Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2265

siponimod 250 microgram and 2mg film-coated tablets (Mayzent®)

Novartis Pharmaceuticals UK Ltd

04 September 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

siponimod (Mayzent®) is accepted for use within NHSScotland.

Indication under review: treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

In a randomised, double-blind, placebo-controlled phase III study, siponimod was associated with a reduction in disability progression confirmed after 3 months in patients with SPMS.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

Treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.[1]

Dosing Information

Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. In patients with a CYP2C9*3*3 genotype, siponimod should not be used. The recommended maintenance dose of siponimod in patients with a CYP2C9*2*3 or *1*3 genotype is 1 mg once daily; the recommended maintenance dose in all other CYP2C9 genotype patients is 2mg once daily.

Treatment has to be started with a titration pack that lasts for 5 days with the recommended daily dose be taken once daily in the morning with or without food. Treatment starts with 250 micrograms once daily on days 1 and 2, followed by once-daily doses of 500 micrograms on day 3, 750 micrograms on day 4, and 1.25 mg on day 5, to reach the patient's prescribed maintenance dose of siponimod starting on day 6. In patients with CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg taken once daily and the additional exposure of 250 micrograms on day 5 does not compromise patient safety. Siponimod is taken orally with or without food, the tablets should be swallowed whole with water.[1]

During the first 6 days of treatment, if a titration dose is missed on one day treatment needs to be re-titrated from the start. If maintenance treatment is interrupted for 4 or more consecutive daily doses, siponimod needs to be re-titrated from the start.[1]

Treatment with siponimod should be initiated and supervised by a physician experienced in the management of multiple sclerosis.[1]

For further information please refer to the Summary of Product Characteristics (SPC).

Product availability date

February 2020

Summary of evidence on comparative efficacy

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator which binds selectively to two out of five G-protein-coupled receptors for S1P, namely S1P1 and S1P5. It acts as a functional antagonist on S1P1 receptors on lymphocytes to prevent egress from lymph nodes. This reduces the recirculation of T cells into the central nervous system (CNS) to limit central inflammation.[1, 2]

The evidence to support the use of siponimod comes from EXPAND, a multicentre, randomised, double-blind, placebo-controlled, phase III study in 1,651 patients with secondary progressive multiple sclerosis (SPMS). It included an event-driven, double-blind phase, followed by an open-label, extension phase. Eligible patients were aged 18 to 60 years with a diagnosis of SPMS,

defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of relapses. They had moderate to advanced disability with an Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5 (range 0 to 10 with higher score indicating greater disability) and documented EDSS progression in the previous 2 years (≥1 point for patients with EDSS <6.0 and ≥0.5 point for patients with EDSS ≥6.0). Patients also had a history of relapsing remitting MS (RRMS) according to the 2010 Revised McDonald criteria and no evidence of relapse or corticosteroid treatment within the previous 3 months.[2, 3]

Eligible patients were randomised, in a ratio of 2:1, to receive siponimod 2mg or placebo orally once daily. Siponimod was titrated as per the dosing recommendations above. Double-blind treatment continued for up to 3 years or until the occurrence of the pre-specified 374 primary events and ≥95% of patients had received treatment for ≥12 months. Patients with a 6-month confirmed disability progression (CDP) during the double-blind treatment were re-consented to continue on double-blind treatment, switched to open-label siponimod or stop study treatment and remain untreated or receive another disease modifying treatment. Randomisation was stratified according to country.[2, 3]

The primary outcome was time to 3-month CDP (defined as a 1-point increase in EDSS if the baseline score was 3.0 to 5.0, or a 0.5 point increase if the baseline was score was 5.5 to 6.5, confirmed at a scheduled visit at least 3 months later). EDSS scores were measured every 3 months by a trained and certified assessor. Efficacy analyses were performed in the full analysis set (FAS), which comprised all randomised and treated patients. A hierarchical statistical testing strategy was applied to the primary and two key secondary outcomes (time to 3-month confirmed worsening of at least 20% from baseline in the timed 25-foot walk test [T25FW] and change from baseline in T2 lesion volume), with no formal testing after the first non-significant outcome in the hierarchy.

