5.11 SIPONIMOD, Tablet, 250 micrograms and 2 mg, Mayzent®, Novartis Pharmaceuticals Australia Pty Ltd.

1 Purpose of Application

1.1 The submission requested a General Schedule Authority Required listing for siponimod for treatment of secondary progressive multiple sclerosis (SPMS). The PBAC has not previously considered any submissions for siponimod or SPMS.

1.2 The basis of the requested listing was a cost-effectiveness analysis versus:

- placebo (for no treatment among SPMS patients who are not currently being treated with relapsing-remitting multiple sclerosis (RRMS) disease modifying therapies (DMTs)); and
- interferon-beta (IFN-beta), glatiramer acetate (GA) and natalizumab among SPMS patients currently being treated with RRMS DMTs.

1.3 The key components of the clinical issue addressed by the submission is presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with SPMS. The submission split this population based on current use of RRMS DMTs to those who are (i) untreated and (ii) treated.
Intervention	Siponimod 1 mg or 2 mg daily (dependent upon recommended optimal maintenance dosage).
Comparator	Best supportive care (BSC); interferon-beta-1a/1b; glatiramer acetate; natalizumab.
Outcomes	3- and 6-month confirmed disability progression; relapse rate; brain lesions and other imaging outcomes; quality of life; cognitive function; upper limb function; adverse effects.
Clinical claim	In the SPMS untreated population: superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo. In the SPMS treated population: superior in terms of comparative effectiveness with comparable but different safety profiles compared with interferon-beta/glatiramer acetate and natalizumab.

Source: Table 1.1 (pg.2 of the submission)
Abbreviations: BSC = best supportive care; DMT = disease modifying treatment; mg = milligram; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

2 Requested listing

2.1 The submission proposed a restriction for (i) initial therapy, (ii) continuing therapy and (iii) grandfathering. An abridged version of the proposed initial therapy and continuing therapy restrictions are presented below, which omits the Definitions and Administrative Advice.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Siponimod,	1	12	0	Published: $[redacted]	Mayzent®

0.25 milligram, Tablet				Effective: $[redacted]	
Siponimod, 0.25 milligram, Tablet	1	120	5	Published: $[redacted] Effective: $[redacted]	Novartis Pharmaceuticals Australia Pty Limited
Siponimod, 2 milligram, Tablet	1	28	5	Published: $[redacted] Effective: $[redacted]	

Category/Program:	Authority Required
PBS indication:	Secondary progressive multiple sclerosis
Treatment phase:	Initial and continuing
Clinical criteria:	**Initial** The condition must 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 experienced a progressive increase in disability of at least 6 months duration, with evidence of mild disability in at least 3 functional systems or moderate disability in at least 1 functional system AND Patient must be ambulatory (with or without assistance or support). **Continuing** Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND Patient must not show continuing progression of disability that is sustained for at least 6 months while on treatment with this drug, AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.

2.2 All requested restrictions are General Schedule Authority Required (Telephone) listings with the same administrative advice. The submission modelled the requested restrictions on the current PBS restrictions for oral DMTs in RRMS. Underlined text in the requested listings represents differences between the proposed siponimod restriction and the current restrictions for DMTs listed for an RRMS indication.

2.3 Overall, the population in the requested restriction is broader than that enrolled in the primary source of evidence of the submission (the EXPAND trial). EXPAND used more specific definitions to describe SPMS and applied exclusion criteria that are not reflected in the requested restriction. The ESC considered it would be appropriate for the restriction to more closely align with the EXPAND trial criteria to better target those with SPMS, and to better restrict use beyond progression by adding an objective measure of disease progression to the continuing restriction. The ESC also noted that the restriction required patients to have experienced progressive disability over at least 6 months prior to initiation, whilst the EXPAND trial required documented evidence of progressive disability over 2 years. The PBAC considered the proposed restriction did not specifically identify patients with SPMS or exclude patients with RRMS.

2.4 The proposed restriction would allow patients to switch back to DMTs for RRMS following treatment with siponimod for SPMS. The Pre-Sub-Committee Response (PSCR) argued there is 'legitimate and appropriate use of and switching between current DMTs, and in the future with siponimod' (due to adverse events (AE) or inadequate response), as it is difficult to determine whether patients are distinctly RRMS or SPMS. The pre-PBAC Response also argued it was reasonable to allow patients to switch back to an alternative RRMS DMT following treatment with siponimod if they meet the RRMS criteria, as patients who fail or not tolerate siponimod may continue to realise a benefit with respect to relapse and lesion development.

2.5 Elimination of siponimod in systemic circulation is through metabolism via the polymorphic enzyme cytochrome P450 CYP2C9 (approximately 80%) and CYP3A4 (approximately 20%). The submission proposed a genotype test requirement to identify patients with reduced CYP2C9 activity which impacts dosage or eligibility. There are two genotyping thresholds between the three groups of patients: (a) eligible for siponimod without dose modification, (b) eligible for siponimod with dose reduction (intermediate metaboliser), and (c) not eligible for siponimod (poor metaboliser). The submission highlighted the importance of knowing metaboliser status prior to treatment initiation and stated that risk minimisation strategies will be implemented to reduce the risk of siponimod use in poor metabolisers. Although the draft Product Information (PI) states the CYP2C9 genotype of the patient should be determined before initiation of treatment and provides dosage advice based on the outcomes of this genotype test, this information is not included within the requested PBS restriction for initial treatment.

2.6 The submission stated that the sponsor plans to offer all prospective patients access to a program encompassing all components of the genotype testing whereby testing on transported blood samples will occur at a centralised [redacted] laboratory in [redacted]. The submission stated this program will bear no cost to the patient or health system. The submission argued that the submission should not be considered co-dependent because (a) the cost of the test will be borne by the sponsor and (b) the genotype test is used to establish correct dose and not the target population. The evaluation noted that this is correct other than for the <1% of the population that may be poor metabolisers, precluding them from treatment.

2.7 The PSCR stated that it assumed that doctors will apply for both the titration pack and initial month of therapy at the same time. The ESC noted a prescriber cannot write more than one PBS prescription for the same pharmaceutical benefit for the same person on the same day. The titration pack and a maintenance pack may therefore not be able to be prescribed on the same day.

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

3 Background

Registration status

3.1 **TGA status at time of PBAC consideration:** The submission was made under TGA/PBAC Parallel Process. Siponimod was TGA registered on 1 November 2019 for the treatment of adult patients with SPMS.

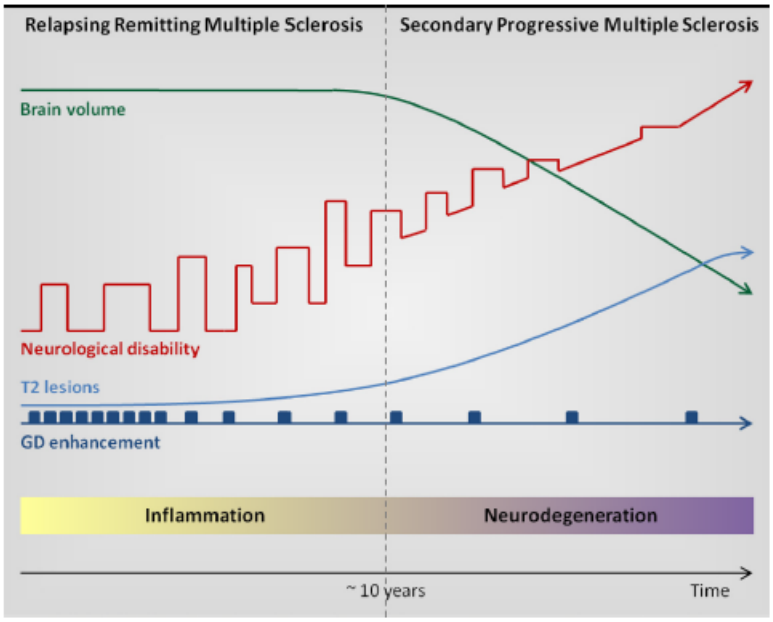
For more detail on PBAC's view, see section 7 PBAC outcome.

