum (PPMS Stakeholder meeting – outcome statement, Nov 2018).

6.17 The indirect comparisons of the EXPAND trial versus the FREEDOMS trials had substantial exchangeability issues (see Table 5). Key differences between EXPAND and the other trials were: baseline EDSS, age, time since diagnosis, number of relapses in

the past two years, and proportion of female patients. All of these differences would be expected to affect results of an indirect comparison. Additionally, there were differences in treatment duration (24 months in FREEDOMS I and II versus 36 months in EXPAND) that could affect the indirect comparison.

6.18 During the evaluation, it was noted that the Institute for Clinical and Effectiveness Research (ICER) report on siponimod (2019 p30) had considered that, in the EXPAND trial, subgroups defined by the presence or absence of gadolinium-enhancing lesions and by the presence or absence of relapses in the prior two years (both associated with disease activity) were not statistically significantly different from each other, although in both cases the point estimates for CDP were more favourable in patients with active disease (HRs 0.64 vs 0.82 and 0.67 vs. 0.87, respectively). The report also noted that post-hoc analyses using three different methods to control for the confounding impact of on-study relapses suggested a smaller but relatively consistent risk reduction amongst non-relapsing groups for disability progression with siponimod. The report also referred to FDA analyses in subgroups with non-active disease (e.g., patients who did not relapse in the two years prior to or during the study). The FDA concluded that these analyses supported the hypothesis that the delay in 3-month CDP was more clearly related to the anti-inflammatory effect of siponimod (yielding a significant treatment effect on the relapsing or active aspect of the disease) than to an effect on the poorly understood degenerative component of the disease.

6.19 The PSCR included the results of post-hoc analyses of the EXPAND trials for time to sustained deterioration to EDSS ≥ 7.0 and subgroup analyses by EDSS for cortical grey matter atrophy.

6.20 Though the resubmission used results from the BOLD trial to conduct indirect comparisons between more similar trial populations in ARR rate and in proportion of patients remaining relapse-free, the BOLD trial was designed as a dose finding study, and consequently had small patient numbers and only had 6 months of placebo controlled treatment versus 24 months in the fingolimod trials. The ARR ratio versus placebo had a wide confidence interval with an upper bounds approaching 1 (0.956) making it unreasonable to claim non-inferiority to fingolimod based on this indirect comparison. The comparison of patients remaining relapse-free at different endpoints (6 months in BOLD and 24 months in FREEDOMS I and II), was not easily interpretable. Additionally, the indirect comparison of the proportion of patients remaining relapse-free between BOLD and FREEDOMS I and II would be expected to be biased against the treatment with the longer treatment duration (fingolimod in FREEDOMS I and II).

6.21 The ESC considered that ideally the indirect comparisons would have matched based on EDSS, however the substantial transitivity issues between the siponimod and fingolimod trials, which resulted from them enrolling patients at fundamentally different parts of the disease trajectory, could not be overcome. The ESC noted these differences impacted on the outcomes measured given expected differences in the number of relapses and nature of the progression.

6.22 The PSCR argued that while the fingolimod trials did not include patients with EDSS of 6.0 or more, real world registry data from the MSBase database suggest approximately [redacted]% of patients at this level of disability are treated with a DMT, and as such there is already use in this population where cost-effectiveness has not been established. The ESC noted [redacted]% of SPMS patients, rather than SPMS patients with EDSS of 6 or more, were treated with a DMT in the MSBase database. The PSCR further argued that listing siponimod at a similar price to fingolimod would allow the realisation of an opportunity benefit in moving use of DMTs with unknown cost-effectiveness to a treatment with a known benefit in patients with an EDSS 6.0 or more at no additional cost. The ESC noted the cost-effectiveness of DMTs in these patients with higher levels of disability and less active disease was unknown, however based on the subgroup analyses of the EXPAND trial, siponimod was likely to be less cost-effective in these patients given the apparent reduced efficacy. The ESC therefore considered the current fingolimod price may not be justified in the proposed expanded population.

6.23 The PSCR included the results of a matching adjusted indirect comparison (MAIC) comparing siponimod with interferon (Samjoo et al 2020)[1] as evidence of the superiority of siponimod to interferon beta with respect to time to confirmed disability progression at 6 months (interferon beta-1a HR 0.43, 95% CI: 0.20, 0.93; interferon beta-1b HR 0.55, 95% CI: 0.33, 0.91). However, the ESC noted that in this study there was no statistically significant difference in the Annualised Relapse Rates (ARR) between siponimod and interferon beta-1b (RR 0.90, 95% CI: 0. 51, 1.59). Overall, the PBAC was satisfied that siponimod provides, for some patients, a significant improvement in effectiveness and safety over interferon beta.

Comparative harms

6.24 Table 9 presents key safety outcomes identified by the PBAC (i.e. any AEs, bradycardia, hypertension, nausea and liver function) at the November PBAC meeting for siponimod (paragraph 6.20, siponimod, PBAC PSD, November 2019) and an indirect comparison with fingolimod for these events.

[1] Samjoo IA, Worthington E, Haltner A, et al. Matching-adjusted indirect treatment comparison of siponimod and other disease modifying treatments in secondary progressive multiple sclerosis. Curr Med Res Opin. 2020; 36(7):1157-1166.