After a median duration of study treatment of 18 months and a total of 461 primary events, the risk of 3-month CDP was statistically significantly lower with siponimod compared with placebo. There was no statistical significance in the first key secondary outcome, therefore further formal statistical testing was not performed. A post hoc subgroup analysis was performed in the subgroup of patients with active SPMS reflecting the licensed population (defined as those with a relapse in previous 2 years and/or presence of gadolinium [Gd]-enhancing T1 lesions at baseline, n=779). [1-4] Results in the FAS and subgroup representing the licensed indication are presented in table 1, below.

Table 1: Results of primary and secondary outcomes in the total population and active SPMS subgroup[2-4]

	FAS population		Active SPMS subgroup	
	Siponimod (n=1099)	Placebo (n=546)	Siponimod (n=516)	Placebo (n=263)
Primary outcome				
3-month CDP events, n/N (%)	288/1096 (26%)	173/545 (32%)	129/516 (25%)	91/263 (35%)
Hazard ratio (95% CI)	0.79 (0.65 to 0.95) p=0.013		0.69 (0.53 to 0.91)	
Secondary outcomes				
Time to 3-month confirmed worsening of ≥20% from baseline in T25FW, N/n (%)	432/1087 (39.7%)	225/543 (41.4%)	215/515 (41.7%)	120/263 (45.6%)
Hazard ratio (95% CI)	0.94 (0.8 to 1.10)[A]		0.86 (0.68 to 1.08)	
Change from baseline in total volume of lesions on T2 weighted images (mm^3), adjusted mean to month 12[B]	Siponimod (n=995) 205	Placebo (n=495) 818	Siponimod (n=473) 93.5	Placebo (n=244) 1117
- Between group difference (95% CI,)	-613 (-800 to -426)		NR	
6-month CDP events, n/N (%)	218/1096 (20%)	139/545 (26%)	99/516 (19%)	74/263 (28%)
Hazard ratio (95% CI)	0.74 (0.60 to 0.92)		0.63 (0.47 to 0.86)	
Adjusted annual relapse rate	0.07	0.16	-	-
Rate ratio (95% CI)	0.45 (0.34 to 0.59)		0.54 (0.39 to 0.77)	

FAS = full analysis set, SPMS=secondary progressive multiple sclerosis, CDP=confirmed disease progression, CI=confidence interval, NR=not reported.

[A] p=0.44; [B] Adjusted mean refers to the change from baseline in T2 lesion volume at each time point

Exploratory outcomes assessed Health Related Quality of Life (HRQoL) using the Multiple Sclerosis Impact Scale (MSIS-29) and the generic European Quality of Life (EuroQol)-5 dimensions (EQ-5D). MSIS-29 measures the physical and psychological impact of MS on quality of life in the previous 2 weeks (range from 0 to 100, with higher scores indicating greater impact). In the FAS population, the adjusted mean differences in physical impact scores were lower at 12 months (-2.89) favouring siponimod but at 24 months the difference was less. There was no between group difference achieved for psychological impact scores at month 12 or 24.[2] At 12 months, there was a small adjusted mean between group difference (0.025) in the EQ-5D utility scores favouring siponimod;

however, this was not maintained at 24 months. There were no adjusted mean differences for the EQ-5D visual analogue scale scores at months 12 or 24.[2] No data were reported for the active SPMS subgroup.

The submitting company presented eleven placebo-anchored matching-adjusted indirect comparisons (MAIC) comparing siponimod against interferon beta-1b, interferon beta-1a, and natalizumab, in patients with SPMS. Propensity score weighting for a number of effect modifiers was used to match individual patient data from EXPAND with aggregate data from the comparator studies and estimate the relative treatment effects of siponimod versus comparators for CDP (at 3 and 6 months) and annualised relapse rate (ARR). These MAICs have been published and results are presented in table 2.[5]

Table 2: Results from MAIC[5]