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. MS symptoms are heterogeneous between patients, but can manifest as problems associated with: motor control; fatigue; continence; neuropsychological symptoms (such as depression, cognitive difficulties and memory loss); and 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. The disease course of MS for RRMS and SPMS patients is shown in Figure 1. Patients with SPMS see a progressive increase in neurological disability and T2 lesions, and a progressive decrease in brain volume, relapse rate and T1 lesions with gadolinium (GD) enhancement.

Figure 1: Disease course from RRMS to SPMS



Source: Figure 1.2 (pg.4 of the submission). Originally from Schaeffer et al 2015: "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)."

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 There are currently no PBS-listed therapies for SPMS.

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

5 Comparator

5.1 The submission split the target population into an 'untreated' and a 'treated' (with DMTs at baseline) population with the justification that different comparators were

relevant to each of these sub-populations, and the nominated comparator was different for each population (Table 2).

Table 2: Comparators nominated by the submission

Population	Comparator
Untreated SPMS (i.e. those without current DMT-use)	'No treatment', or best supportive care (BSC), as the comparator, with placebo acting as proxy. In the economic evaluation, [redacted]% of patients are considered 'untreated'.
Treated SPMS (i.e. those with current DMT-use, representing use beyond the restriction)	Interferon (IFN)-beta, glatiramer acetate (GA), natalizumab, fingolimod and ocrelizumab. In the economic evaluation, among patients who are considered 'treated', [redacted]% are treated with IFN-beta/GA and [redacted]% with natalizumab[a].

[a] based on analyses of the Australian patients in MSBase who fulfil the Lorscheider et al 2016 criteria for SPMS (n=[redacted]), reweighted given the lack of any clinical evidence assessing the effectiveness and safety of fingolimod and ocrelizumab in SPMS (keeping the 'untreated' group constant).

5.2 The use of DMTs was based on analyses of the Australian patients in the MSBase database who fulfilled the Lorscheider et al 2016 criteria for SPMS (defined as ≥1.5 point increase for those with an Expanded Disability Status Scale [EDSS] score of 0; ≥1 point increase for those with EDSS score of 1-≤5.5; and ≥0.5 point increase for those with EDSS score of ≥6.0, confirmed at 3 months). These analyses (limited to therapies used in at least [redacted]% of patients) indicated that the following therapies were used among the [redacted] Australian patients who fulfilled the criteria for (but not necessarily diagnosed with) SPMS: interferon (IFN) – beta / glatiramer acetate (GA) [[redacted]%], natalizumab [[redacted]%], fingolimod [[redacted]%] and ocrelizumab [[redacted]%]. In the economic evaluation, the comparators were reweighted given the lack of any clinical evidence assessing the effectiveness and safety of fingolimod and ocrelizumab in SPMS (keeping the 'untreated' group constant), such that among patients who are considered 'treated', [redacted]% are assumed treated with IFN-beta/GA and [redacted]% with natalizumab.

5.3 PBS use of RRMS DMTs in patients with SPMS may be due to a documented SPMS diagnosis being delayed or due to a lack of awareness of a transition to SPMS from RRMS. As none of the DMT therapies are PBS-listed for SPMS, their effectiveness, safety and cost-effectiveness have not been accepted by the PBAC for this use. Additionally, although the interferon-betas are TGA registered for SPMS indications (Avonex® [where relapse is still a feature of the disease], Betaferon® and Rebif® [should not be initiated in patients who no longer experience relapses]), no other DMTs are TGA-approved for an SPMS indication (although this appears to have recently changed for fingolimod where an SPMS indication was included in a PI dated 24 November 2016, but is no longer included in the PI dated 21 January 2019).

5.4 The PSCR argued that at least some of the use of DMTs in patients with progressed disability is in line with the PBS restrictions, as there is a period where the classification of a patient with RRMS or SPMS is unclear because they may still experience relapses (albeit at a reduced frequency). The ESC considered it was likely that DMTs are being used in practice in some patients with progressive disease, and therefore they could be considered relevant comparators. However, the proportion of the 'treated'

population who should be included in the total target population was highly uncertain because it was unclear how the listing of siponimod would affect the diagnosis rates of SPMS. The ESC considered that:

- Some patients will remain undiagnosed with SPMS (due to the ambiguous and gradual transition between RRMS and SPMS). Technically these patients should be excluded from the total target population of the submission as these patients would not be able to access siponimod upon a successful PBS listing (as their clinician will not have documented them as achieving the proposed PBS restriction criteria required for initial siponimod therapy).
- Some patients who had not previously been diagnosed due to the lack of PBS therapies available for SPMS may now be diagnosed in order to access siponimod.
- Some patients may remain without a documented diagnosis of SPMS if they are unable to return to using existing PBS DMTs for RRMS post siponimod.

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 MS Australia, MS Research Australia and individuals (3), via the Consumer Comments facility on the PBS website. The comments described the high clinical need for effective treatments for SPMS and lack of alternative treatments current available to slow progressive disease in MS. The comments also noted overseas regulatory agencies had accepted siponimod as being effective in SPMS.

Clinical trials

6.3 The submission was based on one head-to-head trial comparing siponimod to placebo (n=1,651), EXPAND.

6.4 The submission also included seven randomised trials comparing interferon-beta (IFN-beta; five trials), glatiramer acetate (GA; one trial) and natalizumab (one trial) to placebo.

6.5 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study 2304 (EXPAND)[a]	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.	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(10127): 1263-1273
IFN-beta (Nordic SG)	Andersen, O., et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis.	Journal of Neurology, Neurosurgery and Psychiatry 2004; 75(5): 706-710
	Wu, X., et al. Once-weekly 22microg subcutaneous IFN-beta-1a in secondary progressive MS: a 3-year follow-up study on brain MRI measurements and serum MMP-9 levels.	Acta Neurologica Scandinavica 2007; 116(1): 43-48
IFN-beta (North American SG)	Panitch, H. Interferon beta-1b in secondary progressive MS: Results from a 3-year controlled study.	Neurology 2004; 63(10): 1788-1795
	Brex, P. A., et al. The effect of IFNβ-1b on the evolution of enhancing lesions in secondary progressive MS.	Neurology 2001; 57(12): 2185-2190
IFN-beta (European SG)[b]	European Study Group on interferon beta-1b in secondary progressive MS. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis.	The Lancet 1998; 352(9139): 1491-1497
	Kappos, L., et al. Final analysis of the European multicenter trial on IFNβ-1b in secondary-progressive MS.	Neurology 2001; 57(11): 1969-1975
IFN-beta (IMPACT)[b]	Cohen, J. A., et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS.	Neurology 2002; 59(5): 679-687
IFN-beta (SPECTRIMS)[b]	SPECTRIMS Study Group. Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS (SPECTRIMS). Randomized controlled trial of interferon- beta-1a in secondary progressive MS: clinical results.	Neurology 2001; 56(11): 1496-1504
Glatiramer acetate (COP-1)	Bornstein, M. B., et al. A placebo-controlled, double-blind, randomized, two-center, pilot trial of Cop 1 in chronic progressive multiple sclerosis.	Neurology 1991; 41(4): 533-539
Natalizumab (ASCEND)[a]	Kapoor, R., et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension.	The Lancet Neurology 2018; 17(5): 405-415

Source: Table 2.6 (pg. 76) of the submission

[a] Includes eligible full-text publications from the database searches and additional eligible publications and study reports identified from other sources.

