

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

**Siponimod for treating secondary progressive
multiple sclerosis**

1 Recommendations

- 1.1 Siponimod is recommended, within its marketing authorisation, as an option for treating secondary progressive multiple sclerosis with evidence of active disease (that is, relapses or imaging features of inflammatory activity) in adults. It is recommended only if the company provides siponimod according to the commercial arrangement (see section 2).

Why the committee made these recommendations

Interferon beta-1b is the only disease-modifying treatment available for people with active secondary progressive multiple sclerosis. However, few people have it. Most people do not have any disease-modifying treatments. Effective treatment options are therefore very limited.

Clinical trial results show that siponimod reduces the number of relapses and slows disability progression compared with placebo. It is uncertain how effective siponimod is compared with interferon beta-1b because there is no evidence directly comparing them.

The most plausible cost-effectiveness estimates for siponimod compared with no disease-modifying treatment and with interferon beta-1b (Extavia) are in the range that NICE normally considers an acceptable use of NHS resources. Therefore, siponimod is recommended.

2 Information about siponimod

Marketing authorisation indication

- 2.1 Siponimod (Mayzent, Novartis) is indicated for ‘the treatment of adult patients with secondary progressive multiple sclerosis with active disease evidenced by relapses or imaging features of inflammatory activity’.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The list price for siponimod is £1,643.72 per pack of 28x2 mg tablets (excluding VAT; BNF online, September 2020).
- 2.4 The company has a commercial arrangement (simple discount patient access scheme) with the NHS. This makes siponimod available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company’s responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Novartis, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

Treatment pathway

Secondary progressive multiple sclerosis is a continuum of relapsing–remitting multiple sclerosis

- 3.1 Relapsing–remitting multiple sclerosis progresses to secondary progressive multiple sclerosis in many people. The patient and clinical

experts, company and ERG all indicated that there is a period of transition in which people with relapsing–remitting multiple sclerosis may be suspected of having secondary progressive disease but are not formally diagnosed. This is especially the case for the population in this appraisal (that is, people with active secondary progressive disease) because they may still have relapses. The clinical experts confirmed that multiple sclerosis is a spectrum and does not consist of distinct phenotypic subtypes. The patient and clinical experts acknowledged that, historically, there has been reluctance to diagnose secondary progressive multiple sclerosis. This is because there is only 1 licensed treatment, interferon beta-1b, which people may have already had. Also, disease-modifying treatments for relapsing–remitting multiple sclerosis are no longer indicated once someone is diagnosed with secondary progressive multiple sclerosis, so treatment usually stops. The clinical experts explained that many factors influence disease progression in multiple sclerosis, including inflammation and age. However, there is a lack of clinical understanding in this area. The committee concluded that secondary progressive multiple sclerosis is a continuum of relapsing–remitting multiple sclerosis, and that various factors contribute to the progression of disease.

Siponimod could change the timing of diagnosis of secondary progressive multiple sclerosis and involve doing an MRI scan

3.2 In its submission, the company explained that the availability of a new treatment option for active secondary progressive multiple sclerosis could lead to diagnosing secondary progressive multiple sclerosis earlier. This is because neurologists are reluctant to make the diagnosis without an effective treatment being available (see section 3.1). The clinical experts explained that, if siponimod becomes available, somebody who would usually be diagnosed with secondary progressive multiple sclerosis at an Expanded Disability Status Scale (EDSS) score of 6 may instead be diagnosed at EDSS 4. They explained that diagnosis is currently based on signs and symptoms rather than biochemical or radiological testing. The committee was aware that siponimod’s marketing authorisation limits its

use to people with 'active' disease, and that the company defined active disease by either relapses or imaging features of inflammatory activity. The clinical experts explained that, if siponimod becomes available, more people would have an MRI scan to assess whether they have secondary progressive disease and identify whether they are eligible for siponimod. They explained that people already diagnosed with secondary progressive disease would have to have MRI scans and visit a neurologist to assess if siponimod is a suitable treatment option. The committee was aware that this additional activity could have a substantial resource impact for the NHS. It concluded that people may be formally diagnosed earlier with secondary progressive multiple sclerosis if siponimod becomes available, and that diagnosis would involve an MRI scan.

