NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ozanimod for treating relapsing–remitting 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 ozanimod 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?

Issue date: January 2021

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 ozanimod 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: 12 February 2021

Second appraisal committee meeting: TBC

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

1 Recommendations

1.1 Ozanimod is not recommended, within its marketing authorisation, for treating relapsing–remitting multiple sclerosis in adults with clinical or imaging features of active disease.

1.2 This recommendation is not intended to affect treatment with ozanimod 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 clinician consider it appropriate to stop.

Why the committee made these recommendations

Disease-modifying treatments for relapsing–remitting multiple sclerosis include alemtuzumab, beta interferons, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, ocrelizumab and teriflunomide. Treatments aim to reduce the number of relapses, slow the progression of disability and maintain or improve quality of life.

Clinical trial evidence shows that ozanimod reduces the number of relapses and brain lesions compared with interferon beta-1a. However, ozanimod's effect on the progression of disability is unclear. It is uncertain how effective ozanimod is compared with other treatments because there is no evidence directly comparing them.

The cost-effectiveness estimates are uncertain because of limitations in the clinical effectiveness evidence and are above what NICE normally considers an acceptable use of NHS resources. Therefore, ozanimod is not recommended.

2 Information about ozanimod

Marketing authorisation indication

2.1 Ozanimod (Zeposia, Celgene) is indicated for 'the treatment of adult patients with relapsing remitting multiple sclerosis with active disease as defined by clinical or imaging features'.

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 ozanimod is (prices exclude VAT; company submission):

- £343.25 per initiation pack: 4 capsules containing 0.25 mg ozanimod hydrochloride (equivalent to 0.23 mg of ozanimod) and 3 capsules containing 0.5 mg ozanimod hydrochloride (equivalent to 0.46 mg of ozanimod)
- £1,373 per maintenance pack of 28 capsules, each containing 1 mg ozanimod hydrochloride (equivalent to 0.92 mg of ozanimod).

The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Celgene, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

Treatment pathway, population and comparators

Ozanimod is likely to be used as a first- or second-line treatment for active relapsing–remitting multiple sclerosis

3.1 Ozanimod's marketing authorisation is for active disease, as defined by clinical or imaging features. The company explained that the ozanimod clinical trials included people who had active disease, defined as:

- at least 1 relapse within the past year or
- at least 1 relapse within the last 2 years and evidence of at least 1 gadolinium-enhancing lesion in the last year.

The company originally positioned ozanimod as a first-line treatment, stating it would not be used for highly active or rapidly evolving severe disease. So it chose the comparators for this appraisal accordingly (see section 3.3). The ERG agreed with the company's positioning of ozanimod. At technical engagement the company updated its positioning of ozanimod to:

- a first-line treatment when infusion or injectable treatments are not suitable because of administration issues or when oral treatments are preferred and
- a second-line treatment when the disease has not responded to 1 or more infusion or injectable treatment.

The clinical experts agreed that ozanimod would be of value as a first-line treatment, because there are no oral drugs available as first-line treatment for people who have only had 1 relapse in the last 2 years. They also recognised that ozanimod would be useful as a second-line treatment as another option to fingolimod, the only sphingosine-1-phosphate receptor (S1PR) modulator currently available for relapsing–remitting multiple sclerosis. Ozanimod is also an S1PR modulator and does not have the same cardiac side effects as fingolimod. Having another first- and second-line treatment option would offer people more choice. The company's

submission states that ozanimod is not likely to be used in highly active disease. However, this subtype of multiple sclerosis is often defined as disease that has inadequately responded to disease-modifying therapy. So, the company's positioning of ozanimod as a second-line treatment implies it would be used for highly active disease. The clinical experts explained that multiple sclerosis categorisations are not always clearly defined and can be complex in clinical practice. The committee concluded that ozanimod was likely to be used as a first- or second-line treatment in people who have active relapsing–remitting multiple sclerosis.

It is not appropriate to limit the population to people for whom an oral treatment is suitable or who request an oral treatment

3.2 The population in the company's submission was originally people with relapsing–remitting multiple sclerosis. Later the company restricted this population to include only people with active relapsing–remitting multiple sclerosis for whom an oral treatment is suitable or who request one. The committee accepted that 'active' was added to update the population in line with ozanimod's marketing authorisation, which was granted after the company's submission was received. The company explained that it restricted the population to people for whom an oral treatment is suitable or who request one because it considered this is how it would be used in practice. It estimated that the oral drugs teriflunomide and dimethyl fumarate account for around 50% of the market share in relapsing–remitting multiple sclerosis treatments, and ozanimod would most likely be used in their place. However, the NHS commissioning expert said that based on the data available, 50% market share was likely to be a significant overestimate. The clinical experts explained that it would be very difficult to identify a group of people for whom only oral treatments are suitable. They agreed that many people would choose an oral drug over an injection or infusion, but highlighted that people often switch between treatments with different routes of administration. The patient experts stated that there are many reasons why someone would change their mind about their treatment. Also, they would not want to be excluded

from having a treatment because of its route of administration. The ERG also had concerns about restricting the population, explaining that it was unclear what is meant by people for whom an oral treatment is suitable or who request one. The committee was concerned that restricting the population would exclude potential comparators that are routinely used in the NHS. It concluded that it was not appropriate to limit the population to people for whom an oral treatment is suitable or who request an oral treatment.