[b] Only main publications included, there are a number of other associated publications.

6.6 The key features of the randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Siponimod versus placebo						
EXPAND	1,651	R, DB 3 years	Low	SPMS	3- and 6-month CDP ARR	6-month CDP ARR
Interferon-beta (IFN-beta) versus placebo						
Nordic SG	371	R, DB 3 years	Unclear	SPMS	6-month CDP ARR	Not used
North America SG	939	R, DB 3 years	Unclear	SPMS	6-month CDP ARR	Not used
European SG	718	R, DB 3 years	Unclear	SPMS	6-month CDP ARR	Not used
IMPACT	436	R, DB 2 years	Unclear	SPMS	6-month CDP ARR	Not used
SPECTRIMS	618	R, DB 3 years	Unclear	SPMS	3-month CDP ARR	Not used
Meta-analysis	3,082	Included Nordic SG, North America SG, European SG, IMPACTS, SPECTRUMS				ARR
Glatiramer acetate (GA) versus placebo						
COP-1	106	R, DB 2 years	Unclear	Chronic progressive MS	3-month CDP	Not used
Natalizumab versus placebo						
ASCEND	889	R, DB 2 years	Unclear	SPMS	6-month CDP (proportion); ARR	ARR

ARR=annualised relapse rate; CDP=confirmed disability progression; DB=double blind; MC=multi-centre; MS = multiple sclerosis; R=randomised; SPMS = secondary progressive multiple sclerosis.
Source: Source: Table 2.10 (pg.90) and Table 2.11 (pg 92) of the submission.

6.7 The submission did not provide an indirect comparison of siponimod versus the RRMS DMTs considered as comparators.

6.8 The ESC noted differences between the EXPAND trial population and the Australian population identified in the MSBase database. The trial population had a higher proportion of males, shorter time since MS diagnosis, higher mean EDSS score and tended to have more relapses over the two years prior to commencing therapy. However, the ESC also noted that MSBase population was small, with a sample size of only [redacted] patients, which may impact its reliability as a data source.

Comparative effectiveness

6.9 The confirmed disability progression results from EXPAND and the comparator DMT trials are presented in Table 5. The definition of CDP differs between trials (see table footnotes), and treatment duration also varied between trials.

Table 5: Results of confirmed disability progression (CDP) in EXPAND and the comparator DMT trials

Treatment	n/N	(%)	Risk reduction	Hazard ratio (95% CI)	p-value
EXPAND					

Treatment	n/N	(%)	Risk reduction	Hazard ratio (95% CI)	p-value
3-month CDP					
Siponimod	288/1096	26.3	21.2%	**0.79 (0.65, 0.95)**	**0.0134**
Placebo	173/545	31.7			
6-month CDP					
Siponimod	218/1096	19.9	25.9%	**0.74 (0.60, 0.92)**	**0.0058**
Placebo	139/545	25.5			
Nordic SG[1]					
IFN-beta-1a	77/186	41.4	-	1.13 (0.82, 1.57)	0.45
Placebo	68/178	38.2			
North America SG[2]					
IFN-beta-1b	227/631	36.0	-	1.05 (0.87, 1.26)	0.64
Placebo	106/308	34.4			
European SG[3]					
IFN-beta-1b	147/360	40.8	16.0%	**0.84 (0.71, 0.99)**	**0.04**
Placebo	174/358	48.6			
IMPACT[4]					
IFN-beta-1a	56/217	25.8	-	0.977 (0.679, 1.407)	0.90
Placebo	60/219	27.4			
SPECTRUMS[5]					
IFN-beta-1a	245/413	59.3	-	0.91 (0.80, 1.04)	0.17
Placebo	133/205	64.9			
Meta-analysis of IFN trials (3- and 6-month CDP combined)				Risk ratio = 0.94 (0.86, 1.03)	-
COP-1[6]					
Glatiramer acetate	9/51	17.6	-	0.69 (0.33, 1.46)	0.34
Placebo	14/55	25.5			
ASCEND[7]					
Natalizumab	69/439	15.7	-	1.06 (0.74, 1.53)	0.753
Placebo	67/448	15.0			

Source: Table 2.24 (pg.131), Table 2.25 (pg.132) and Table 2.36 (pg.149) of the submission

Abbreviations, CI, confidence interval; n, number of participants, N=total participants in group, HR=hazard ratio, OR=odds ratio

[1] Anderson 2004 – 6-month confirmed, 3 years, HR

[2] Panitch 2004 – supplementary appendix, pooled for both doses, 6-month confirmed, 3 years, RR via La Mantia (Expanded Disability Status Scale [EDSS] during relapse excluded)

[3] Kappos 2001, EU SG 1998 – 6-month confirmed, 3 years, RR via La Mantia

[4] Cohen 2002 – secondary outcome, 3-month confirmed, 2-3 years, HR

[5] Francis 2001, SPECTRIMS 2001 – pooled for both doses, 3-month confirmed, 3 years, RR via La Mantia

[6] Bornstein 1991 – 3-month confirmed, 2 years, RR via La Mantia

[7] Kapoor 2018 – 6-month confirmed, 2 years

6.10 Statistically significantly fewer patients treated with siponimod had 3- or 6-month CDP compared with those treated with placebo. The CDP results show the respective DMTs were not statistically significantly better than placebo, except for IFN-beta in the European SG trial. The submission also presented results from an IFN-beta meta-analysis which did not yield statistically significant results for CDP.

6.11 The annualised relapse rate (ARR) results from EXPAND and the comparator DMT trials are presented in Table 6.

Table 6: Results of annualised relapse rate (ARR) for confirmed relapses in EXPAND and the comparator DMT trials

Treatment	N	n/time	ARR	Adjusted ARR (95% CI)[a]	Rate reduction	ARR ratio (95% CI)[8]	p-value
EXPAND							
ITT							
Siponimod	1099	134/691980	0.071	0.071 (0.055,0.092)	55.5%	**0.445 (0.337, 0.587)**	**<0.0001**
Placebo	546	143/343285	0.152	0.160 (0.123,0.207)			
PP							
Siponimod	1037	116/554281	0.076	0.079 (0.060,0.103)	58.4%	**0.416 (0.310, 0.560)**	**<0.0001**
Placebo	523	126/273562	0.168	0.189 (0.143,0.250)			
Nordic SG[1]							
IFN-beta-1a	209	-	0.250	-	-	0.90 (0.64, 1.27)	0.55
Placebo	205	-	0.270	-			
North America SG[2]							
IFN-beta-1b (high dose)	317	-	0.160	-	-	0.57 (0.17, 1.90)	-
Placebo	308	-	0.280	-			
European SG[3]							
IFN-beta-1b	360	-	0.440	-	-	0.690 (0.09, 5.12)	
Placebo	358	-	0.640	-			
IMPACT							
IFN-beta-1a	217	-	0.190	-	-	0.61 (0.18, 2.14)	-
Placebo	219	-	0.310	-			
SPECTRIMS							
IFN-beta-1a	204	-	0.500	-	31.0%	**0.690 (0.56, 0.85)**	**0.0005**
Placebo	205	-	0.710	-			
				Meta-analysis of IFN trials		**0.73 (0.62, 0.87)**	-
COP-1							
Glatiramer acetate	51	-	NR	-	-	NR	-
Placebo	55	-	NR	-			
ASCEND							
Natalizumab	439	-	0.080	-	54.7%	**0.453 (0.323, 0.634)**	**<0.0001**
Placebo	448	-	0.170	-			