Comparators

Interferon beta-1b and best supportive care are the relevant comparators

3.3 Interferon beta-1b is the only treatment licensed for secondary progressive multiple sclerosis with active disease evidenced by relapses. One brand, Extavia, is recommended in [NICE's technology appraisal of beta interferons for multiple sclerosis](#). The patient and clinical experts explained that many people have difficulty tolerating interferon beta-1b because it can cause adverse effects such as flu-like symptoms, and involves having subcutaneous injections every other day. Also, the clinical experts reported that healthcare professionals query the efficacy of interferon beta-1b, so few people with secondary progressive multiple sclerosis have it. An NHS commissioning expert estimated that only about 75 people with secondary progressive multiple sclerosis in England have interferon beta-1b. So, most people do not have any disease-modifying treatment. In its original base-case analysis, the company compared siponimod with interferon beta-1b. It also provided scenario analyses comparing siponimod with a range of disease-modifying treatments licensed for relapsing–remitting multiple sclerosis. In its updated base case, the company compared siponimod with best supportive care and

with interferon beta-1b, but not with other disease-modifying treatments. This was in line with the committee conclusions from its first meeting. The company also presented a scenario using a weighted comparator. This included some people who were assumed to be having disease-modifying treatments licensed for relapsing–remitting multiple sclerosis and others who were not. The clinical experts explained that disease-modifying treatments are sometimes used outside of their licensed indications in people with secondary progressive multiple sclerosis during the transition period from relapsing–remitting disease. However, the NHS commissioning expert clarified that the NHS does not commission these drugs for secondary progressive multiple sclerosis, so they should not be considered relevant comparators. The committee concluded that some people diagnosed with active secondary progressive multiple sclerosis have interferon beta-1b, but that most people have no disease-modifying treatment. This means that patients and their clinicians have limited treatment options, and best supportive care or interferon beta-1b are the only relevant comparators. The committee further concluded not to consider the weighted comparator in its decision making.

EXPAND clinical trial

Characteristics of people in the subgroup with active disease from EXPAND reflect the population with active disease in NHS clinical practice

3.4 The main clinical evidence for siponimod came from EXPAND, a double-blind, randomised, placebo-controlled trial in adults with secondary progressive multiple sclerosis. The randomised part of the trial was followed by an observational period in which everyone was switched to open-label (unblinded) siponimod and followed for up to 10 years. This part of the trial is ongoing. The committee was aware that the marketing authorisation, being limited to active disease, reflected only a portion of the overall trial population. EXPAND enrolled people in 31 countries, including the UK. The primary outcome was the percentage of people with sustained disability lasting at least 3 months, 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 score was 5.5 to 6.5. Health-related quality of life data were collected using EQ-5D. The company suggested that EXPAND was generalisable to the secondary progressive multiple sclerosis population seen in NHS clinical practice because the study had UK sites. However, the committee noted that most sites were not in the UK. The ERG was concerned that outcomes and clinical practice may vary across the countries in the trial. The clinical experts advised that the baseline characteristics reflected people with the condition seen in the NHS. The committee concluded that the baseline characteristics of the subgroup with active disease in EXPAND were similar to the NHS population with active secondary progressive multiple sclerosis, and that the trial results are likely to be generalisable to the NHS population.

Siponimod is an effective treatment compared with placebo for active secondary progressive multiple sclerosis

3.5 In the subgroup of people with active disease in EXPAND, both time to 3-month (the primary endpoint) and 6-month confirmed disability progression (defined by the same EDSS changes as for the primary endpoint, but lasting at least 6 months) were longer with siponimod than with placebo. The annualised relapse rate was lower with siponimod than with placebo. The full results cannot be reported here because the company considers them confidential. The patient experts explained that the endpoints of 6-month confirmed disability progression and annualised relapse rate are important to patients, and the clinical experts considered the improvements seen in these endpoints to be clinically meaningful. The committee concluded that siponimod is an effective treatment for active secondary progressive multiple sclerosis compared with placebo.

It is uncertain whether siponimod has the same effect in disease with and without imaging features of inflammatory activity

3.6 Based on the possibility that it could not recommend siponimod for use in all patients covered in the marketing authorisation, in its first meeting, the

committee was interested in whether siponimod is of more benefit in disease with imaging features of inflammatory activity than without. The clinical experts advised that it is possible to have active disease without any changes in imaging features, and that it is possible to progress in terms of changes on MRI without evidence of clinical progression. For the committee's second meeting, the company provided results for subgroups of the EXPAND active population according to whether the disease was relapsing and whether there were imaging features of inflammatory activity. Based on these results, the company considered siponimod to be an effective treatment regardless of whether or not people have imaging features of inflammatory activity. However, it did not provide a test for interaction. The committee concluded that it remains uncertain whether siponimod compared with placebo has the same effect on disease with and without imaging features of inflammatory activity.