Table 9: **Indirect comparison – siponimod (EXPAND) vs fingolimod (FREEDOMS I/II) – key safety outcomes**

Adverse event	Siponimod 2mg			Fingolimod 0.5mg			Indirect effect OR (95% CI)[a] p value
	SIP n/N (%)	PBO n/N (%)	OR (95%CI)	FIN n/N (%)	PBO n/N (%)	OR (95%CI)	
Any AE	975/1099 (88.7)	445/546 (81.5)	**1.78 (1.34, 2.37)**	751/783 (95.9)	730/773 (94.4)	1.39 (0.87,2.22)	1.281 (0.740, 2.216) p=0.38
Bradycardia	50/1099 (4.5)	14/546 (2.6)	1.81 (0.99, 3.31)	8/783 (1.0)	5/773 (0.6)	1.57 (0.50,4.90)	1.153 (0.317, 4.192) p=0.83
Hypertension	115/1099 (10.5)	41/546 (7.5)	1.44 (0.99, 2.09)	24/783 (3.1)	6/773 (0.8)	**4.03 (1.64,9.93)**	**0.357 (0.135, 0.947) p=0.04**
Nausea	74/1099 (6.7)	19/546 (3.5)	**2.00 (1.20, 3.35)**	41/783 (5.2)	32/773 (4.1)	1.28 (0.60,2.72)	1.563 (0.627, 3.896) p=0.34
Raised LFTs	108/1099 (9.8)	14/546 (2.6)	**4.14 (2.35, 7.30)**	123/783 (15.7)	32/773 (4.1)	**4.46 (2.29,8.66)**	0.928 (0.387, 2.224) p=0.87

Source: Table 2.61, p152 of the resubmission.
CI=confidence interval, FIN=fingolimod, OR=odds ratio, PBO=placebo, SIP=siponimod
Bold typography indicates statistically significant differences between groups
[a] Indirect comparison via Bucher's method

6.25 Siponimod and fingolimod were associated with a statistically significant increase in abnormal liver function results compared to placebo (OR=4.14, 95%CI 2.35, 7.30 and OR=4.46, 95% CI 2.29, 8.66). There were no statistically significant differences between siponimod and fingolimod for any AE, bradycardia or raised LFTs. Siponimod appeared to be associated with less hypertension compared to fingolimod (OR=0.350, 95% CI: 0.135, 0.947), though differences in placebo preclude a conclusion of comparative safety.

Clinical claim

6.26 The resubmission stated siponimod was non-inferior to fingolimod with respect to efficacy and safety in patients with relapse-onset MS, including patients with the 'highest unmet need' (equivalent EDSS up to and including 6.5).

6.27 The resubmission's clinical claim could be considered to encompass three sub populations, or three portions of the relapsing MS spectrum: (1) the higher disability end of the spectrum (consistent with EDSS 6.0-6.5), which the resubmission referred to as 'highest unmet need population'; (2) the lower end of the disability spectrum (consistent with EDSS 0-2.5); and (3) the patients in between (EDSS 3.0-5.5).

6.28 For the higher end of the spectrum, the comparator trials of fingolimod versus placebo (FREEDOMS I and II) included only RRMS patients with a maximum EDSS score at baseline of 5.5), noting the exclusion of high EDSS population (EDSS 6.0-6.5). Because there was no evidence for fingolimod in this high EDSS population the ESC considered the indirect comparisons were uninformative for evaluating a clinical claim for siponimod versus fingolimod in this population.

6.29 For the lower end of the spectrum, the pivotal EXPAND trial did not include less progressed patients (EDSS 0-2.5). Though the BOLD trial included patients in this EDSS range, the ARR ratio estimates versus placebo had a wide confidence interval approaching 1, and so could not reasonably claim non-inferiority to fingolimod based on this comparison. Consequently, the ESC considered no reasonable claim can be

made for this sub-population, and considered that this concern could be addressed by amending the requested restriction to exclude less progressed patients. In the PSCR it was noted that the sponsor would agree to restriction criteria that would limit use to patients with disability that was equivalent to an EDSS of at least 3.0, if requested by the PBAC.

6.30 Lastly, in patients with disability consistent with EDSS 3.0-5.5, both the EXPAND and the FREEDOMS I and II trials included this population, and each trial supported that the intervention was superior in efficacy to placebo. However, because the trials include other, differing parts of the MS disease spectrum, the 'average' patient in EXPAND and FREEDOMS I and II were substantially different, and the resulting indirect comparisons had critical issues. The ESC considered there were substantial exchangeability issues with the EXPAND and FREEDOMS trials in this population, and comparing EDSS-based progression between two populations with markedly different average EDSS scores at baseline was not considered valid. The ESC considered the clinical claim of non-inferior efficacy for this population to be highly uncertain.

6.31 The PBAC considered that the claim of non-inferior comparative effectiveness to fingolimod was likely to be reasonable, however considered there was residual uncertainty due to the exchangeability issues with the clinical trials.

6.32 The PBAC considered that the claim of non-inferior comparative safety to fingolimod was reasonable.

Economic analysis

6.33 The resubmission presented a cost minimisation analysis against fingolimod. In the previous submission, a cost utility analysis was presented against placebo and versus interferon-beta/glatiramer acetate; and siponimod versus natalizumab.