Source: Table 2.27 (pg.134) and Table 2.37 (pg. 150) of the submission

Abbreviations: ARR=annualized relapse rate; ITT=intention-to-treat; PP=per-protocol; CI=confidence interval; n=overall number of relapses in the analysis period for all subjects; N=number of subjects in the analysis; time=total number of days in the analysis period overall for all subjects

[1] Anderson 2004 – 3 years;

[2] Panitch 2004, La Mantia 2012 - high dose only, ARR ratio via RevMan (Attachment 12);

[3] Kappos 2001, EU SG 1998, La Mantia 2012, ARR ratio via RevMan (Attachment 12);

[4] Cohen 2002, La Mantia 2012, ARR ratio via RevMan (Attachment 12);

[5] Francis 2001, SPECTRIMS 2001 – high dose only;

[6] Bornstein 1991 – ARR not reported

[7] Kapoor 2018 – ASCEND supplementary appendix

[8] Obtained from fitting a negative binomial regression model adjusted for treatment, country/region, baseline EDSS, SPMS group (with/without superimposed relapses, baseline definition) and baseline number of T1 Gd-enhancing lesions (offset = time in analysis period in years.

6.12 Patients treated with siponimod had a statistically significantly reduced ARR compared with those treated with placebo (by intention-to-treat (ITT) and per-protocol (PP) analyses). The PP analyses were used in the economic evaluation given patients could switch therapies after experiencing 6-month CDP. The ARR results show that one IFN-beta trial (SPECTRIMS) and the natalizumab trial (ASCEND) showed the respective DMT resulted in a statistically significantly reduction in the ARR. One trial did not include ARR results (COP-1 for glatiramer). The remaining four trials did not yield statistically significant results. As such, it is unclear from this evidence whether the RRMS DMTs provide statistically significant benefits with respect to ARR compared to placebo.

6.13 The submission inappropriately did not present indirect comparisons of siponimod versus the nominated RRMS DMT comparators. Based on a lack of statistical significance between DMTs and placebo, and statistical significance between siponimod vs placebo (from EXPAND), the submission assumed siponimod is statistically significantly better than the DMTs.

6.14 The PSCR argued the approach of assuming DMTs are no more effective than placebo rather than undertaking an indirect comparison was reasonable as, 'an indirect comparison would add artificial uncertainty which would complicate the comparison against treatments that are not effective from either a statistical or clinical relevance point of view'. The ESC disagreed and considered the arguments in the submission and PSCR that RRMS DMTs were both simultaneously not clinically effective and widely used in practice were contradictory. As these therapies are likely to be used in practice, the ESC considered it was reasonable to undertake indirect comparisons of siponimod and the RRMS DMTs.

6.15 Quality of life (QoL) was measured in the EXPAND trial using the Multiple Sclerosis Impact Scale (MSIS-29; physical and psychological) and EQ-5D-3L at Months 12 and 24. Statistically significant differences in favour of siponimod were observed between the treatment arms at Month 12 (MSIS physical and EQ-5D), however no differences were observed between the treatment arms by MSIS psychological at Month 12 or by any measure at Month 24. The lack of a statistically significant difference between the siponimod and placebo arms at 24 months in the MSIS scores and EQ-5D scores may suggest siponimod does not provide an improvement in QoL compared with placebo 2 years after treatment initiation. The health domains included within the EQ-5D-3L are highly relevant to SPMS, and it was therefore considered by ESC that the EQ-5D-3L should be sensitive to QoL impacts in SPMS patients.

Comparative harms

6.16 A statistically significantly greater proportion of patients treated with siponimod experienced at least one adverse event compared with placebo in the EXPAND trial. No differences between treatment arms were observed for the proportion of patients with at least one serious AE, discontinuation due to AE or deaths.

6.17 No statistically significant differences between the comparator DMTs and placebo were observed in the trials for serious AEs, or deaths. The outcome 'any AE' was only reported for the natalizumab ASCEND trial and no differences between the treatment arms were observed. A statistically significantly greater proportion of patients treated with IFN-beta discontinued treatment compared with placebo (but no differences were observed for glatiramer acetate and natalizumab versus placebo).

6.18 Table 7 shows the specific AEs with notable (>2%) between arm differences in the EXPAND safety analysis set (comprising of all patients who took at least one study dose through to 30 days after last blinded study drug dose or the day before open-label siponimod treatment). A higher proportion of siponimod patients exhibited each of these specific AEs. A higher proportion of siponimod patients exhibiting bradycardia is to be expected. The submission noted patients at a higher risk of bradycardia were to be monitored for the first 6 hours after the first siponimod dose for signs of bradycardia. The PSCR claimed that AEs relating to bradycardia, hypertension, nausea, peripheral oedema and liver function tests increases were all consistent with the known safety profile of treatments that act on the S1P pathway in multiple sclerosis (i.e. fingolimod). The PBAC noted that 3% of patients in the siponimod group and 0.4% of placebo group had bradyarrhythmia events during dose initiation (Kappos et al 2018). In addition, the PBAC noted that a higher incidence of herpes zoster (2% versus 1%) and herpes viral infections (5% versus 3%) reported for patients on siponimod compared to placebo (Kappos et al 2018).

Table 7: Proportion of patients exhibiting specific AEs in EXPAND

Adverse drug reactions, %	Siponimod N= 1,099	Placebo N=546	Frequency category[a]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			
Melanocytic naevus[b]	4.9	2.9	common
Nervous system disorders			
Dizziness	6.8	4.8	common
Cardiac disorders			
Bradycardia[b]	**6.2**	**3.1**	common
Vascular disorders			
Hypertension[b]	**12.6**	**9.0**	very common
Gastrointestinal disorders			
Nausea	**6.7**	**3.5**	common
Diarrhoea	6.4	4.2	common
Musculoskeletal and connective tissue disorders			
Pain in extremity[b]	6.3	4.0	common
General disorders and administration site conditions			
Oedema peripheral[b]	**8.1**	**4.4**	common
Investigations			
Liver function test increased[b]	**11.3**	**3.1**	very common

Source: Table 2.40 (pg. 153) in the submission
Abbreviations: ADR=Adverse drug reaction; AE=adverse event
Bold typography indicates statistically significant differences
[a] Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)
[b] Grouping of preferred terms (PTs) were considered for ADR frequency determination

Benefits/harms

6.19 A comparison of the benefits and harms of treatment with siponimod compared with placebo is presented in Table 8.

Table 8: **Summary of comparative benefits and harms for siponimod and placebo from the EXPAND trial**

Outcome	Siponimod n/N (%)	Placebo n/N (%)	Absolute difference	HR (95% CI)
3-month CDP	288/1096 (26.3)	173/545 (31.7)	-5.4%	**0.79 (0.65, 0.95)**
6-month CDP	218/1096 (19.9)	139/545 (25.5)	-5.6%	**0.74 (0.60, 0.92)**
Outcome	**Siponimod n/time [Adjusted ARR (95% CI)]**	**Siponimod n/time [Adjusted ARR (95% CI)]**	**Rate reduction**	**ARR ratio**
ARR - ITT	134/691,980 [0.071 (0.055,0.092)]	143/343,285 [0.160 (0.123,0.207)]	55.5%	**0.445 (0.337, 0.587)**
ARR - PP	116/554,281 [0.079 (0.060,0.103)]	126/273,562 [0.189 (0.143,0.250)]	58.4%	**0.416 (0.310, 0.560)**