Indirect treatment comparisons

All of the company's and ERG's indirect treatment comparisons have limitations

- 3.7 There is no trial comparing siponimod with interferon beta-1b. Therefore, the company did an indirect comparison using data from EXPAND and 2 trials of interferon beta-1b, which reported relevant efficacy outcomes. One trial by the European Study Group, known as the 'European trial', reported annualised relapse rate and 3-month confirmed disability progression. The other, a North American trial, reported annualised relapse rate and 6-month confirmed disability progression. The company chose a matching-adjusted indirect comparison as its base case because it considered that differences between EXPAND and the 2 interferon beta-1b trials made a network meta-analysis unfeasible. The company stated that its analysis used the full trial populations because the trials did not report relevant results separately for people with active disease. The company highlighted differences in the inclusion and exclusion criteria, placebo regimens and response in the placebo arms. The ERG stated

that the company did not match for all relevant confounders and effect modifiers in its matching-adjusted indirect comparison. It noted that matching to the data for interferon beta-1b reduced the EXPAND effective sample size, which increased uncertainty. The ERG did its own network meta-analysis because it did not consider the company's reasons for doing a matching-adjusted indirect comparison instead of a network meta-analysis reasonable. Both the company's and the ERG's analyses favoured siponimod over interferon beta-1b for the outcome of 6-month confirmed disability progression, but the wide confidence interval around the ERG's estimate included the possibility of no effect. For annualised relapse rate, both the company's and the ERG's analyses favoured siponimod over interferon beta-1b, but the confidence intervals for both analyses included the possibility of no effect. The company considered that any network meta-analysis should be based on the population in the marketing authorisation (that is, people with active disease), whereas the ERG used the full EXPAND population. At technical engagement, the company provided an additional network meta-analysis based on the active-disease population from EXPAND. The point estimate of effectiveness for 6-month confirmed disability progression favoured siponimod compared with interferon beta-1b, but the confidence interval included the possibility of no benefit. The results cannot be reported here because they are considered confidential by the company. The committee was concerned that, although this network meta-analysis used the active-disease population from EXPAND, it used the full trial populations for the trials of interferon beta-1b. The committee noted that, in the European trial, about 70% of people had relapses, indicating probable active disease. It questioned whether a matching-adjusted indirect comparison using only this trial data may provide a more reliable result than any of the indirect comparisons it had been presented with so far. However, the committee was aware that the European trial collected only 3-month rather than 6-month confirmed disability progression data, which it would normally prefer. In response to consultation, the company explained that

the point estimate of effectiveness for 3-month confirmed disability progression favoured siponimod compared with interferon beta-1b, but the confidence interval included the possibility of no benefit. The company also expressed concerns that the population in the European trial was younger than in the EXPAND and North American trials, and the effective sample size was lower when using European trial data. The committee concluded that there were substantial uncertainties associated with all of the indirect comparisons.

The company's economic model

Data from the placebo arm of EXPAND and the London Ontario registry should be used to model untreated secondary progressive multiple sclerosis

3.8 The company modelled disease progression using 11 health states, 10 defined by EDSS scores ranging from 0 to 9 (with a higher score indicating worse disease) and a death state. It assumed that an effective treatment for secondary progressive multiple sclerosis improves quality of life by delaying the progression of disease to higher EDSS states, and by reducing the frequency of relapses. The company also assumed that treatment improves a carer's quality of life, and that an effective treatment prolongs life by delaying progression to higher EDSS states that are associated with higher rates of death. To model untreated disease (best supportive care), the company used the placebo group from EXPAND supplemented with data from the London Ontario registry. In each cycle, people could move to a higher or lower EDSS state (that is, their disability could worsen or improve) or remain in the same state. The ERG, in discussion with its clinical adviser, highlighted that, over the long term, people with secondary progressive multiple sclerosis will progress to (or sometimes plateau at) higher EDSS states. But, in the short term, if people have a relapse from which they recover, they could improve before they worsen again. The ERG assumed that this short timeframe may be about 2 to 3 months and pointed out that transitions in the model were yearly, so improvements were likely to be very rare. Because the London

Ontario data do not allow improvements in the EDSS, the ERG considered it to be more appropriate than the trial data. It also highlighted that these data were collected over 25 years compared with the 2-year duration of EXPAND. The committee was aware that previous appraisals for relapsing–remitting multiple sclerosis had used both the London Ontario data alone and the trial placebo data supplemented by registry data. The committee considered that, because improvements in EDSS had been seen in the trial, it was reasonable for the model to capture them. The committee concluded that it was appropriate for the company to model untreated disease using data from the placebo arm of EXPAND supplemented by the London Ontario registry.