6.34 The equi-effective doses were estimated as siponimod 2 mg daily and fingolimod 0.5 mg daily.

6.35 The resubmission did not state the proposed equi-effective doses for the siponimod 1 mg daily maintenance dose (administered as 4*0.25mg tablets), but requested a price for 120 tablets (which provides 30 days of treatment) that was equal to the price of 28 * 2 mg tablets (which provides 28 days of treatment).

6.36 Table 10 presents the results of a cost minimisation analysis presented in the resubmission. Because both siponimod and fingolimod are daily tablets with equivalent pack sizes and maximum quantities, a side-by-side comparison of the requested siponimod price and the fingolimod price was presented.

Table 10: **Results of the cost minimisation analysis** [a]

Drug, strength & form	Max quantity	Pricing status	AEMP
Fingolimod 0.25mg capsule	28	Effective	$ [redacted]
Fingolimod 0.5mg capsule	28	Effective	$ [redacted]
Fingolimod 0.5mg capsule	28	Effective, net of SPA & [redacted]*	$ [redacted]
Siponimod 0.25mg tablet	12	Effective[b]	$ [redacted]
Siponimod 0.25mg tablet	120	Effective[b]	$ [redacted]
Siponimod 2mg tablet	28	Effective[b]	$ [redacted]

Source Tables 3.2 and 3.3, pp172-173 of the resubmission.

AEMP = Australian ex-manufacturer price; DPMQ = dispensed price per maximum quantity; PTP = price to pharmacist

* Effective price net of SPA and SC rebates at [redacted]; **Pricing as of Feb 2020

[a] Special Pricing Arrangement (SPA) is requested for listing siponimod on the PBS – to be discussed with the Pricing Section following PBAC recommendation. Note that the proposed Published price of siponimod 0.25mg*120 and 2mg*28 is the same as that for fingolimod 0.25mg*28 and 0.5 mg*28 as at 1 February 2020.

[b] The proposed Effective price is equivalent to the fingolimod price after the SPA and subsidisation cap (SC) rebates, and is lower than that proposed in the original submission

6.37 The resubmission proposed that the effective price of fingolimod [redacted], the price reduction required is estimated at [redacted]%. The PBAC considered the [redacted] would be more appropriate to use in the cost-minimisation analysis versus fingolimod.

6.38 The cost minimisation analysis presented in the submission was based on claim of non-inferiority which the ESC considered was not well supported by the clinical evidence presented.

6.39 As previously noted, the majority of the financial impact in the resubmission's financial estimates was in the patient population with higher EDSS disability. The ESC considered that a cost minimisation price against fingolimod was unlikely to be appropriate in this population. The ESC considered siponimod is likely to be less cost effective in the expanded population given the apparent reduced efficacy when used to treat less active disease, and hence a price equivalent to that of fingolimod may not be justified in the expanded population.

6.40 The pre-PBAC response offered a reduced price for siponimod based on a weighted cost minimisation approach, with the fingolimod price to apply for the proportion of use that would replace fingolimod and other DMTs (≤ EDSS 5.5); and for the interferon beta price (weighted for use of its four forms) to apply for use in patients with EDSS ≥ 6.0 where cost-effectiveness was uncertain. The pre-PBAC response stated that interferon beta represents the 'minimum value' in patients with EDSS ≥ 6.0 treated and untreated. However, the weighted proportions only appeared to be applied to the group of patients with EDSS ≥ 6.0 who are currently untreated.

6.41 The Sponsor proposed a weighting of [redacted]% to the price of fingolimod and [redacted]% to the price of interferon beta, based on Years 5 and 6 of the revised utilisation estimates. The resulting proposed weighted AEMP is presented in the table below.

Table 11: Summary of the weighted pricing approach proposed in the pre-PBAC response

Population	Comparator/basis for pricing offer	Weight (relative utilisation)	Price (AEMP)
Patients currently on a DMT	fingolimod	[redacted]	$[redacted]
Patients not currently on a DMT with EDSS ≥ 6 [a]	interferon beta	[redacted]	$[redacted]
Weighted AEMP			$[redacted] [b]

Source: Table 1 of the Pre-PBAC Response and Attachment 17 Revised Utilisation and Financial Estimates
[a] The pre-PBAC response stated this was the 'High Unmet Need group (treated and untreated)' group but, in the spreadsheet provided, the interferon beta price was only applied to patients not currently on a DMT with EDSS ≥ 6.
[b] Proposed AEMP for the 2 mg and 0.25 mg maintenance packs.

Drug cost/patient/year

Table 12: Drug cost per patient for siponimod and fingolimod (pre-PBAC response)

	Siponimod Trial dose	Siponimod Financial estimates	Fingolimod Trial dose	Fingolimod Financial estimates
Mean dose	2 mg	2 mg	0.5 mg	0.5 mg
Cost/patient/year	$[redacted]	$[redacted]	$[redacted] [a]	$[redacted] [a]

Source: Tables 3.2 and 3.3, pp172-173 of the resubmission, and the revised financial estimates spreadsheet provided in the pre-PBAC response.
[a] Including the rebate of approximately [redacted]% to account for the RSA rebate, as proposed in the resubmission. Using the effective price of fingolimod would result in a cost/patient/year of $[redacted]

6.42 The cost of siponimod per year is $[redacted], representing 13.04 packs per year with a requested effective DPMQ of $[redacted] proposed in the Pre-PBAC Response. Treatment is ongoing until a patient no longer satisfies the criteria in the PBS restrictions for continuing treatment. The cost per patient per year was reduced from $[redacted] in the previous submission and $[redacted] in the resubmission base case.