Comparator	Confirmed disability progression		Annual relapse rate	
Interferon beta-1b (Betaferon)[A] (North American Study)	Time to 6-month CDP, HR (95% CI)	0.55 (0.33 to 0.91)	Rate ratio (95% CI)	0.90[B] (0.51 to 1.59)
Natalizumab[A] (ASCEND study)	Proportion with 6-month CDP by 96 weeks, OR (95% CI)	0.76 (0.44 to 1.30)		1.43 (0.78 to 2.61)
Interferon beta-1a (Rebif) 22 micrograms three times weekly (SPECTRIMS study)	Time to 3-month CDP, HR (95% CI)	0.80 (0.46 to 1.38)		0.73 (0.40 to 1.31)
Interferon beta-1a (Rebif) 44 micrograms three times weekly (SPECTRIMS study)		0.84 (0.49 to 1.47)		0.73 (0.40 to 1.32)
Interferon beta-1b (Betaferon)[A] (European study)		0.82 (0.42 to 1.63)		-
Interferon beta-1a (Avonex)[C] (IMPACT study)		0.42 (0.20 to 0.88)		0.997 (0.46 to 2.18)

HR=hazard ratio, CI=confidence interval, CDP=confirmed disability progression, OR= odds ratio. [A]at licensed dose, [B]combined data from North American Study and European study, [C]60 micrograms once a week (licensed dose is 30micrograms once a week).

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

Safety data are reported for the total study population only and not for the active SPMS subgroup. In the EXPAND study (Core Part), the mean duration of treatment in the siponimod group was 18.5 months and in the placebo group was 18 months. Any treatment-emergent adverse event (AE) was reported by 89% (975/1099) of patients in the siponimod group and 82% (445/546) in the placebo group. At least one serious AE was reported by 18% and 15% of patients respectively and 7.6% and 5.1% of patients respectively discontinued study treatment due to an AE.[2, 3, 6]

The most frequently reported treatment-emergent AEs of any grade with an incidence >5% in the siponimod and placebo groups respectively were headache (15% and 13%), nasopharyngitis (14% and 15%), urinary tract infection (12% and 15%), fall (12% and 11%), hypertension (10% and 7.5%), fatigue (9.1% and 9.3%),upper respiratory tract infection (8.3% and 7.5%), dizziness (6.8% and 4.8%), nausea (6.7% and 3.5%), influenza (6.6% and 7.3%), diarrhoea (6.4% and 4.2%), back pain (6.1% and 7.9%), increased alanine aminotransferase (5.9% and 1.5%), pain in extremities (5.5% and 3.8%), arthralgia (4.5% and 6.4%) and depression (4.5% and 5.5%).[3]

More patients in the siponimod group had AEs previously associated with S1P-receptor modulation, such as hypertension (12% versus 9.2%), bradycardia at treatment initiation (4.4% versus 2.6%), macular oedema (1.6% versus 0.2%) and lymphopenia (0.8% versus 0%). Convulsions were also more common with siponimod than with placebo (1.7% versus 0.4%). The rate of infections was similar in both groups (49%) but herpes viral infection was more common in siponimod than placebo patients (4.8% versus 2.7%). Rates of malignancies, including basal cell carcinoma, were similar in the two treatment groups (1%).[3]

*Other data were also assessed but remain confidential.**

Summary of clinical effectiveness issues

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system (CNS) characterised by inflammation, demyelination, and degenerative changes including neuroaxonal loss and progressive atrophy.[7] Relapsing remitting multiple sclerosis (RRMS) is the most common form and affects approximately 85% of patients at disease onset. This develops into SPMS in more than 50% of patients over 15 to 20 years. SPMS occurs when there is a gradual accumulation of disability with or without superimposed relapses. The transition from RRMS to SPMS may be a gradual progression and the diagnosis of SPMS may be unclear or delayed. Patients who progress from RRMS to SPMS may continue to have relapses and so may continue to receive DMT. Interferon beta-1b is currently the only other medicine licensed for use in SPMS with active disease. Other treatment options for SPMS are supportive measures to control disease symptoms. The delay in diagnosing SPMS may be influenced by a lack of available effective treatments and in practice, patients may continue to be treated with DMT not licensed for use in SPMS.[2, 8-10] Clinical experts consulted by SMC considered that there is an unmet need for effective

treatments for patients with active SPMS. Siponimod may offer a treatment option for patients confirmed to have transitioned from RRMS to SPMS who have active disease.