The modelled population should have active disease to reflect the marketing authorisation

3.9 In its base case, the company used baseline characteristics reflecting the subgroup of people with active disease in EXPAND. The ERG considered that the characteristics from the full (intention-to-treat) population should have been used instead because this is the population in whom the treatment effect estimates were derived in both the company's and the ERG's preferred indirect comparison (see section 3.7). The committee was aware that it could appraise treatments only within the marketing authorisation. It considered that the modelled population should match the marketing authorisation for siponimod, which covers people with active secondary progressive multiple sclerosis. The committee concluded that the modelled population should have active disease at baseline.

Treatment discontinuation rather than study discontinuation provides a better estimate of the number of people stopping siponimod in clinical practice

3.10 The committee noted that it was unclear whether the company had used study discontinuation or treatment discontinuation from EXPAND to model stopping treatment with siponimod for any reason in its original model. The committee considered that treatment discontinuation rather than study discontinuation would provide a better estimate of the number of

people stopping siponimod in clinical practice. The company clarified that its original model used study discontinuation. It agreed with the committee's suggested change and in response to consultation used treatment discontinuation instead in its updated base case.

Utility values in the economic model

The model should include utility values from the active subgroup of EXPAND supplemented by Orme et al. (2007)

3.11 To estimate health-related quality of life, the company used EQ-5D-3L utility values from EXPAND. It supplemented these with values from a published paper, Orme et al. (2007), for EDSS states 0, 1, 2, 8 and 9 because there were few people with these EDSS values in the EXPAND trial. The ERG considered that there was uncertainty about the EQ-5D values from EXPAND and that they might not be generalisable to people in the NHS. The ERG preferred to use the data from Orme et al. because they were based on more people than EXPAND. The committee noted that the utility value for EDSS 3 (0.529) from Orme et al. was lower than the value for EDSS 4 (0.565), which the committee considered to lack face validity. The clinical experts explained that the EXPAND data were more recent than the Orme data, so may better reflect advances in supportive care. The committee considered that the model should have included utility values from the subgroup of people with active disease, rather than the full EXPAND population. The company updated its base case in response to consultation to reflect the committee's preferences.

Costs in the economic model

Costs associated with starting siponimod are appropriately included in the company's model

3.12 The committee was aware that the company estimated costs for each EDSS state using data from the UK Multiple Sclerosis Survey, which was used in [NICE's technology appraisal of dimethyl fumarate for relapsing–](#)

[remitting multiple sclerosis](#). The company inflated the prices to 2017/2018 values. The patient and clinical experts explained that many people with secondary progressive multiple sclerosis do not regularly attend a specialist service, especially if they are not having disease-modifying treatments. The clinical and commissioning experts agreed that, if siponimod was offered in the NHS, it would be prescribed by healthcare professionals in a specialist service. Before starting treatment, people being considered for siponimod would attend a neurology clinic and have an MRI scan that they may not previously have been offered (see section 3.2). The clinical experts highlighted that these costs would apply only to people who had already been diagnosed with secondary progressive multiple sclerosis. It would not apply to people who are transitioning from relapsing–remitting to secondary progressive disease, who would generally have regular MRI scans. The company clarified that its original model already included 2 neurology appointments for siponimod each year, including a higher cost of a first appointment as well as a follow-up appointment in the first year. In response to consultation, it also presented a scenario in which it included a third annual neurology appointment and explained that its updated base case included the cost of an additional MRI scan for people starting siponimod. The committee concluded that the company had appropriately modelled costs associated with additional neurology visits and scans in its updated base case.