Estimated PBS usage & financial implications

6.43 This resubmission was not considered by DUSC. The resubmission took an epidemiological approach to estimate the financial impact of patients receiving siponimod who would not otherwise have been treated with a PBS-listed DMT and a market share approach to estimate the financial impact in patients who would be treated with an RRMS DMT. Overall, given the challenges in diagnosing SPMS, the financial estimates were highly uncertain.

6.44 The Pre-PBAC Response included revised utilisation and financial estimates in response to the ESC Advice and due to the revised weighted cost minimisation analysis approach proposed. Table 13 presents key inputs for the financial estimates, updated with changes proposed in the Pre-PBAC Response.

Table 13: Key inputs for financial estimates including Pre-PBAC Response updates

Parameter	Value applied and source	Comment
% patients in (EDSS 6.0/6.5)	The EDSS distribution for the whole MS population, and the proportion of patients EDSS 6.0 and above was sourced from the Global MSBase registry. The proportion of patients EDSS 6.0 and above was **19.61%** (excluding EDSS 10). Pre-PBAC Response: Updated to 18.35% to include only patients between EDSS 6.0-8.0.	Given the difficulty in diagnosing SPMS, the SPMS population who are not currently receiving treatment remains uncertain. The estimate of 19.61% was based on patients with an EDSS of 6.0 and above. However, patients with EDSS 6.0 and 6.5 (consistent with listing and evidence) would be 11.9%. The ESC agreed with the commentary and considered using the proportion of patients only in EDSS 6.0-6.5 was appropriate.
% patients with EDSS 6.0/6.5 treated with a DMT	[redacted]% based on the [redacted]% from MSBase patient cohort (Australian set). Pre-PBAC Response: Uses the [redacted]% value from MS Base Australian registry data.	
Uptake Epi approach	**Uptake** **Year** / **2021** / **2022** / **2023** / **2024** / **2025** / **2026** Resubmission: [redacted]% / [redacted]% / [redacted]% / [redacted]% / [redacted]% / [redacted]% Previous sub (untreated): [redacted]% / [redacted]% / [redacted]% / [redacted]% / [redacted]% / [redacted]% Source: p182-183 of the resubmission. In its previous consideration, the PBAC noted that DUSC considered the uptake rate applied to untreated MS patients in Year 1 in the original submission ([redacted]%) to be low and that the rate to likely to be "much higher in Year 1 as there are little to no other treatment options" (paragraph 6.54, siponimod, PBAC PSD November 2019). The resubmission considered that these patients are not routinely visiting a neurologist, and may not even have a relationship with a neurologist, so mobilising them to seek treatment is likely to be a lengthy process.	In relation to the previous submission, DUSC considered that, in the untreated population the uptake is likely be to be much higher than [redacted]% in Year 1 as there are little to no other treatment options (p1, Siponimod DUSC advice, November 2019).
Persistence to siponimod	**Proportion of siponimod patients remaining on treatment** **Year** / **2021** / **2022** / **2023** / **2024** / **2025** / **2026** Continuation rates: 0.723 / 0.64 / 0.591 / 0.556 / 0.53 / 0.508 Source: Table 4.9, p185 of the resubmission. The resubmission used a 10% PBS Sample to extrapolate persistence of fingolimod. Fingolimod was considered a viable proxy for estimating persistence to siponimod in untreated siponimod population as they are pharmaceutical analogues. No adjustment was made for persistence and compliance in the market share section of the model. It was assumed that currently, observed persistence and compliance to other DMTs will also apply to siponimod. This assumption may lead to a slight overestimate of siponimod scripts where they replace cladribine and alemtuzumab which are annual treatments and are therefore likely to have higher compliance than a daily therapy.	In relation to the previous submission, DUSC considered that the assumptions that the treatment persistence of siponimod would be the same as fingolimod for the RRMS population were not adequately justified (p1, Siponimod DUSC advice, November 2019). The resubmission did not address this.
% scripts replaced by siponimod	**Proportion of DMT scripts replaced by siponimod** **Year** / **2021** / **2022** / **2023** / **2024** / **2025** / **2026** all RRMS DMTs: [redacted]% / [redacted]% / [redacted]% / [redacted]% / [redacted]% / [redacted]%	The ESC considered an analysis of the proportion of patients using DMTs by EDSS score would help inform the EDSS

Parameter	Value applied and source	Comment
	Exception: Cladribine, alemtuzumab [redacted]% [redacted]% [redacted]% [redacted]% [redacted]% [redacted]% Source: p188 of the resubmission The resubmission considered that for many reasons, it is likely that uptake of siponimod in patients already treated with a DMT will be low and gradual due to: difficulty in switching within this group of drugs, interval between neurologist appointments, genotype testing needed prior to treatment with siponimod, the number of PBS-listed options for treatment of RRMS. The resubmission noted that cladribine and alemtuzumab had lower market uptake in Year 2 as a result of their infrequent dosing regimen.	6.0/6.5 DMT-treated estimates. The pre-PBAC response stated that the sponsor does not have access to DMT usage data split by EDSS.
Proposed price (Pre-PBAC Response)	Effective DPMQ for maintenance pack reduced to $[redacted] (AEMP $[redacted]) and for titration pack to $[redacted] (AEMP $[redacted]), based on the weighted CMA with proportional split of [redacted] (fingolimod:IFN beta) using years 5 and 6 of the utilisation estimates.	