Harms						
Adverse event	**Siponimod n/N**	**Placebo n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Siponimod	**Placebo**	
Any AE	975/1099	445/546	**1.09 (1.04, 1.14)**	88.7	81.5	**0.07 (0.03, 0.11)**
Bradycardia	68/1099	16/546	**1.99 (1.19, 3.34)**	6.2	3.1	**0.03 (0.01, 0.05)**
Hypertension	138/1099	49/546	**1.40 (1.03, 1.91)**	12.6	9.0	**0.03 (0.003, 0.07)**
Nausea	74/1099	23/546	**1.93 (1.19, 3.16)**	6.7	3.5	**0.03 (0.01, 0.05)**
Oedema peripheral	89/1099	24/546	**1.84 (1.19, 2.85)**	8.1	4.4	**0.04 (0.01, 0.06)**
Liver function test increase	124/1099	17/546	**3.62 (2.22, 5.94)**	11.3	3.1	**0.08 (0.06, 0.11)**

ARR=annualised relapse ratio; CDP=confirmed disability progression; HR = hazard ratio; ITT=intention-to-treat; PP=per protocol; RD = risk difference; RR = risk ratio
Source: compiled during the evaluation

6.20 On the basis of direct evidence presented by the submission, for every 100 patients treated with siponimod in comparison to placebo and over a maximum duration of follow-up of 3 years:

- Approximately 5 fewer patients will have progression of disability confirmed at 3 months (3-month CDP).
- Approximately 6 fewer patients will have progression of disability confirmed at 6 months (6-month CDP).
- Approximately 7 additional patients will experience an adverse event.
- Approximately 3 additional patients will have bradycardia (a slow heart rate).
- Approximately 3 additional patients will have hypertension (increased blood pressure).
- Approximately 3 additional patients will have nausea.
- Approximately 4 additional patients will have peripheral oedema (accumulation of fluid causing swelling usually in the lower limbs).
- Approximately 8 additional patients will have liver function test increases.

6.21 As no indirect comparison with the currently listed DMTs was presented, a quantitative comparison of the benefits and harms of siponimod versus these treatments could not be undertaken. Accordingly, a benefits/harms table has not been presented for this comparison.

Clinical claim

6.22 The submission described siponimod as superior in terms of effectiveness and equivalent in terms of safety to BSC (placebo).

6.23 The claim of superior clinical efficacy versus placebo was supported for the 3- and 6-month CDP and ARR outcomes. The claim of equivalent safety was not supported based on the EXPAND trial as siponimod patients were significantly more likely to exhibit at least one AE compared with placebo patients, in addition to being statistically significantly more likely to experience bradycardia, hypertension, nausea, peripheral oedema and liver function test increase.

6.24 The submission described siponimod as superior in terms of comparative effectiveness and 'comparable but different safety profiles' compared to IFN-beta/GA and natalizumab in the treated SPMS population. These therapeutic claims were not adequately supported as no direct head-to-head evidence, nor any indirect comparisons, of siponimod vs IFN-beta, GA or natalizumab were provided.

6.25 The PBAC considered that the claim of superior comparative effectiveness to placebo was reasonable.

6.26 The PBAC considered that the claim of non-inferior comparative safety to placebo was not adequately supported by the data.

6.27 The PBAC considered it was not possible to draw meaningful conclusions on the comparative efficacy and safety of siponimod to RRMS DMTs as indirect comparisons were not presented in the submission.

Economic analysis

6.28 The submission presented a stepped economic evaluation in the form of a Markov cohort health state-transition cost-utility model. A weighted ICER was calculated from three separate economic comparisons using the same model structure (siponimod vs best supportive care (placebo); siponimod vs interferon-beta/glatiramer acetate; siponimod vs natalizumab). The DPMQ applied for siponimod differed between the models: (i) $[redacted] vs placebo, (ii) $[redacted] vs IFN-beta/GA and (iii) $[redacted] vs natalizumab. A summary of the model structure and rationale are provided in Table 9. The ESC considered use of three different prices to generate three ICERs was inappropriate and noted that it had a substantial impact on the individual ICERs.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	30 years in the model base case vs. 3 years in EXPAND
Outcomes	Quality-adjusted life-years (QALYs)
Methods used to generate results	Markov cohort expected value analysis
Health states	18 Expanded Disability Status Scale (EDSS)-based health states (EDSS 1-9 for patients on treatment with siponimod or the comparator and EDSS 1-9 for patients who have discontinued treatment and are being managed by best supportive care) and a dead state
Cycle length	1 year
Transition probabilities	Trial based (EXPAND) supplemented with MSBase registry (Lorscheider definition – Global set) for EDSS transitions 1-2, 7-8, 8-9, 2-1, 8-7 and 9-8.

Source: Table 3.2 (pg. 187) of the submission

6.29 Both the siponimod and comparator arms (BSC, IFN-beta/GA and natalizumab) of the model were identically structured, with the same health states, transitions (but not transition probabilities) and health state events. The model included two-lines of treatment. In the siponimod arm, siponimod and BSC; and in the comparator arms, BSC, IFN-beta/GA or natalizumab as first-line treatment and BSC (placebo) as second-line treatment for those who discontinued first-line treatment.

6.30 Within each treatment arm, a patient could be in one of 19 different health states (9 health states for Expanded Disability Status Scale (EDSS) scores 1-9 on-treatment or off-treatment, and 1 death state). Patients were allowed to be on-treatment regardless of EDSS health state, which was unlikely for the most severe EDSS state (EDSS 9), given the proposed PBS continuation criterion of "Patient must not show continuing progression of disability that is sustained for at least 6 months while on treatment with this drug".

6.31 The model allowed patients to regress to lower EDSS score health states. As such, the model allowed patients with SPMS to improve to an EDSS score of 1 and 2. In EXPAND, 99.5% of patients had a baseline EDSS of 3 or greater and the evaluation considered it is implausible that they would improve to an EDSS 1 health state given their diagnosis of SPMS. Furthermore, the inclusion of EDSS 1 and 2 health states in the model, coupled with the ability for patients to improve, meant that in the final model cycle (i.e. year 30) 2.2% of siponimod patients and 0.9% of BSC patients were in an EDSS 1 or 2 health state, which the evaluation considered did not seem compatible with a diagnosis of SPMS.

6.32 Transitions between EDSS health states for the comparator (placebo, IFN-beta/GA or natalizumab) were based on the EXPAND placebo-arm data, supplemented by MSBase Registry data for EDSS transitions using the Lorscheider 2016 Global set definitions for SPMS missing in EXPAND. A relative risk reduction (RRR; 26% for 6-month CDP) was applied to these to inform siponimod transitions, regardless of EDSS state or treatment duration. No relative risk reductions were applied to the active comparators as the submission assumed the RRMS DMTs were equivalent to placebo for 6-month CDP.

6.33 The ESC considered it was inappropriate to assume a constant RRR would be sustained over 30 years, noting that EXPAND showed a statistically significant QoL improvement for siponimod lasting less than 2 years. However, no data upon which to estimate a decline in treatment effect over time for the model was available. The ESC considered this assumption in the model overestimated the health effects of siponimod over the 30 year time horizon. Moreover, during this time period, RRMS DMTs attracted no health gain but a disutility, resulting in a substantially larger (almost double) incremental difference in QALYs for siponimod versus IFN-beta/GA and natalizumab compared with versus placebo. The ESC considered it was implausible that clinicians would continue therapy with DMTs with no assumed clinical benefit in terms of disease progression, which have negative impacts on quality of life.