In EXPAND, the risk of 3-month CDP was reduced from 32% in the placebo group to 26% in the siponimod group in the FAS and from 35% to 25% in the active SPMS subgroup, relevant to the licensed indication. The relative risk reductions were 21% and 31% respectively but the absolute reductions were more modest: 3-month CDP benefit of 6% in the FAS and of 10% in the active SPMS subgroup. The EMA considered this a clinically relevant treatment effect in the active SPMS subgroup of patients. This was supported by reduction in 6-month CDP from 28% to 19% (relative and absolute reductions of 37% and 9% respectively) in the active subgroup.[1, 2]

There were a number of limitations in the evidence. In SPMS, preventing or delaying the accumulation of disability is considered the most clinically relevant treatment goal. In EXPAND, the primary outcome assessed disability progression confirmed after 3 months and not after 6 months as recommended by the EMA; 6-month CDP was a secondary outcome. CDP was based on the EDSS score and it is recognised that this does not adequately assess upper limb function and cognitive impairment.[2, 11]

The EXPAND study included patients with active and inactive SPMS and a post hoc subgroup analysis of patients with active disease represents the licensed population. This was because the EMA did not consider the efficacy of siponimod independent of relapses demonstrated and the effect of siponimod on disability progression appeared small in patients without relapses and without focal MRI activity. However since the study was neither planned nor powered for this post hoc analysis, these results should be interpreted with caution.[1, 2]

The double-blind phase of the study was event-driven and median duration of treatment was 18 months which is relatively short to determine the long-term effect on disability progression. The EMA recommends that disability progression is maintained on a long-term basis and since the course of disability in MS is slow, a follow up of at least 5 years may be needed. The results on longer term treatment effects from the open-label extension phase of EXPAND, with treatment up to 10 years, should address this.[2, 3, 11]

Patients in the EXPAND study were aged 18 to 60 years (mean age 48 years) and had a baseline EDSS score of 3.0 to 6.5 (mean 5.4). However, in clinical practice, patients with SPMS may be older and have higher EDSS scores and this may affect the generalisability of the study results to the Scottish population. The EMA considered that the EXPAND study population represented those in the early phase of SPMS where focal inflammatory activity is still a relevant pathogenic mechanism.[2, 3]

There is no direct evidence versus active comparators and the submitting company presented the results of MAICs as indirect evidence. The MAICs had with a number of limitations affecting their validity. The population included in the MAIC was wider than the licensed indication for siponimod and therefore the results may not be generalisable to the licensed with active disease. It was not possible to match all identified treatment effect modifiers and in some MAICs the level of

matching was limited. There was a marked difference between the level of previous interferon beta therapy in the EXPAND study and the interferon studies in which patients were interferon beta-naïve and this difference was matched for in the MAIC by excluding patients with prior treatment experience, which may have introduced bias. The reduction of the effective sample size in the MAIC ranged between 63% and 93% for the comparisons of siponimod versus the comparator treatments in the CDP and ARR analyses, which increases uncertainty in the results of the analyses. The analyses did not assess safety, treatment discontinuation, or health-related quality of life, which may be clinically relevant when considering the risk/benefit of treatments.

Siponimod may offer patients with SPMS and active disease a second licensed treatment option. The only other licensed treatment is interferon beta-1b and many patients may have already received this during earlier disease management. Siponimod is administered orally and avoids the need for subcutaneous injections (required for interferon beta-1b) with minimal practical issues for patients and the service. All patients require a genotype test before initiation of siponimod treatment to assess cytochrome P450 2C9 (CYP2C9) status and identify those patients who should not receive siponimod or receive a lower maintenance dose.[1]

Clinical experts consulted by SMC considered that siponimod is a therapeutic advancement as there are a limited number of licensed treatment options to slow disability in this patient population. They indicated its place in therapy would be for patients with SPMS who show evidence of active disease to slow progression and preserve function. The introduction of this medicine may impact service delivery as clinical time, clinic capacity and MRI scans will be required to assess suitability. The SPC notes monitoring for bradyarrhythmia and macular oedema may be required for some patients.[1]

Summary of comparative health economic evidence

The company submitted a cost-utility analysis to evaluate siponimod versus interferon-beta 1b for the treatment of adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity. Interferon beta-1b is the only available licensed treatment option in the UK for patients with active SPMS. However, in scenario analysis beta-interferon 1a, fingolimod, natalizumab, ocrelizumab, glatiramer acetate, dimethyl fumerate and teriflunomide were considered, as was a comparator of best supportive care (BSC).