Source: p177-202 of the resubmission and Attachment 17 of the resubmission.

CMA = cost minimisation analysis; DMT = disease modifying treatment; DPMQ dispensed price per maximum quantity; DUSC = Drug Utilisation sub-committee; EDSS = Expanded Disability Status Scale; MBS = Medicare Benefits Schedule; MS = multiple sclerosis; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

6.45 Table 14 presents estimated use and financial implications, updated with revised assumptions from the Pre-PBAC Response.

Table 14: Estimated use and financial implications (Pre-PBAC Response)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated (epi segment only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patient treated (market share segment)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed (epi approach segment) [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed (market share segment) [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of siponimod						
Net cost in epi segment (EDSS 6.0-8.0)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to in market share segment	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for replaced RRMS DMTs						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to Government	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
July 2019 submission base case						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Previous submission November 2019						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Revised financial estimates spreadsheet provided with the pre-PBAC response: Attachment 17 – Section 4 Utilisation and Financial Estimates (Pre-PBAC Response), Sheet 'PBS-RPBS Overview EFF'

6.46 The total net cost to the PBS/RPBS of listing siponimod (including offsets) was estimated to be $10 - $20 million in Year 1 increasing to $10 - $20 million in Year 6, and a total of $60 - $100 million in the first 6 years of listing. The total impact of siponimod (including offsets) in the market share segment over the first six years of listing was net cost saving versus $60 - $100 million in the epidemiological approach segment of the financial estimates.

6.47 Overall, despite the challenges associated with estimating use in MS patients not currently being treated with PBS listed DMTs, the commentary and the ESC considered that the net financial impact was likely overestimated for the following reasons:

- The resubmission applied an estimate that 19.1% of MS patients were EDSS of 6.0 and above. However, the commentary and the ESC considered that the estimate of 11.9% of patients with EDSS 6.0 and 6.5 was more consistent with the requested restriction and included evidence. The pre-PBAC response proposed changing this estimate to 18.35% to include patients in an EDSS range of 6.0-8.0. However, the PBAC agreed with the ESC and considered the proportion of MS patients between

EDSS 6.0 and 6.5 (11.9%) should be applied, in line with its view that PBS subsidised treatment should cease when patients have confirmed disability progression or become non-ambulatory.

- The resubmission estimated that [redacted]% of patients with EDSS 6.0 and above would be untreated with DMTs, in contrast to [redacted]% in the MSBase registry (Australian cohort, based on all EDSS levels). The ESC considered that this underestimated current use of DMTs and potential cost-offsets. The ESC noted that the MSBase analysis was based on clinician designated SPMS, which may be different from the requested listing which does not exclude RRMS patients. Though uncertain, the ESC considered it would be reasonable to assume that a greater number of patients would be on DMTs in a non-SPMS specific population. The PSCR noted the proportion untreated with DMTs varies by year and in Year Six is similar to the proportion of untreated patients from the MSBase registry ([redacted]%). The pre-PBAC response proposed changing the proportion of patients with EDSS ≥ 6.0 who are untreated with DMTs from [redacted]% to [redacted]%. However, the PBAC considered the MSBase database may potentially underestimate the proportion of patients who are currently untreated as participants are often recruited and followed opportunistically and a large proportion of patient interactions were associated with use or monitoring of DMTs. Further, the PBAC noted that the figure of [redacted]% was derived from all patients with clinician-designated SPMS regardless of EDSS level, despite this being applied as the proportion of patients with EDSS ≥ 6.0 who are untreated with DMTs. Overall, the PBAC considered that it was more reasonable to estimate that [redacted]% of patients with EDSS ≥ 6.0 are untreated with DMTs (per the submission).
- Continuation rates were based on continuation in RRMS at lower EDSS levels. DUSC previously stated that the assumptions that the treatment persistence of siponimod would be the same as fingolimod for the RRMS population were not adequately justified (p1, Siponimod DUSC advice, November 2019). The ESC considered that continuation rates would be expected to be substantially lower in the high EDSS population. However, the PBAC considered the assumption that siponimod continuation rates would be the same as current observed fingolimod persistence rates was reasonable as they are pharmacological analogues and have similar safety profiles.