6.34 In each cycle patients may have a relapse. The structure of the model reasonably allowed patients to experience only one relapse per annual cycle. The relapse event did not impact subsequent transition probabilities between EDSS health states, but was associated with additional cost and disutility.

6.35 The ESC noted that the cycle length was 1 year, and considered that a 6 month cycle length may have been more appropriate given the requested PBS restriction for continuing therapy requires patients to cease siponimod when disability progression is sustained for 6 months. This would also have aligned with the 6-month CDP outcome in EXPAND.

6.36 A constant risk of relapse (regardless of EDSS health state) of 0.189 (PP ARR for placebo patients in EXPAND) was applied throughout the model. The evaluation considered this was not an appropriate assumption given the low sample sizes associated with the lower and higher EDSS health states captured in EXPAND, and given that relapses become less frequent and less pronounced as SPMS disability progresses. Relative risks were applied to the siponimod arm of the model which resulted in a reduction in the risk of relapse.

6.37 Decreasing utilities with increasing EDSS score health states were applied (EDSS 8 and 9 health states had utilities representative of 'worse than death'). Disutilities were also applied to relapses, use of DMTs and progressive multifocal leukoencephalopathy (PML) adverse events. The utilities were generated from BAC-MS, a sponsor-driven study conducted on a small number of patients in one Australian hospital. The ESC considered that due to the low sample numbers and considerable divergence from published utility values for EDSS states, that utility values from the EXPAND trial would be more appropriate to use in the model base case. The ESC considered it would also be appropriate to make an assumption to apply the utility value of [redacted] for EDSS 2 to EDSS 1.

6.38 Increasing costs with increasing EDSS score health states were applied. These were derived from the BAC-MS study. The ESC noted that there was little detail provided for the cost composition (e.g. number of GP visits, number of specialist consults, etc.) and it was thus difficult to judge plausibility. The PBAC considered it was unclear

whether the costs associated with monitoring for bradyarrhythmia during siponimod initiation or with treating the higher frequency of herpes viral infections (see paragraph 6.18) were included in the economic model.

6.39 In addition, patient out of pocket (OOP) costs were included, which is a broader perspective than recommended in the PBAC guidelines for the base case. The ESC also noted that the submission costs were much higher than other published cost estimates of MS patients by EDSS state (Ahmad 2018). The table below shows disease management costs applied in the base case, excluding OOP costs, and comparative costs from the Australian Multiple Sclerosis Longitudinal Study, reported in Ahmad 2018.

Table 10: Comparison of disease management costs, model and published literature

From BAC-MS as applied in the model base case (excluding societal, pharmaceutical, and inpatient costs[a])			From BAC-MS as applied in the model base case (excluding societal, pharmaceutical, out of pocket[b] and inpatient costs[a])	From Ahmad 2018 – "Health Professionals", "Nursing Services", "Community/Private Services" and "Medical Tests"
Health state	n			
EDSS1	[redacted]	$[redacted]	$[redacted]	$3,621 (EDSS 0-3.5)
EDSS 2	[redacted]	$[redacted]	$[redacted]	
EDSS 3	[redacted]	$[redacted]	$[redacted]	
EDSS 4	[redacted]	$[redacted]	$[redacted]	$6,006 (EDSS 4.0-6.0)
EDSS 5	[redacted]	$[redacted]	$[redacted]	
EDSS 6	[redacted]	$[redacted]	$[redacted]	
EDSS 7	[redacted]	$[redacted]	$[redacted]	$10,493 (EDSS 6.5-9.5)
EDSS 8[c]	[redacted]	$[redacted]	$[redacted]	
EDSS 9[c]	[redacted]	$[redacted]	$[redacted]	

Source: Table 3.22 (p255) of the submission, and Ahmad 2018.

[a] Hospital inpatient costs are used as a proxy for relapse costs, hence they are excluded here to avoid double counting

[b] Corrected during the evaluation

[c] Costs were reported for EDSS 8+

6.40 The BAC-MS study collected data from participants' National Disability Insurance Scheme (NDIS) plans, which were included in the model. The PBAC has not previously considered NDIS costs. The ESC considered that these costs should not be considered as a part of the base case because of the low sample numbers in BAC-MS and the uncertainty around the costs reported in the NDIS plans versus the actual expenditure incurred.

6.41 Patients discontinued therapy based on the application of the annual discontinuation rate derived from the PBS 10% sample of fingolimod, rather than based on the proposed PBS continuation restriction, which would require patients to cease siponimod treatment upon 'continuing progression of disability that is sustained for at least 6 months'. The ESC considered this was inappropriate and discontinuations in the model should reflect the proposed PBS discontinuation criteria.

6.42 The PSCR stated that the continuation criteria was not explicitly modelled in the base case, rather it was implicitly captured in through discontinuations applied in the model. A 'stopping rule' (EDSS = 8) (applied in addition to discontinuations) was applied in sensitivity analysis. The PSCR further noted the economic model for siponimod in SPMS used the same approach for modelling the impact of continuation criteria in the PBS restriction as was used in the fingolimod model in RRMS, which was accepted by the PBAC. The PSCR argued that sensitivity analysis in both models showed that the application of the 'stopping rule' has minimal impact on the ICER. The ESC noted that to align with the proposed continuation criteria, patients in the model should cease treatment upon any transition to a higher EDSS state (rather than the stopping rule at EDSS=8 conducted in the sensitivity analysis).

6.43 An error in the structure of the model was identified during the evaluation where patients in an 'off-treatment' EDSS health state (i.e. on BSC treatment) who did not die or did not discontinue due to treatment persistence inappropriately transitioned back to an 'on-treatment' health state. This resulted in 91.2% of siponimod patients remaining 'on-treatment' at Year 11 in the model, rather than the intended 43.5% of patients according to the submission. Evaluator-conducted analyses showed that this substantially increased the weighted base case ICER (from $45,000 - $75,000 to $105,000- $200,000 per QALY gained), yet slightly decreased the siponimod vs placebo ICER ($105,000 - $200,000 per QALY gained). The PSCR acknowledged this error.

6.44 Sensitivity analyses (presented in the submission or conducted during the evaluation) indicated that EDSS matrix transitions (i.e. comparator arm EDSS state transitions), siponimod disability progression treatment effect, EDSS state NDIS costs, EDSS health state utility values, IFN-beta/GA and natalizumab disutility values and model duration were the key model drivers. Sensitivity analyses conducted during the evaluation also indicated that (i) correcting the inappropriate transition of siponimod off-treatment patients in the model and (ii) assuming transition to death after progressing from an EDSS 7 health state (assessing impact of utilities <0), substantially increased the weighted ICER.