A Markov model was used consisting of 11 health states, one state being death the other ten states being categories 0-9 on the EDSS instrument used to measure MS progression. The perspective was NHS and Personal & Social Services for costs but the base case presented by the company included carer effects for benefits. The time horizon was the lifetime of the patient and in the base case this was 53 cycles of cycle length 1 year.

Clinical data for the economic evaluation were taken from the EXPAND study using the secondary trial outcome (but preferred) time to 6 month CDP. Data were modelled beyond the study follow up period by using supplementary database information to inform transition probabilities that could not be informed by the trial placebo arm (EDSS 0–2 and 7–10). The source of database used

to inform these transition probabilities was tested in scenario analysis. A treatment effect was assumed to apply until discontinuation. The treatment effect in the economic model was informed by the MAIC and applied to estimates of the natural history of disease progression through EDSS states using the transition probabilities.[5] For the best supportive care comparator provided in updated scenario analysis from the company, the hazard ratio for the active SPMS group from the EXPAND study was used which was 0.63 (95% CI: 0.47 to 0.86).[1, 2]

The proportion of patients remaining on treatment over time was modelled using a Weibull distribution and this choice was not tested in scenario analysis even though the AIC results were similar for other distributions (notably the exponential had a slightly higher AIC but exhibited unrealistically high continuation rates at later time points). A scenario analysis explored the impact of discontinuations occurring at a constant rate over time rather than being time dependent. The model also assumes that people ceased treatment once they reached EDSS state 7, receiving best supportive care after this point. Scenario analysis provided by the submitting company also explored two treatment waning effects; firstly of 50% from year 11 and secondly of 25% from year 7 followed by 50% from year 10.

Adverse event data informing the model were taken from the siponimod arm of the EXPAND study and supplemented with data used in the NICE appraisal of ocrelizumab for treating RRMS. This was explored in scenario analysis using adverse events reported in the individual NICE appraisals for each comparator. The number of different adverse events reported across the NICE appraisals for each of the comparator means that there are sometimes inconsistencies in disutility (and duration) and costs applied to each event where it is very similar to another one listed for a different comparator. However, this is not expected to considerably influence the model.

Utilities data in the base case used the EQ-5D-3L data from the EXPAND study, pooled across treatment arms since there was no significant difference found in the study results for this secondary outcome, and used to create values for each EDSS state. This had to be supplemented with data from the literature.[12] Resulting utility values used in the model ranged from 0.825 for EDSS0 to -0.240 for EDSS9. The impact of using this source was tested in scenario analysis. Caregiver disutility was incorporated into the base case using literature values, and an alternative source was tested in scenario analysis, as was removing it from the model entirely.

Costs included the cost of medicines including administration and monitoring costs, plus the costs incurred in each EDSS state and the cost of managing adverse events. Monitoring costs typically included neurology visits and follow-ups, MS nurse visits as well as full blood count and liver function tests. Some monitoring costs for siponimod may reflect either study protocol stringency or adverse event issues that may not have been captured by the current method used to account for adverse events in the model. The most common sources for adverse event costs were existing NICE Technology Appraisals.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount has been offered on the list price. Base case results are provided in table 2. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the list price figures can be presented.

Table 2: Base case results (list price)

Technologies	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Interferon beta-1b	-	-	-
Siponimod	0.28	1.29	£38,271
Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; QALYs: quality-adjusted life-years;			

Deterministic, probabilistic and scenario analysis were undertaken. The deterministic analysis found the model only sensitive to the MAIC hazard ratios. While the lower and upper bound deterministic values represent the confidence intervals, SMC statistician feedback noted that because the EXPAND study is large and uses individual patient data it will be useful but will swamp the comparative data which is based on aggregates of much smaller studies. As such, confidence intervals will be driven by the larger study and may give spurious precision, so it remains possible that the HR parameters could alter the conclusions regarding the cost effectiveness.