6.48 In the market share approach, the resubmission assumed that the proportion of scripts replaced by siponimod would be [redacted]% in Year 1 increasing to [redacted]% in Years 4-6 for most RRMS DMTs (slightly lower rates were assumed in the first few years for cladribine, ocrelizumab and alemtuzumab). The pre-PBAC response stated that utilisation of siponimod in patients with EDSS < 3 'is unlikely to occur' (given the TGA registration is for SPMS) and the market uptake rates applied 'account for there being no usage in this population'. As patients with EDSS < 3 comprise around [redacted]% of the MS population, the pre-PBAC response argued that uptake rates should be doubled if patients with EDSS < 3 are excluded. As outlined above, the PBAC considered that the restriction should exclude use of siponimod in patients with EDSS < 3. The PBAC noted

that this would mean that the uptake /displacement rates in the 'revised' population (comprising patients with EDSS ≥ 3) would be [redacted]% in Year 6 (i.e. the submission and pre-PBAC response effectively assumed that in Year 6 siponimod would displace [redacted]% of the use of each of interferon, teriflunomide, alemtuzumab, cladribine, fingolimod, natalizumab and ocrelizumab in patients with EDSS ≥ 3). The PBAC considered this was unreasonably high given the number of DMTs available, and considered that a more reasonable estimate of the uptake/displacement in Year 6 would be [redacted]% (rather than [redacted]% as proposed in the pre-PBAC response).

6.49 The resubmission included less than 500 grandfather patients in the financial estimates. It was unclear what proportion of grandfather patients would fall within the requested restriction.

Financial Management – Risk Sharing Arrangements

6.50 The resubmission proposed to share the risk of the overall budget impact of a PBS listing for siponimod through a subsidisation cap and rebate arrangement to give the PBAC confidence in the budget estimates. The submission indicated a willingness from the sponsor to negotiate a rebate level above the expenditure caps proposed (which were based on the cost to the PBS/RPBS of siponimod without offsets for replaced DMTs), with relevant adjustments to the cap amount if a PBAC recommendation varies from the submission.

6.51 The resubmission stated "as the PBS population to be treated with siponimod differs from the population eligible for the current DMTs (by including patients with the highest unmet need, EDSS 6.0/6.5), the subsidisation caps should be unique to siponimod and based on the agreed estimates". Given the overlapping populations (e.g. the estimates include some uptake from DMTs currently listed for RRMS), adjustments would likely be required to the rebate arrangements for other DMTs to take into account reductions in the use of currently listed DMTs for RRMS.

6.52 The revised financial estimated proposed in the pre-PBAC response would lead to proposed subsidisation caps being different to those stated in the resubmission. The pre-PBAC response reiterated the Sponsor's willingness to enter into a risk sharing arrangement, with financial caps and rebate levels to be negotiated following a positive recommendation.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule, Authority Required (Streamlined) listing of siponimod for secondary progressive MS (SPMS). Among other matters, the recommendation was made on a cost minimisation basis versus fingolimod in the group of patients who would otherwise be treated with fingolimod. The PBAC considered the uncertainty associated with the cost-effectiveness of siponimod when used in a broader patient population than fingolimod was likely to be adequately

addressed with a reduced price, which was consistent with that of interferon beta, for this broader population. The PBAC considered that some of the assumptions applied in the pre-PBAC response's financials estimates were not reasonable and that adjustments would be required. The PBAC noted these adjustments would lead to a reduction in the proposed weighted price and the financial estimates.

7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of siponimod would be acceptable if it were cost-minimised against fingolimod in the group of patients who would otherwise be treated with fingolimod and if the following measures were implemented to contain risks associated with the cost of the drug to the PBS: the price should be equivalent to the cost of interferon beta in patients with EDSS ≥ 6 who are currently untreated, with the weighted price and a risk sharing arrangement based on the assumptions outlined below.

7.3 The equi-effective doses were estimated as follows for the group of patients who would otherwise be treated with fingolimod: siponimod 2 mg once daily is equi-effective to fingolimod 500 mcg once daily.

7.4 The PBAC acknowledged the high clinical need for effective therapies for patients with progressive forms of relapse-onset MS and for patients who are ambulant but require support (equivalent to EDSS 6.0-6.5).

7.5 The requested listing would permit use in patients with RRMS or SPMS. The PBAC noted that the key evidence for siponimod is in patients with SPMS, but considered that it may not be appropriate for the restriction to specifically exclude patients with RRMS given that it can be clinically difficult to determine when patients transition from RRMS to SPMS.

7.6 The PBAC considered that the restriction should exclude use of siponimod in patients with EDSS < 3 given the limited clinical evidence for siponimod in this patient population.

7.7 The requested listing included a continuation criterion 'patient must not show continuing progression of disability while on treatment with this drug' which aligns with that for existing RRMS DMT listings. The PBAC noted that this meant that the maximum level of disability at which a patient could use siponimod would be equivalent to an EDSS of 6.5 (i.e. for a patient commencing siponimod with EDSS 6.5, treatment must cease when the patient progresses to no longer being ambulant, or an EDSS score greater than 6.5). The PBAC considered the proposed continuation criterion was appropriate and consistent with the clinical evidence presented.

7.8 The PBAC considered it was reasonable to list the titration pack (comprising 12x250 mcg tablets), which is required for initiation of siponimod in patients who require the 2 mg once daily dose, given there may be circumstances where prescribers do not have capacity to store the packs (i.e. no refrigerator).