Waning of siponimod treatment effect

It is appropriate to model waning of the effect of treatment with siponimod

3.13 The company presented an analysis of 6-year data from the open-label extension of EXPAND. It argued that this shows the effect of siponimod treatment does not diminish over time. The committee considered this analysis to be highly uncertain because everyone in the open-label extension had siponimod. Also, there was no comparator arm that could be used to confidently estimate siponimod's relative treatment effect. In its original analysis, the company considered the rate at which people stop

treatment for any reason to be a suitable proxy for the waning of treatment effect with siponimod in the model. This was because, if siponimod stops working, people are likely to stop taking it. The committee considered that the company's original approach may have overestimated the benefits of siponimod if people remain on treatment even if its efficacy decreases over time. Including a waning of the treatment effect in the model would help to address this possibility. The clinical experts explained that it is difficult to comment on whether the effect of treatment with siponimod is likely to wane over time. The committee noted [NICE's technology appraisal guidance for fingolimod](#), which has a related mechanism of action to siponimod. In that appraisal, the committee concluded that the treatment effect was likely to wane. In response to consultation, the company updated its base case to include a 50% decrease in siponimod's effectiveness from year 11 of treatment onwards. It also presented a scenario with a 25% decrease in effectiveness from year 7 to year 10 of treatment, then a 50% decrease from year 10 onwards. The committee concluded that the company appropriately included waning of siponimod's treatment effect in its updated model.

Innovation

The company's model may not capture all the benefits of treatment with siponimod

3.14 The company explained that it considered siponimod to be innovative because it is taken orally, whereas interferon beta-1b is a powder that must be mixed with solvent and injected subcutaneously. Therefore, people are likely to find siponimod easier to take. Consultees noted that people with impaired motor function are likely to find it particularly difficult to self-administer interferon beta-1b, so this is a potential equality issue. The company also suggested that the beneficial effects of siponimod on cognitive processing have not been captured in the modelling. It presented results from EXPAND showing improvements in the symbol digit modalities test score (a test for assessing cognitive processing in

multiple sclerosis) with siponimod compared with placebo. The ERG agreed with the company that there was some evidence suggesting that siponimod benefits cognitive processing speed and that the EQ-5D may not have fully captured this. The committee agreed that such benefits could be important. However, the symbol digit modalities test score was only 1 exploratory endpoint of the EXPAND trial, and the committee did not see the other exploratory endpoints, so it was difficult to draw conclusions using this score alone. However, the committee concluded that the benefits related to ease of administration had likely not been captured in the model.

Cost-effectiveness estimate

The company's updated base case reflects the committee's preferred assumptions

3.15 Following changes made in response to consultation, the company's updated analysis reflected the committee's preferences as follows:

- a comparison of siponimod with interferon beta-1b and best supportive care in a probabilistic fully-incremental analysis
- treatment discontinuation rather than study discontinuation used to estimate the numbers stopping siponimod in clinical practice
- utility values from the subgroup of people with active disease from EXPAND supplemented by Orme et al. (2007)
- costs of neurology appointments and MRI scans for people starting siponimod
- a waning of the effect of treatment for siponimod.

Because of confidential commercial arrangements for siponimod and interferon beta-1b, the cost-effectiveness results cannot be reported here.

Siponimod is likely to be a cost-effective use of NHS resources

3.16 The committee considered the company's base-case cost-effectiveness results based on its matching-adjusted indirect treatment comparison, and a scenario analysis based on its network meta-analysis using the active population from EXPAND. For the comparison with best supportive care, the committee noted that the EXPAND trial compared siponimod with placebo directly. Therefore, the company could have used the trial results as a source of effectiveness evidence in the model without the need for an indirect comparison. This analysis was not available. However, the committee noted that the hazard ratio for 6-month confirmed disability progression was more favourable for siponimod in EXPAND than in the company's network meta-analysis. It was therefore satisfied that the incremental cost-effectiveness ratio would decrease if the EXPAND results were used instead of the network meta-analysis. The committee noted that some uncertainty remained about the cost-effectiveness results because of uncertainties associated with the indirect comparisons. However, the committee appreciated the steps taken by the company to resolve some of this uncertainty, including presenting an updated analysis that was in line with its preferences. The committee also noted that there were limited alternative treatment options for this population (see section 3.3). Taking this into account, the committee was satisfied that the cost-effectiveness estimates were within the range that NICE normally considers an acceptable use of NHS resources.

4 Implementation

4.1 [Section 7\(6\) of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has secondary progressive multiple sclerosis with active disease evidenced by relapses or imaging features of inflammatory activity and the doctor responsible for their care thinks that siponimod is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Review of guidance

- 5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
September 2020

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Hannah Nicholas

Technical lead

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