The scenario analyses tested a variety of different model inputs and assumptions, particularly with regard to the comparators of most relevance to clinical practice. These are provided below for all comparator DMTs considered in the MAIC. Notably, there was not sufficient data from the MAIC to provide sufficient data for each comparator for both the 6-month CDP and ARR outcomes. Hazard ratios for dimethyl fumarate, fingolimod, ocrelizumab and teriflunomide were assumed to be 1 (95%CI: 0.8 to 1.2), for glatiramer acetate it was felt that the interferon-beta 1b results offered a more conservative proxy and so the interferon-beta 1b data from the MAIC were used for this interferon-beta 1a comparator.

PAS discounts are in place for ocrelizumab, dimethyl fumarate, and teriflunomide and these were included in the results used for decision-making by using estimates of the comparator PAS prices. SMC is unable to present the results provided by the company which used an estimate of the PAS price for these medicines due to commercial confidentiality and competition law issues. As such, results at list prices for all medicines are presented in table 3 for relevant comparisons.

Table 3: Scenario analysis for comparator DMTs (list prices)

Scenario	Treatment	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Fingolimod	Fingolimod	-	-	-
	Siponimod	0.21	1.00	£8,557
Ocrelizumab	Ocrelizumab	-	-	-
	Siponimod	0.21	1.03	£2,940
Dimethyl fumarate	Dimethyl fumarate	-	-	-
	Siponimod	0.21	0.99	£14,175
Teriflunomide	Teriflunomide	-	-	-
	Siponimod	021	0.98	£31,865
Glatiramer acetate	Glatiramer acetate	-	-	-
	Siponimod	0.28	1.29	£42,831
Natalizumab	Natalizumab	-	-	-

	Siponimod	0.14	0.72	Dominant

Scenario analyses against BSC and a weighted comparator of BSC and DMTs are shown in table 4 below.

Table 4: Scenario analyses for BSC (unless stated) using list prices

Scenario	Treatment	QALYs	Incremental QALYs	ICER (£/QALY)
Alternative comparator Base case: Interferon beta-1b Scenario: BSC	BSC	2.96	-	-
	Siponimod	3.93	0.97	£86,186
Base case: All-cause treatment discontinuation as a proxy for treatment waning; versus interferon beta-1b Scenario: Treatment waning of 50% from Year 11; versus BSC	BSC	2.96	-	-
	Siponimod	3.87	0.91	£92,306
Base case: All-cause treatment discontinuation as a proxy for treatment waning; versus interferon beta-1b Scenario: Treatment waning of 25% from Year 7, 50% from Year 10; versus BSC	BSC	2.96	-	-
	Siponimod	3.82	0.86	£98,345
Use of British Columbia database for transition probabilities	BSC	5.56	-	-
	Siponimod	6.35	0.79	£110,638
Use of the British Columbia database for transition probabilities, a time horizon of 40 years and excluding caregiver disutility	BSC	6.34	-	-
	Siponimod	7.04	0.71	£123,463
Use of the London Ontario database for transition probabilities, a time horizon of 40 years and excluding caregiver disutility	BSC	3.03	-	-
	Siponimod	3.76	0.72	£107,655
MRI monitoring costs for siponimod equivalent to natalizumab	BSC	2.96	-	
	Siponimod	3.93	0.97	£88,830
Alternative comparator Base case: Interferon beta-1b Scenario: Basket of DMTs and BSC	Weighted comparator	-		
	Weighted siponimod	-	-	£59,780

For best supportive care, the ICER was more sensitive to combined assumptions, particularly the choice of database for transition probabilities. However, the use of the British Columbia database in the combined scenario analysis in table 4 may be a conservative estimate, as this database includes data for those who do not have active SPMS.