7.9 The PBAC considered fingolimod (as a point of reference for other DMTs, noting that cladribine, ocrelizumab and alemtuzumab were all listed on the basis of similar efficacy and safety compared to fingolimod) was a reasonable comparator.

7.10 The PBAC noted the submission presented an indirect comparison of siponimod and fingolimod using the EXPAND, BOLD and FREEDOMS studies and agreed with the ESC there were exchangeability issues with the trials which affected the reliability of the clinical comparison. The PBAC also noted that no evidence had been presented regarding the efficacy of fingolimod in patients with baseline EDSS scores above 5.5. On balance, the PBAC considered the results of the indirect comparison reasonably supported a conclusion that siponimod was likely to be non-inferior to fingolimod.

7.11 The PBAC noted the indirect comparison of adverse events between siponimod and fingolimod presented in the submission, and noted that siponimod was associated with statistically significantly fewer hypertension events and considered on balance the safety profile of siponimod was non-inferior to fingolimod.

7.12 The requested listing for siponimod was broader than the PBS listing for fingolimod and other DMTs in that it includes ambulatory patients who require assistance to walk (i.e. EDSS ≥ 6.0). The PBAC agreed with the ESC that the cost-effectiveness of fingolimod in this population (who have higher levels of disability) has not been established. The PBAC also agreed with the ESC that, based on the subgroup analyses of the EXPAND trial, siponimod was likely to be less cost-effective in these patients given the apparent reduced efficacy. The PBAC therefore considered that the current fingolimod price was not justified in the proposed expanded population.

7.13 The pre-PBAC response proposed a lower price for siponimod in the proportion of patients with EDSS ≥ 6.0 (i.e. EDSS 6.0/6.5) who are currently untreated. The lower price was equivalent to the price of interferon beta, with the pre-PBAC response stating interferon beta is considered to be part of the treatment mix that is standard of care, and that interferon beta-1b (and interferon beta-1a intramuscular injection) are the only DMTs that are TGA-registered for use in patients with SPMS. The pre-PBAC response stated that interferon beta "represents the minimum value" in the patients with EDSS ≥ 6.0.

7.14 For the EDSS 6.0/6.5 population, the PBAC reaffirmed its view from the November 2019 meeting that the results of the EXPAND trial (which enrolled patients with SPMS and EDSS scores of 3 to 6.5 at baseline) supported a claim that siponimod is superior to placebo with regards to confirmed disability progression (CDP) and annualised relapse rate (ARR) outcomes. The PBAC also noted the MAIC presented in the PSCR found that siponimod was associated with a statistically significant improvement in time to confirmed disability progression at 6 months versus interferon beta (interferon beta-1a HR 0.43, 95% CI: 0.20, 0.93; interferon beta-1b HR 0.55, 95% CI: 0.33, 0.91). The PBAC was satisfied that siponimod provides, for some patients, a significant improvement in effectiveness and safety over interferon beta. Overall, the PBAC considered that the expanded use of siponimod compared with the currently

listed DMTs would be cost-effective at a price consistent with interferon beta.

7.15 The pre-PBAC response presented a revised price offer with a weighted price based on: the cost-minimisation analysis between siponimod and fingolimod in the patient population currently treated with DMTs; and a price consistent with interferon beta in the expanded population. The PBAC considered that a number of assumptions in the pre-PBAC response's derivation of the weighted price were unreasonable and considered that an acceptable weighted price, with these changes also incorporated in the financial estimates, should be based on the following:

- The weighting (relative utilisation) between the DMT-treated population and the expanded population should be based on the average weightings between the two populations over the first five years of listing, rather than only being based on Years 5 and 6 as was proposed in the pre-PBAC response. The PBAC noted that this would change the weighting from [redacted]% fingolimod and [redacted]% interferon beta, to [redacted]% fingolimod and [redacted]% interferon beta, but also noted that the other changes outlined below would further change these weightings;
- Noting its view that PBS subsidised treatment should cease when patients have confirmed disability progression or become non-ambulatory, the PBAC considered the proportion of all MS patients between EDSS 6.0 and 8.0 in the pre-PBAC Response (18.35%) should be changed to include only those patients with EDSS 6.0 or 6.5 (11.9%), consistent with the ESC's view.
- The PBAC considered the proportion of DMT scripts replaced by siponimod (the uptake/displacement rate in the market share portion of the estimates) was overestimated. The PBAC considered, given the number of DMTs available, that the uptake/displacement of treatments, other than fingolimod, may be less than estimated in the resubmission. The PBAC further noted that if the uptake/displacement is overestimated, the weighted price for siponimod will be higher and considered this may lead to the use of siponimod in the broader population not being cost-effective. The PBAC considered a more reasonable estimate of the uptake/displacement in Year 6 would be [redacted]% in the revised population comprising patients with EDSS ≥ 3 (rather than [redacted]% as effectively proposed in the pre-PBAC response).
- The pre-PBAC response proposed to change the proportion of patients with EDSS ≥ 6.0 who are untreated with DMTs from [redacted]% to [redacted]% based on the Australian cohort of the MSBase registry with clinician-designated SPMS. This change was based on the ESC's advice that treatment uptake may be higher in the requested population (which includes RRMS) than in patients with clinician-designated SPMS. However, the PBAC considered the MSBase database may potentially underestimate the proportion of patients who are currently untreated as participants are often recruited and followed opportunistically and a large proportion of patient interactions were associated with use or monitoring of DMTs. Overall, the PBAC considered that

it was more reasonable to estimate that [redacted]% of patients with EDSS ≥ 6.0 are untreated with DMTs (per the submission).