All first-and second-line treatments used for active relapsing–remitting multiple sclerosis, including ocrelizumab, are comparators

3.3 In its submission, the company included beta interferons (1a and 1b), dimethyl fumarate, glatiramer acetate, teriflunomide and peginterferon beta-1a as comparators. Alemtuzumab and ocrelizumab were included in the scope, but the company excluded them as comparators in its base-case analysis (although it provided analyses with them as comparators in an appendix). Alemtuzumab was excluded because a safety review restricted its use to highly active disease, and ozanimod was not expected to be used in highly active disease. Ocrelizumab was excluded because NICE only recommends it when alemtuzumab is contraindicated or otherwise unsuitable. However, clinical experts advising the ERG and the clinical experts at the meeting confirmed that ocrelizumab is being used as a first-line treatment for relapsing–remitting multiple sclerosis in the NHS. For the restricted population (see section 3.2), the company's only comparators were dimethyl fumarate and teriflunomide. This was because these are the only oral drugs used as first-line treatment for active relapsing–remitting multiple sclerosis. The ERG did not agree with the company restricting the population and having only dimethyl fumarate and teriflunomide as comparators. The committee agreed with the ERG that all the company's original comparators, plus ocrelizumab, are relevant comparators for first-line treatment. Also, the company and experts had explained that ozanimod could also be used as a second-line treatment when relapsing–remitting multiple sclerosis has not responded to 1 or

more of the infusion or injectable treatments (see section 3.1). So, the committee considered second-line treatments to also be comparators, several of which had not been included by the company. The committee concluded that all first- and second-line treatments used for active relapsing–remitting multiple sclerosis, including ocrelizumab, were comparators.

Ozanimod clinical trials

Baseline characteristics in the trials are generalisable to people in the NHS with active relapsing–remitting multiple sclerosis

3.4 The phase 3 trials RADIANCE part B and SUNBEAM compared ozanimod with interferon beta-1a. The trials had very similar designs, inclusion and exclusion criteria and outcomes, but differed in duration (RADIANCE part B had a 24-month follow-up period, whereas SUNBEAM had a 12-month follow-up period). The ERG considered that although the baseline characteristics of people in the trials were broadly generalisable to people having treatment in the NHS, there were some characteristics that may limit generalisability. For example, around 23% of people in the trials had highly active or rapidly evolving severe relapsing–remitting multiple sclerosis and about 30% had already had a prior disease-modifying therapy. The ERG explained that this was not in line with the company submission but may have become less of an issue since the company updated ozanimod's positioning to a second-line treatment. The ERG also highlighted that there was a higher proportion of people of white family origin and from Eastern Europe than in the NHS population. The clinical experts advised that the trial population and the more diverse population in NHS practice were likely to have a similar natural history of relapsing–remitting multiple sclerosis. They therefore considered the baseline characteristics in RADIANCE part B and SUNBEAM to be generalisable to NHS practice. The committee concluded that the baseline characteristics in RADIANCE part B and SUNBEAM were generalisable to people in the NHS with active relapsing–remitting multiple sclerosis.

Ozanimod reduces relapses and brain lesions compared with interferon beta-1a, but its effects on disability progression are uncertain

3.5 In RADIANCE part B and SUNBEAM, the primary outcome was annualised relapse rate. Key secondary outcomes included:

- number of new or enlarging hyperintense T2-weighted brain MRI lesions
- number of gadolinium-enhanced T1 brain MRI lesions and
- time to onset of confirmed disability progression (CDP) after 3 months (CDP-3M) and after 6 months (CDP-6M).

