

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Siponimod for treating secondary progressive multiple sclerosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using siponimod in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using siponimod in the NHS in England.

For further details, see [NICE's guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 16 July 2020

Second appraisal committee meeting: Date to be confirmed

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 1.1 Siponimod is not recommended, within its marketing authorisation, for treating secondary progressive multiple sclerosis with evidence of active disease (that is, relapses or imaging features of inflammatory activity) in adults.
- 1.2 This recommendation is not intended to affect treatment with siponimod that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

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 take it. Most people do not have any disease-modifying treatment.

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.

Because of the limited clinical evidence, the cost-effectiveness estimates are uncertain, and none of the analyses reflect the committee's preferred assumptions. Therefore, siponimod is not 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 £1,648.23 per pack of 28 tablets, each containing 2 milligrams (excluding VAT; BNF online, May 2020). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) 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 The committee noted that in many people relapsing–remitting multiple sclerosis progresses to secondary progressive multiple sclerosis. The clinical experts, patient 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

of interest in this appraisal, people with active secondary progressive disease, because they may still have relapses. The clinical expert confirmed that multiple sclerosis is a spectrum and does not consist of distinct phenotypic subtypes. The patient and clinical experts also acknowledged that historically, there has been reluctance to diagnose patients with secondary progressive multiple sclerosis because there is only 1 licensed treatment, which people may already have taken. 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 disease progression in multiple sclerosis is multifactorial and that inflammation and age are known contributing factors. 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 multiple factors contribute to the progression of disease.

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

3.2 In its submission the company explained that a treatment for active secondary progressive multiple sclerosis could lead to secondary progressive multiple sclerosis being diagnosed earlier, 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 were 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 more people would have an MRI scan as part of

their diagnosis to identify if they are eligible for siponimod. They also 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. The committee concluded that people may be formally diagnosed with secondary progressive multiple sclerosis earlier if siponimod is 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 side effects such as flu-like symptoms, and it must be taken every other day. Also, the clinical expert reported that healthcare professionals are uncertain about the efficacy of interferon beta-1b, so very few people with secondary progressive multiple sclerosis take it. An NHS commissioning expert estimated that out of about 9,000 people with secondary progressive multiple sclerosis in England, only about 75 people take interferon beta-1b. So most people do not have any disease-modifying treatment. In the company's main analysis (base case) it compared siponimod with interferon beta-1b. It also provided scenario analyses comparing siponimod with a range of disease-modifying therapies licensed for relapsing–remitting multiple sclerosis. The clinical expert explained that disease-modifying therapies 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 and therefore they should not be considered relevant comparators. The committee concluded that some people with active secondary progressive multiple sclerosis take interferon beta-1b but most people have no disease-modifying treatment. Therefore, the relevant comparators are best supportive care and interferon beta-1b.

EXPAND clinical trial

Baseline characteristics in the active subgroup of EXPAND reflect the NHS population with active secondary progressive multiple sclerosis

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 all participants were 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 participants in 31 countries, including the UK. The primary outcome was the percentage of participants 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 is generalisable to the secondary progressive multiple sclerosis population seen in NHS clinical practice because the study had UK sites. But the committee was aware 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 expert advised that the baseline characteristics reflect people with the disease seen in the NHS. The committee concluded that the baseline characteristics of the active disease subgroup in EXPAND are 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 confirmed disability progression and 6-month confirmed disability progression (defined by the same EDSS changes as for the primary end point noted in section 3.4, 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 they are considered confidential by the company. The patient experts explained that the endpoints of 6-month confirmed disability progression and annualised relapse rate are important to patients, and the clinical expert considered the improvements in these endpoints to be clinically meaningful. The committee concluded that siponimod is an effective treatment compared with placebo for active secondary progressive multiple sclerosis.

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

3.6 Although EXPAND provides evidence of the effect of siponimod in active secondary progressive multiple sclerosis, the company did not provide evidence on whether effects differ between disease with and without imaging features of inflammatory activity. The clinical expert 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. The committee was interested in whether siponimod is of more benefit in disease with imaging features of inflammatory activity than without, but the company did not explore this. The committee concluded that it is uncertain whether siponimod has the same effect in disease with and without imaging features of inflammatory activity.

Indirect treatment comparisons

The company's and ERG's indirect comparisons produce different results

3.7 Because there is no trial comparing siponimod with interferon beta-1b, the company did an indirect comparison using data from EXPAND and 2 trials of interferon beta-1b. The company chose a matching-adjusted indirect comparison, because it considered that differences between EXPAND and the 2 interferon beta-1b trials made a network meta-analysis unfeasible. The analysis used the full trial populations because the company said the trials did not report relevant results separately for patients with active disease. The company highlighted differences in the inclusion and exclusion criteria, placebo regimens and response in the placebo arms. The ERG highlighted 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 interferon beta-1b data made the EXPAND effective sample size much smaller, which increases the uncertainty. The clinical experts considered that the effect modifiers chosen by the company had face validity, but highlighted that it is difficult to identify effect modifiers. The ERG did their own network meta-analysis because they did not think the company's reasons for doing a matching-adjusted indirect comparison instead of a network meta-analysis were adequate. 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 interferon beta-1b studies. The committee concluded that there were substantial uncertainties associated with all of the indirect comparisons.