- The fingolimod price applied in the cost-minimisation analysis should include the post-RSA rebate price over the past five years, rather than that proposed in the submission, which was based only on Year 3 of the RSA, noting that this was a long term and consistent arrangement, and that siponimod was not proposed to be subject to that arrangement.

7.16 The PBAC considered the revised utilisation estimates in the pre-PBAC response overestimated the financial impact, and should be amended as outlined in the paragraph above.

7.17 The PBAC advised an RSA, based on the revised economic and utilisation parameters outlined above, would be required to address the risk of the uncertain patient population and the risk of use beyond disease progression.

7.18 The PBAC advised that siponimod is not suitable for prescribing by nurse practitioners.

7.19 The Grandfather listing could be removed following 12 months.

7.20 The PBAC recommended that the Early Supply Rule should apply for the 2 mg and 0.25 mg maintenance packs, but not for the 0.25 mg titration pack.

7.21 The PBAC advised siponimod should not be treated as interchangeable with any other drugs.

7.22 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because there was insufficient evidence to conclude siponimod is expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, or not expected to address a high and urgent unmet clinical need, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

7.23 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new medicinal product as follows (indicative listing shown below):

Medicinal Product Pack (Name, form & strength and pack size)	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SIPONIMOD siponimod 250 microgram tablet, 12	NEW	1	12	0	Mayzent®
siponimod 250 microgram tablet, 120	NEW	1	120	5	
siponimod 2 mg tablet, 28	NEW	1	28	5	

Restriction Summary (new) / Treatment of Concept: (new)

Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒ Authority Required – Streamlined (new code)
	Episodicity: [blank]
	Severity: [blank]
	Condition: Multiple sclerosis
9504	**Indication:** Multiple sclerosis
	Treatment Phase: Initial treatment
New	**Clinical criteria:**
New	The condition must be/have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of at least one of the brain/spinal cord; OR
New	The condition must be/have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis supported by written certification, which is documented in the patient's medical records, from a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient
20585	**AND**
	The treatment must be a sole PBS-subsidised disease modifying therapy for this condition
	AND
New (9511 variation)	Patient must be ambulatory, with/without assistance/support
	AND
	Patient must have mild disability in at least 3 functional systems OR
	Patient must have moderate disability in at least 1 functional system
new	**Prescriber Instructions:** Select a dose and pack size appropriate for the patient's CYP2C9 metabolising enzyme status.
New	**Administrative Advice:** There is no specific Medical Benefits Schedule item for CYP2C9 metabolising enzyme status testing.
	Administrative Advice: For evidence of mild disability in at least 3 functional systems or moderate disability in at least 1 functional system – the functional systems include visual, brain stem, pyramidal, cerebellar, sensory, bowel/bladder, and cerebral/cognitive.
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
7608	**Administrative Advice:** Special Pricing Arrangements apply.

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒Authority Required – Streamlined (new code)
	Episodicity: [blank]
	Severity: [blank]

	Condition: Multiple sclerosis
9504	**Indication:** Multiple sclerosis
	Treatment Phase: Continuing treatment (including recommencement of treatment)
	Clinical criteria:
20585	The treatment must be a sole PBS-subsidised disease modifying therapy for this condition
	AND
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
9514	Patient must not show continuing progression of disability while on treatment with this drug
	AND
New (9511 variation)	Patient must be ambulatory, with/without assistance/support
	AND
10876	Patient must have demonstrated compliance with, and an ability to tolerate this therapy
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
7607	No increase in the maximum number of repeats may be authorised.
7608	Special Pricing Arrangements apply.

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction Type / Method: ☒ Authority Required – Streamlined (new code)
9504	**Indication:** Multiple sclerosis
	Treatment Phase: Transition from non-PBS subsidised to PBS-subsidised treatment – 'Grandfather' treatment
	Clinical criteria:
New [Placeholder 22175]	Patient must have been receiving treatment with this drug for this PBS indication prior to <PBS listing date>.
	AND
new	Patient must have met all PBS eligibility criteria set out in the Initial treatment restriction for a non-'Grandfather'' patient prior to having commenced non-PBS subsidised treatment with this drug
	AND
20585	The treatment must be a sole PBS-subsidised disease modifying therapy for this condition
	AND
9514	Patient must not show continuing progression of disability while on treatment with this drug
	AND
New (9511 variation)	Patient must be ambulatory, with/without assistance/support
	AND
10876	Patient must have demonstrated compliance with, and an ability to tolerate this therapy
24060	**Prescriber instructions:** A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only.
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised
7607	No increase in the maximum number of repeats may be authorised
7608	Special Pricing Arrangements apply
25398 draft	This Grandfather restriction will cease to operate from 12 months after the date specified in the Clinical criteria.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Novartis is pleased that the PBAC has agreed to provide patients with relapse-onset MS, including those patients with the 'highest unmet need', access to this treatment.