The committee confirmed that in previous appraisals it had preferred to use CDP-6M instead of CDP-3M because CDP-6M is a more robust measure of disability progression and is less likely to be influenced by relapses. Ozanimod was effective at reducing relapses compared with interferon beta-1a in RADIANCE part B, SUNBEAM and a pooled analysis using 12-month data from each trial. It was also better than interferon beta-1a for both MRI outcomes. However, there was no statistically significant difference between ozanimod and interferon beta-1a for either CDP outcome. The company explained that ozanimod's benefits may have been underestimated because there were low rates of CDP in both treatment arms in the trials. This meant there was high variability and a wide statistical range in the results, and a reduced ability to detect a meaningful difference in CDP between treatments. The company also requested that the CDP results be considered alongside other outcomes for which ozanimod had been shown to be more effective than interferon beta-1a, that is, annualised relapse rate and brain MRI lesions. This was because it considered it implausible that ozanimod could be worse than interferon beta-1a for CDP outcomes but better for relapse and MRI outcomes. It also suggested that CDP was a less important outcome in clinical practice than in clinical trials and cost-effectiveness models. The ERG highlighted the relative difference in CDP between ozanimod and interferon beta-1a. It also noted that the rates of CDP-6M were lower with

interferon beta-1a than ozanimod in both trials (as shown by a hazard ratio greater than 1 for ozanimod compared with interferon beta-1a) but the difference was not statistically significant. The clinical experts explained that a treatment that reduced MRI activity and relapses would also be expected to reduce CDP. They considered that the people enrolled in RADIANCE part B and SUNBEAM may have milder relapsing–remitting multiple sclerosis than average. So, they would be less likely to progress in terms of disability over the short duration of the trials. The clinical experts thought it unlikely that ozanimod would be worse than interferon beta-1a for CDP outcomes. They noted that interferon beta-1a is usually considered as having lower efficacy than some of the other available treatments. The NHS commissioning expert confirmed this view. Considering the expert statements and trial evidence, the committee concluded that ozanimod was effective at reducing relapses and brain lesions compared with interferon beta-1a, but its effects on disability progression were uncertain.

Indirect treatment comparison

The company's network meta-analysis is generally well conducted, but should account for variability

3.6 The company did a Bayesian network meta-analysis (NMA) to estimate ozanimod's relative effectiveness compared with all comparators in the scope. It modelled annualised relapse rate, CDP-3M, CDP-6M, treatment discontinuation, adverse events and serious adverse events. Some older studies did not report CDP-6M so the company also analysed CDP-3M and -6M combined in a single model so that CDP-6M could be predicted for all comparators. In this analysis it assumed that the hazard ratios for CDP-6M between treatments were proportional to the hazard ratios for CDP-3M between treatments. The ERG considered the company's approach to the NMA to be generally appropriate. It was satisfied that any heterogeneity or inconsistency did not have an important effect on results. It did, however, highlight that the assumption of a linear relationship

between the CDP-3M and CDP-6M hazard ratios for ozanimod appeared to have been violated and advised caution when drawing conclusions from the company's CDP-6M combined analysis. The committee noted the ERG's concerns and preferred the CDP-6M NMA estimated from the trial data directly, rather than the combined CDP-6M NMA that was estimated from the CDP-3M data. The company explained that the proportional relationship between CDP-3M and CDP-6M in its combined analysis was assumed to be fixed and to be the same for all studies and treatments. The committee considered it would have preferred for between-study or between-treatment variability, or both, to have been accounted for in the company's combined CDP-6M NMA. The ERG identified a potential issue with the glatiramer acetate 40 mg CDP data used in the company's NMA. It explained that the company may have made an error in data extraction, in which CDP at 12 months may have been extracted as CDP at 12 weeks by mistake. The ERG suspected this data had then been used in the CDP-6M combined analysis in the company's NMA. The company could not confirm whether there had been an error in data extraction for glatiramer acetate 40 mg. Therefore the committee interpreted the results for this comparator with caution. It concluded that the company's NMA was generally well conducted but should have accounted for between-study or between-treatment variability, or both.

The company's cost–utility model

The company's model is generally appropriate and aligns with previous models in the disease area

3.7 The company's model structure was similar to that of models used in previous multiple sclerosis technology appraisals. The model was a Markov transition model consisting of 21 health states (10 Expanded Disability Status Scale [EDSS] states for relapsing–remitting multiple sclerosis, 10 for secondary progressive multiple sclerosis, and death). The model used the British Columbia Multiple Sclerosis registry as a source of

natural history data. Treatment effects for ozanimod and all comparators were obtained from the company's NMA and applied as:

- annualised relapse rates
- CDP-6M (using the combined outcome, see section 3.8)
- adverse events and
- treatment discontinuation (see section 3.9).

The company incorporated a treatment waning effect for all treatments and explained that no treatment switching was allowed in its model. The ERG highlighted that the lack of treatment switching or sequencing in the model may over-simplify what happens in NHS practice. However, it acknowledged that a model that can simulate treatment switching or treatment sequencing would be complex to construct, and difficult to populate because of limited data. The committee acknowledged the lack of treatment switching as a limitation of the model. It concluded that the company's model was generally appropriate and in line with previous models in the disease area.