6.45 Table 11 indicates the key model drivers.

Table 11: **Key drivers of the model**

Description	Method/Value	Impact [on submission base case weighted ICER]
EDSS progression	Used EDSS transitions from the EXPAND trial, supplemented by MSBase Registry data.	Unclear, unable to test
Siponimod disability progression treatment effect	Relative risk reduction applied from hazard ratio of 6-month confirmed disability progression outcome in EXPAND	High. Use of 95% CI around the treatment effect results in a 22% reduction to 336% increase
NDIS costs by EDSS	Includes NDIS costs by EDSS health state. Estimates derived from a sponsor- driven study (BAC-MS) with very low sample sizes.	High, favours siponimod if NDIS costs removed (100% increase)
EDSS state utilities	Includes utility values by EDSS health state. Derived from BAC-MS study which had very low sample sizes and reported utilities <0 for EDSS health states >8.	High, favours siponimod. Making EDSS >8 health state utilities '0' increased ICER by 115%
IFN-beta/GA and natalizumab treatment health outcomes	No relative risk reduction in EDSS progression applied, but a -0.052 disutility applied annually. Derived from a source that applied the disutility for the first 6 months only.	High, favours siponimod. Removing disutility increases ICER by 75%
Time horizon	30 years based on 3 years of clinical data with sustained treatment effects. 10 year time horizon substantially increases ICER.	High, favours siponimod. 10 year time horizon increases ICER by 57%.

Source: Section 3 of the submission

6.46 Considering the range of issues identified above, the ESC considered a more appropriate base case for the model should: correct the error in the structure of model transitions; apply the same weighted DPMQ for siponimod across the economic comparisons; exclude NDIS costs; exclude double counted out-of-pocket costs; and use EXPAND EDSS utilities (and making an assumption to apply the utility value of [redacted] (for EDSS 2) also to EDSS 1). These revisions increased the weighted ICER from $45,000 - $75,000 per QALY gained to more than $200,000 per QALY gained. Results of the stepped economic model for the submission base case, the ESC-revised base case and select sensitivity analyses are presented in the table below.

Table 12: Results of the stepped economic model for the ESC-revised base case

Variable/ Assumptions	SIP vs PBO (SPMS - not treated)			SIP vs IFN-beta/GA (SPMS - treated)			SIP vs NAT (SPMS - treated)			Weighted		
	Inc Costs	Inc QALY	ICER	Inc Costs	Inc QALY	ICER	Inc Costs	Inc QALY	ICER	Inc Costs	Inc QALY	ICER
SUBMISSION BASE CASE	[redacted]											
Base-case with siponimod off-treatment transition probabilities corrected	[redacted]											
Base-case with siponimod off-treatment transition probabilities corrected & the same weighted DPMQ ($[redacted]) in each individual comparison	[redacted]											
Base-case with siponimod off-treatment transition probabilities corrected, the same weighted DPMQ & exclusion of NDIS costs	[redacted]											
Base-case with siponimod off-treatment transition probabilities corrected, the same weighted DPMQ, exclusion of NDIS costs & excluding double-counted OOP EDSS costs	[redacted]											
Base-case with siponimod off-treatment transition probabilities corrected, the same weighted DPMQ, exclusion of NDIS costs, excluding double-counted OOP EDSS costs & using EXPAND EDSS utilities[a] (**RE-SPECIFIED BASE CASE**)	[redacted]											
[redacted]												
Re-specified base case with no DMT comparator treatment disutility (vs with (-0.052) in base-case)	[redacted]											
Re-specified base case with EXPAND 6-month CDP HR upper (0.92) 95% CI around the HR (vs mean estimate (0.74) in base-case)	[redacted]											
Re-specified base-case with transition probabilities corrected, the same weighted DPMQ, excluding double-counted OOP EDSS costs & using EXPAND EDSS utilities **but including NDIS costs**	[redacted]											

Abbreviations: NDIS = National Disability Insurance Scheme; OOP = Out-of-pocket; EDSS = Expanded Disability Status Scale; DMT = disease modifying therapy; HR = Hazard ratio; SIP = Siponimod; PBO = Placebo; IFN = Interferon; GA = Glatiramer acetate ICER = incremental cost-effectiveness ratio; IFN-beta = interferon-beta; NAT = Natalizumab; Inc = incremental; QALY = quality adjusted life year

[a] From EXPAND mixed effects model in submission (Table 3.14, pg.233 of submission), and making an assumption to apply the utility value of [redacted] (for EDSS 2) also to EDSS 1

The redacted table shows that further adjustments to the re-specified base case with no DMT comparator treatment disutility and use of 95%CI around the 6-month CDP HR increased the weighted ICER to more than $200,000 per QALY gained.

Additional analyses that include corrected transition probabilities, the same weighted DPMQ, excluding double-counted OOP EDSS costs, using EXPAND EDSS utilities and including NDIS costs resulted in a weighted ICER of more than $200,000 per QALY gained.

6.47 The pre-PBAC Response maintained the BAC-MS cohort study was the most appropriate source of treatment costs and utilities in the Australian setting, and the EQ-5D-5L QoL instrument used was more relevant and sensitive to QoL impacts than the -3L tool used in the EXPAND trial and therefore was a better source for treatments costs and utilities in the model. The pre-PBAC Response also proposed a revised economic model which: corrected off-treatment transition probabilities; used the comparator disutilities for RRMS DMTs used in the fingolimod model (March 2011 PBAC); adjusted the health state utilities in EDSS 8 and 9 to 0; and changed the model so no patients were commencing at EDSS 1 or 2. The revised model retained costs and utilities (including NDIS costs) derived from the BAC-MS study. The resultant pre-PBAC revised base case weighted ICER was $105,000 - $200,000/QALY.

6.48 The PBAC noted the revised model provided in the pre-PBAC response. However, the PBAC considered the weighted ICER an unreliable basis to assess the cost-effectiveness of siponimod because the cost-effectiveness of DMTs has not previously been assessed for this specific patient population, and the implausible assumptions regarding no clinical benefit of the DMTs together with reduced quality of life.

6.49 Average EDSS health state over time by treatment arm is shown in Figure 2. All comparator arms had the same transition probabilities; as such, the placebo arm is representative of all three comparator arms. However, the siponimod curve in this Markov trace should be treated with caution for the reason described in paragraph 6.43 (the error in the transitions in the model).

Figure 2: Markov traces – average EDSS health state over time

Source: Figure 3.14 (pg. 314) of the submission

Drug cost/patient/year

6.50 The cost of siponimod per year is $[redacted], representing 13.04 packs per year with a requested effective DPMQ of $[redacted]. Treatment is ongoing until a patient no longer satisfies the criteria in the requested PBS restrictions for continuing treatment. This estimated cost for siponimod is not consistent with the siponimod costs derived from any of the individual economic analyses comprising the weighted ICER presented in the submission (given different siponimod costs were applied in each model). The average cost per patient per year was approximately $[redacted] in the financial estimates (accounting for compliance and discontinuations).

Estimated PBS usage & financial implications

6.51 The submission was considered by DUSC.

6.52 The estimated financial implications of listing siponimod on the PBS are summarised in Table 13.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of siponimod						
Cost to PBS/RPBS less copayments[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for RRMS DMTs						
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS/MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] assuming 13.04 scripts per year as estimated by the submission.

[b] corrected copayment

Source: compiled during the evaluation

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $30 million - $60 million per year.

6.53 The financial estimates were sensitive to the assumption that the majority ([redacted]%) of patients who will be treated with siponimod are currently treated with other DMTs (which the evaluation considered is beyond the PBS restrictions for all the DMTs as they are restricted to RRMS). Assuming only 'untreated' patients receive siponimod, all else being equal, more than doubles the estimated financial impact over the first six years of listing. Other assumptions, including assuming that non-adherence translates directly into fewer packs dispensed and potentially low uptake rates (given that siponimod will be the only PBS listed treatment for SPMS), also lead to underestimates in the financial estimates but the magnitude is much smaller compared to the assumption of a large 'treated' population using DMTs beyond requested restriction.