There were a number of weaknesses with the analysis, namely:

- There is uncertainty over the most appropriate comparator for consideration between the licensed comparator (interferon-beta 1b) and expert responses indicating best supportive care may be the most valid comparator in clinical practice. While this is not an issue with the economics model itself, the choice of comparator has a considerable impact on the modelling results. SMC considered the results against BSC were the most relevant for decision-making.
- There is still a lack of clarity with regard to the implications of certain choices inputted into the model from the MAIC, which relied on the matching of ITT population data from the EXPAND study but has also used the data for the active SPMS subgroup in places. It was not possible to obtain information on the non-active SPMS subgroup within the ITT population from the submitting company to understand more about the characteristics of those outwith the active SPMS population whose data have been utilised to facilitate the MAIC.
- There is uncertainty with regard to the appropriateness of using the MAIC values in the economic model. SMC statistician feedback has been helpful, as has the provision of hazard ratios informing the model from the MAIC and the unadjusted naïve comparison for the comparator of interferon-beta 1b.
- The method for applying adverse events in the model relies on previous NICE Technology Appraisals. Of note is that siponimod appears to have the most favourable adverse event profile of any of the comparators of interest including the DMTs. Monitoring costs varied between the comparators. The submitting company clarified that the SmPCs had been used to identify monitoring costs but notably for siponimod this did not include MRIs. However, sensitivity analysis was provided which showed the inclusion of additional MRI monitoring costs resulted in a small increase to the ICER.

Despite these limitations, the economic case has been demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from The MS Society Scotland and The MS Trust, which are both registered charities.
- The MS Society has received 0.5% pharmaceutical company funding in the past two years, including from the submitting company. The MS Trust has received 10.4% pharmaceutical company funding in the past two years, including from the submitting company.
- MS is one of the most common disabling neurological conditions affecting young adults. Two thirds of people initially diagnosed with relapsing remitting MS (RRMS) develop secondary progressive MS (SPMS), with a small number diagnosed with SPMS from the outset. Cognitive problems are more severe in SPMS compared to RRMS, leading to lower quality of life. Other symptoms can include balance issues, visual problems, sensory

problems (pain), tremor, speech and swallowing difficulties, depression and anxiety. There are significant challenges to remaining in employment for people with SPMS and increasing carer burden as the condition progresses.

- Siponimod is a disease modifying therapy for secondary progressive MS for people with active disease; this is a wider classification than for beta Interferon which is only available for people with secondary progressive MS with relapses. This means that for the majority of people with secondary progressive MS there are no comparable treatments currently available. For those people with secondary progressive MS that are experiencing relapses who are eligible for beta Interferon, siponimod offers an alternative as an oral therapy as opposed to an injection.
- Siponimod would be expected to improve the patient's quality of life as it would be the first widely available DMT for secondary progressive MS. In clinical trials it has been shown to slow progression and as a result slow the accumulation of disability therefore offering hope to people living with SPMS. The slowing of disability could help individuals remain independent and need less help from family and carers. It could also help reduce the costs associated with living with severe MS.
- As an oral therapy siponimod offers many advantages over injectable therapies. The patient groups described how in general the MS community welcomes the potential for an oral treatment not only for its simplicity but also as a means of reducing the complications from regular injections.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published Multiple sclerosis in adults: management (Clinical guideline 186) in October 2014 and the guidance was updated in November 2019.[8] This guidance does not make any specific recommendations regarding the treatment of SPMS, however a number of research recommendations are related to secondary progressive disease. Furthermore, the guidance highlights that "*while a variety of symptomatic treatments is available, progression in secondary progressive MS is currently intractable, and immunomodulatory strategies used for relapsing–remitting MS have not proven effective when extended into secondary progressive MS (for example, beta interferon). Direct neuroprotection strategies (for example tetrahydrocannabinol) have also been ineffective. The critical and as yet unmet challenge therefore is to find effective and well-tolerated treatments for secondary progressive MS.*"

The European Academy of Neurology (EAN) and European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) published a Guideline on the pharmacological treatment of people with multiple sclerosis in 2018.[13] This guideline makes the following relevant recommendations, which are highlighted as having weak supportive evidence:

- Consider treatment with interferon-1a (sc) or -1b for patients with active secondary-progressive MS taking into account, in discussion with the patient, the dubious efficacy, as well as the safety and tolerability profile of these drugs.

- Consider treatment with mitoxantrone for patients with active secondary-progressive MS taking into account, in discussion with the patient, the efficacy, and specifically the safety and tolerability profile of this agent.

Consider treatment with ocrelizumab or cladribine for patients with active secondary-progressive MS.

Additional information: comparators

Interferon beta-1b

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Siponimod	2mg orally once daily	21,368

Costs from eMC Dictionary of Medicines and Devices Browser on 17 April 2020. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 15 July 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.