Ozanimod's disability progression hazard ratio from the NMA should be used, rather than the interferon beta-1a hazard ratio

3.8 The company explained that it had used the combined CDP-6M outcome from its NMA to model the effects of treatments on disability progression. It had advised about the issues with the CDP data in the ozanimod clinical trials (see section 3.5) and noted that these trial results underpinned the NMA results for ozanimod. The company also explained that it set ozanimod's CDP-6M hazard ratio as equal to the CDP-6M hazard ratio for interferon beta-1a in its model, which it considered to be a conservative assumption. This was because it considered it would be implausible that using interferon beta-1a could lead to a lower rate of disability progression than ozanimod (see section 3.5). The ERG highlighted that the company had only set ozanimod as equivalent to interferon beta-1a for CDP-6M and not for relapses, and this was inconsistent. It further highlighted that

the point estimate in the NMA suggested that ozanimod was not as beneficial as interferon beta-1a for CDP-6M. Also, there are other drugs available that have been shown in clinical trials to work better than interferon beta-1a for this outcome. The committee recognised that the clinical experts suspected the non-statistically significant CDP-6M results in the ozanimod trials could be because of milder disease and short trial duration. That is, not because ozanimod does not work as well as interferon beta-1a for this outcome (see section 3.5). However, the committee also understood that the ozanimod trials were of high quality. So, given the uncertainty and for consistency with other outcomes, the committee considered that ozanimod's CDP-6M hazard ratio from the NMA should be used. The committee also considered that the NMA results estimated directly from the CDP-6M trial data, rather than the CDP-6M results from the combined outcome estimated from the CDP-3M data, should be used in the model when possible (see section 3.6). The committee concluded that ozanimod's disability progression hazard ratio from the NMA should be used, rather than the interferon beta-1a hazard ratio.

Both the company's and ERG's approaches to modelling treatment discontinuation have limitations

3.9 The company's cost–utility model did not allow people to switch between treatments, so people were assumed to only have 1 disease-modifying treatment. The company took rates of discontinuation for each treatment from its NMA. It assumed that the rate of discontinuation was the same over the entire model time horizon. People stopped treatment if they reached EDSS state 7 or above, developed secondary progressive multiple sclerosis or died. The ERG preferred a different approach. Its clinical advisers suggested that if no switching of treatments were allowed (as was the case in the model), people would only stop treatment if they were no longer benefitting, even if they still had relapses. Based on this, the ERG used trial treatment discontinuation rates when possible, then assumed everyone stayed on treatment until they reached EDSS state 7

or above, developed secondary progressive multiple sclerosis or died. The clinical experts explained that it was difficult to determine whether the company or ERG's approach better represented NHS practice because people usually switch between several disease-modifying treatments over their lifetime. So, neither approach wholly reflected what would happen in practice. The committee considered the lack of treatment switching to be a limitation of the company's model (see section 3.7). It concluded that both the company and ERG's approaches to modelling treatment discontinuation had limitations.

Cost-effectiveness estimate

The most likely cost-effectiveness estimates are outside what NICE normally considers an acceptable use of NHS resources

3.10 Because of confidential commercial arrangements for ozanimod and comparator treatments, the cost-effectiveness results cannot be reported here. However, the cost-effectiveness estimates for ozanimod compared with other first-line treatments for relapsing–remitting multiple sclerosis were outside what NICE normally considers an acceptable use of NHS resources. Also, neither the company nor the ERG's analyses reflected the committee's preferred assumptions, which were likely to increase the incremental cost-effectiveness ratios. The committee noted that although the company had mentioned at technical engagement that ozanimod may be used as a second-line treatment, it had not explained why it had changed its opinion or provided any updated analyses to reflect this. For example, the company's base case only included comparators used as first-line treatment (see section 3.3).

The committee would have preferred to see a cost–utility analysis that:

- uses ozanimod's CDP-6M hazard ratio from the NMA, rather than setting ozanimod as equivalent to interferon beta-1a
- uses the trials' CDP-6M hazard ratios when possible, and only used the combined CDP-6M hazard ratios for treatments that do not have

CDP-6M data available (glatiramer acetate 40 mg [if available; see section 3.6], interferon beta-1a 22 micrograms and peginterferon beta-1a)

- uses combined CDP-6M hazard ratios, when these are used, from an NMA that accounts for between-study or between-treatment variability, or both
- includes comparisons with second-line treatments (alemtuzumab, cladribine, fingolimod and ocrelizumab) if ozanimod is positioned for second-line treatment.

Other factors

3.11 The committee concluded that ozanimod's benefits were adequately captured in the economic analysis so did not consider it innovative.

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.

Sanjeev Patel
Chair, appraisal committee
January 2021

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

Carl Prescott
Technical adviser

Jeremy Powell
Project manager

Joanne Ekeledo
Project manager

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