6.54 DUSC considered the estimates presented in the submission to be an underestimate of untreated patients and an overestimate of treated patients. The main issues were:

- Key assumptions were not adequately justified, including:
  - Using the growth rate of 1.7% for the general Australian population applied to the number of patients with MS rather than growth in the MS population;
  - The growth rate of 1% applied to the prevalence of SPMS;
  - The uptake of siponimod in untreated patients being [redacted];
  - The assumptions that the treatment persistence of siponimod would be the same as fingolimod for the RRMS population; and
  - The compliance rate of 87% which was not supported by data from the MSBase registry.

- The uptake may be high as siponimod is the first treatment for SPMS, however this possible high uptake may be mitigated by reluctance to diagnose SPMS and limit further treatment options.
- 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.
- Duration may be overestimated as the proposed PBS restriction for siponimod includes stopping rules, however the definition of response is ambiguous.
- Base case estimates are likely underestimates but sensitivity analysis, where 100% of siponimod patients are currently untreated and there are no offsets for other medicines displaced, is an overestimate.

Financial Management – Risk Sharing Arrangements

6.55 The submission did not propose any risk sharing arrangements.

6.56 The pre-PBAC response noted DUSC advice that 'this is a new patient population and the estimates may be over or underestimated', and that 'overall the DUSC considered it is difficult to predict prescriber behaviour' in the context of SPMS. The sponsor acknowledged these uncertainties and stated that it expects to enter into a risk sharing arrangement with the Commonwealth to address this situation.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of siponimod for the treatment of secondary progressive multiple sclerosis (SPMS). The PBAC acknowledged the high clinical need for effective treatments in this therapeutic area. However, the PBAC considered that the appropriate place of siponimod in the treatment algorithm for multiple sclerosis (MS) was uncertain, and the submission did not provide a reliable basis to assess the cost-effectiveness of siponimod. The PBAC also considered the financial estimates to be uncertain.

7.2 The PBAC welcomed the input from individuals and organisations which described the high clinical need for effective treatments for patients with progressive forms of MS.

7.3 The PBAC acknowledged that as there are no treatments currently listed on the PBS for progressive forms of MS, there is a high unmet clinical need for effective treatments in this context.

7.4 The PBAC considered that, despite the high unmet clinical need, the appropriate place of siponimod in the treatment algorithm for MS was uncertain, and noted the proposed restriction did not specifically identify patients with SPMS or exclude patients with relapsing-remitting multiple sclerosis (RRMS). The PBAC acknowledged a key reason for this uncertainty is that it can be clinically difficult to determine when patients transition from RRMS to SPMS. As such, the PBAC considered that it is likely some people currently treated with RRMS disease modifying therapies (DMTs) may meet the criteria for siponimod under the requested listing.

7.5 In addition, the PBAC noted the submission, PSCR and pre-PBAC response requested a treatment algorithm where patients are able to transition back to PBS listed therapies for RRMS (following treatment with siponimod), if they meet the initiation criteria for treatment. The PBAC was uncertain if the requested treatment algorithm was appropriate, given the evidence base indicates patients generally do not frequently revert to a relapsing-only disease state following the start of progressive disease. However, the PBAC considered that, given there is a period where the classification of a patient with RRMS or SPMS is unclear because they may still experience relapses (albeit at a reduced frequency), some patients may continue to realise a benefit from treatment with RRMS therapies after failure with or an inability to tolerate siponimod.

7.6 The PBAC noted treatment with siponimod was contingent upon patients receiving a genetic test for the CYP2C9 enzyme to determine if patients were good, intermediate or poor metabolisers, with poor metabolisers ineligible for treatment. The PBAC considered that any future resubmission should include consultation with clinicians about the role of genetic testing and the extent to which any testing should be reflected in the restriction.

7.7 The PBAC considered the nominated mixed comparator of an 'untreated population' (placebo) and a 'treated population' with RRMS DMTs (interferon beta, glatiramer acetate, natalizumab, fingolimod and ocrelizumab) was not appropriate, as none of

the therapies currently PBS listed for RRMS have been evaluated or had their cost-effectiveness established in SPMS. On that basis, the PBAC considered placebo (best supportive care) was the appropriate comparator.

7.8 The PBAC noted the ESC advice that there were some differences between the pivotal clinical trial (EXPAND) population and the Australian population identified in the MSBase database. Overall, the PBAC considered on balance that the EXPAND trial population was likely to be applicable to the Australian SPMS population.

7.9 The PBAC considered the results of the EXPAND trial supported the clinical claim that siponimod is superior to placebo with regards to 3- and 6-month confirmed disability progression (CDP) and annualised relapse rate (ARR).

7.10 The PBAC considered the clinical claim that siponimod had an equivalent safety profile to placebo was not supported, as more patients receiving siponimod experienced hypertension, nausea, peripheral oedema and adverse liver function outcomes compared with placebo in the EXPAND trial. The PBAC considered siponimod was of inferior comparative safety to placebo.

7.11 The PBAC considered it was not possible to draw meaningful conclusions on the comparative efficacy and safety of siponimod to RRMS DMTs as indirect comparisons were not presented in the submission. The PBAC noted such comparisons would be limited by the quality of the available evidence for RRMD DMTs in the treatment of SPMS, however considered the assumption in the economic model that these treatments result in no clinical benefit together with a reduced quality of life to be implausible.

7.12 The PBAC noted the submission presented a weighted ICER calculated from three separate economic comparisons: siponimod vs placebo; siponimod vs interferon-beta/glatiramer acetate; and siponimod vs natalizumab. The PBAC did not accepted the weighted ICER as the Committee considered placebo to be the appropriate comparator for the reasons outlined in paragraph 7.7. The PBAC did not consider the individual ICERs to be informative because of the use of a different price for siponimod for each of the three comparisons.

7.13 The PBAC noted the issues raised by ESC with the economic model and considered these were not adequately addressed with the re-specified base case in the pre-PBAC response.

7.14 The PBAC considered the 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. The PBAC agreed with DUSC that the uptake of siponimod was highly uncertain and dependent on factors such as whether patients would be permitted to return to treatment with RRMS therapies following treatment with siponimod.

7.15 The PBAC considered a future resubmission should assess the cost-effectiveness of siponimod versus placebo among people with SPMS, addressing the issues outlined

above in the 'economic analysis' section. However, the PBAC also acknowledged the clinical difficulty of determining when patients transition from RRMS to SPMS and hence the likelihood that some patients may continue to realise a benefit after failure with or an inability to tolerate siponimod. As such, the PBAC considered it may also be appropriate to include siponimod within the existing treatment algorithm for RRMS DMTs. Given the evidence base in reducing 3- and 6- month CDP, the PBAC considered such a listing would provide flexibility for clinicians to select the most appropriate therapy for individual patients based on clinical judgment, which may include siponimod when deemed clinically appropriate. Such an approach would also allow patients to transition back to RRMS DMTs following treatment with siponimod. Consistent with this the PBAC considered in a resubmission the cost-effectiveness of siponimod could alternatively be informed by a comparison with the DMTs among people with RRMS, and the Committee noted a previous trial of siponimod in this patient group (BOLD). Any resubmission should also provide revised financial estimates in which the issues as noted by DUSC are addressed.

7.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

Novartis is disappointed with the PBAC outcome but will continue to work collaboratively with the PBAC, the Department of Health and Federal Government to ensure that Australians with multiple sclerosis receive access to Mayzent® (siponimod) through the Pharmaceutical Benefits Scheme (PBS) at the earliest opportunity.