A matching-adjusted indirect comparison using data from the European trial may provide the best estimate of siponimod compared with interferon beta-1b

3.8 The committee noted that in the trial of interferon beta-1b by the European Study Group, known as the European trial, about 70% of people had relapses, indicating probable active disease. It considered that 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 confirmed disability progression rather than 6-month confirmed disability progression data, which it would normally prefer. The committee concluded that, given the uncertainties in the indirect comparisons, it would be valuable to see a matching-adjusted indirect comparison using data from the European trial.

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

3.9 The company modelled disease progression using 11 health states, 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, the company used the placebo group from EXPAND supplemented with data from the London Ontario registry. In each cycle a patient 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 are yearly, so improvements are 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 have 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 untreated disease should be modelled using data from the placebo arm of EXPAND supplemented by the London Ontario registry.

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

- 3.10 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

considered that the modelled population should match the marketing authorisation for siponimod, which covers people with active secondary progressive multiple sclerosis. The committee therefore concluded that the modelled population should have active disease at baseline.

It is unclear whether the company used data on trial discontinuation or treatment discontinuation to model the rate at which people stop siponimod

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

Utility values in the economic model

Utility values from the active subgroup of EXPAND supplemented by Orme et al. (2007) should be used in the model

3.12 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 trial. The ERG noted that there is uncertainty about the EQ-5D values from EXPAND and they might not be generalisable to people in the NHS. The ERG preferred to use the data from Orme et al. because they are based on more patients. The committee noted that the utility value for EDSS 3 (0.529) from Orme et al. is lower than the value for EDSS 4 (0.565), which the committee considered to lack face validity. The clinical expert explained that the EXPAND data were more recent than the Orme data and so may better reflect advances in supportive care. The committee was concerned that the company had derived utility values from the full EXPAND population, rather than the subgroup of people with active disease. The committee concluded that utility values from the subgroup of

people with active disease from EXPAND supplemented by Orme et al. (2007) should be used in the model.

Costs in the economic model

Costs associated with starting siponimod should be included in the model

3.13 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 therapy. 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 would not normally have been offered (see section 3.2). The clinical expert highlighted that these costs would apply only to people who had already been diagnosed with secondary progressive multiple sclerosis, and not to people who are transitioning from relapsing–remitting to secondary progressive disease who would generally have regular MRI scans. The committee concluded that costs associated with additional neurology visits and scans should be included in the model.

Waning of siponimod treatment effect

Waning of the effect of treatment with siponimod should be included in the model

3.14 The company presented an analysis of 6-year data from the open-label extension of EXPAND, which it said shows the effect of treatment with siponimod does not diminish over time. The committee considered this analysis to be highly uncertain because everyone in the open-label

extension had siponimod and there was no comparator arm that could be used to confidently estimate siponimod's relative treatment effect. The company considered that the rate at which people stop treatment for any reason is a suitable proxy for the waning of the effect of treatment with siponimod in the model. This is because if siponimod stops working, people are likely to stop taking it. The committee considered that the company's approach may overestimate the benefits of siponimod if people remain on treatment even if its efficacy decreases over time. Including a waning of the effect of treatment in the model would help to address this possibility. The clinical expert explained that it is difficult to know whether the effect of treatment with siponimod is likely to wane. 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 there was likely to be a waning of treatment effect. After technical engagement, the company presented 2 scenarios modelling a waning treatment effect. One scenario modelled a 50% decrease in siponimod's effectiveness from year 11 of treatment onwards. The other scenario modelled 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 waning of the effect of treatment with siponimod should be included in the model, and that it would consider both of the company's scenarios.

Cost-effectiveness estimate

No analyses reflect the committee's preferred assumptions

3.15 Because of confidential commercial arrangements for siponimod and interferon beta-1b, the cost-effectiveness results cannot be reported here. However, none of the company's nor the ERG's analyses reflected the committee's preferences. The committee would have preferred to see analyses that:

- compare siponimod with interferon beta-1b and best supportive care in a probabilistic fully-incremental analysis (see section 3.3)
- use treatment discontinuation rather than study discontinuation to estimate the numbers stopping siponimod in clinical practice
- use utility values from the subgroup of people with active disease from EXPAND supplemented by Orme et al. (2007)
- include the costs of neurology appointments and MRI scans for people starting siponimod
- include a waning of the effect of treatment for siponimod.

The committee would also prefer to see a scenario in which the siponimod treatment effect compared with interferon beta-1b is estimated by adjusting the active siponimod population to match the population in the European trial of interferon beta-1b (see section 3.8).

Innovation

The company suggests that its modelling does not capture additional benefits, but has not presented this evidence to the committee

3.16 The company explained that it considered siponimod to be innovative because it is taken orally, whereas interferon beta-1b is a solvent and powder which must be mixed and injected. Therefore, people are likely to find siponimod easier to take. The company also suggested that the beneficial effects of siponimod on cognitive processing have not been captured in the modelling. The ERG agreed that there is some evidence suggesting that siponimod benefits cognitive processing speed and that the EQ-5D may not fully capture this. The committee considered that such benefits could be important but the company had not included them in its model, nor had the company presented it with sufficient evidence of these benefits.

4 Proposed date for review of guidance

- 4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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
April 2020

5 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

Ross Dent

Technical adviser

Joanne Ekeledo

Project manager

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