NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Ozanimod for treating moderately to severely active ulcerative colitis

1 Recommendations

1.1 Ozanimod is recommended as an option for treating moderately to severely active ulcerative colitis in adults, only if:

- conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable, or
- biological treatment cannot be tolerated or is not working well enough, and
- the company provides it according to the commercial arrangement (see section 2).

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

Standard treatments for moderately to severely active ulcerative colitis after conventional treatments are biological treatments (adalimumab, golimumab, infliximab, ustekinumab or vedolizumab) or tofacitinib.

Clinical trial evidence shows that ozanimod is more effective than placebo for treating moderately to severely active ulcerative colitis. There is no direct evidence comparing ozanimod with standard treatments that are offered after conventional

treatment, but indirect comparisons suggest that it is likely to be as effective as some of them.

When conventional treatment is not tolerated or not working well enough, infliximab is more cost effective than ozanimod. But the most likely cost-effectiveness estimates for ozanimod compared with most other treatments are within the range that NICE normally considers an acceptable use of NHS resources. So, ozanimod is recommended, but only if conventional treatment is not tolerated or not working well enough, and only if infliximab is not suitable. Ozanimod is also recommended if a biological treatment is not tolerated or not working well enough.

2 Information about ozanimod

Marketing authorisation indication

2.1 Ozanimod (Zeposia, Celgene, a Bristol Myers Squibb Company) is indicated for 'the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for ozanimod.

Price

2.3 The price of an ozanimod induction pack is £343 (4 capsules of 0.23 mg and 3 capsules of 0.46 mg per pack). The price of a maintenance pack is £1,373 (0.92 mg, 28-capsule pack) or £4,806 (0.92 mg, 98-capsule pack; all prices excluding VAT; company submission). The estimated cost for the induction and maintenance phases of treatment is £17,910 per person per year (company submission, excluding VAT).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes ozanimod 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 considered evidence submitted by Celgene, a Bristol Myers Squibb Company, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Ulcerative colitis is a lifelong condition affecting all aspects of a person's life

3.1 Ulcerative colitis is a chronic, unpredictable condition characterised by relapsing and remitting periods of inflammation of the rectal and colonic lining. The patient experts explained that the symptoms of the condition and the side effects of treatments can have a profound and devastating impact on all aspects of a person's life. Symptoms can affect the ability to work, study, socialise, take part in leisure activities and have intimate relationships. They explained that fears of needing surgery or developing cancer or even dying can affect a person's mental and emotional wellbeing, leading to feelings of anxiety, stress, depression and hopelessness. They explained that the impact of living with ulcerative colitis can be exacerbated because of the stigma of having the condition and frustration from a lack of understanding of the condition by others. Unlike symptoms of gastroenteritis that may last for 1 or 2 days, symptoms of active ulcerative colitis can last for months. People with active disease may experience debilitating, multiple daily episodes of explosive, painful diarrhoea with blood loss and pus. The committee concluded that symptoms of ulcerative colitis and the side effects of treatments for moderately to severely active ulcerative colitis can have a profound impact on quality of life.

Clinical management

Management of ulcerative colitis is highly individualised and there is an unmet need for new treatments

3.2 The clinical experts explained that management of ulcerative colitis is highly individualised. Factors including previous therapies, the need for concomitant medicines such as corticosteroids and thiopurines, tolerability, and personal preferences and circumstances such as planned pregnancy can affect treatment options. They explained that current treatments are not very effective at achieving and maintaining clinical remission, so treatment switching often occurs. Some treatments also have serious side effects, for example thiopurines are associated with an increased risk of cancer, and there are also some serious side effects associated with biological treatments. At initial diagnosis, people typically have conventional treatments such as corticosteroids, mesalazine and thiopurines (azathioprine and mercaptopurine). If the condition does not respond well enough or stops responding to conventional treatment, a biological treatment, usually a tumour necrosis factor (TNF)-alpha inhibitor, commonly infliximab, is most often offered. The clinical experts explained that TNF-alpha inhibitors should be used with thiopurines to be most effective. In about 30% of people, the condition does not respond to a TNF-alpha inhibitor (primary non-response), and about 40% of people the condition will lose response over 12 months (secondary non-response). For a minority of people, another TNF-alpha inhibitor such as adalimumab or golimumab may be offered, but other options include vedolizumab, ustekinumab, tofacitinib, and filgotinib. These treatments have different mechanisms of action to TNF-alpha inhibitors which people may benefit from. However, the clinical experts explained that at this point in the treatment pathway, response to further treatment, regardless of its mechanism of action, is likely to be lower. They emphasised the importance of using the most effective option for the person in the first instance. They explained that medicines that result in clinical remission are not stopped if they continue to be effective. They highlighted that an

oral treatment, such as tofacitinib is attractive because it is easy to take and any response can be judged after 1 or 2 weeks. However, response is usually assessed after a few months for TNF-alpha inhibitors and ustekinumab. Importantly, tofacitinib can be used without corticosteroids or thiopurines. They highlighted that tofacitinib use is variable across England and suggested that uptake may have been affected by safety concerns about deep vein thrombosis (DVT). They explained that under-treated ulcerative colitis also increases the risk of DVTs and that tofacitinib has been effectively used in carefully selected people. The patient experts emphasised the importance of having access to a range of effective treatment options to avoid or delay the need for surgery. The committee acknowledged the need for new treatments that can be taken without concomitant medicines and that are fast-acting, well tolerated and easy to administer. The committee concluded that treatment options are highly individualised and that there is an unmet need for new treatments with different mechanisms of action.

Ozanimod could be used after conventional treatment or after a TNF-alpha inhibitor

3.3 The marketing authorisation for ozanimod is for people with moderately to severely active ulcerative colitis whose condition had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological treatment. The company submission presented ozanimod at 2 positions in the treatment pathway:

- A treatment for 'TNF-alpha inhibitor-naive' – people who have never had a TNF-alpha inhibitor, but have had conventional treatment and their condition has not responded or has lost response to it or it cannot be tolerated.
- A treatment for 'TNF-alpha inhibitor-experienced' – people who have had at least 1 TNF-alpha inhibitor and their condition has not responded or has lost response to it, or it cannot be tolerated.

The clinical experts confirmed that it was reasonable to divide people according to TNF-alpha inhibitor experience, rather than biological treatment experience because TNF-alpha inhibitors are more commonly used than other treatments after conventional treatment stops being effective. The committee concluded that the company's categorisation based on TNF-alpha inhibitor experience was appropriate.

TNF-alpha inhibitors, vedolizumab, ustekinumab, and tofacitinib are all relevant comparators because management of ulcerative colitis is highly individualised

3.4 The company proposed the following comparators:

- For the TNF-alpha inhibitor-naive subgroup: TNF-alpha inhibitors and vedolizumab.
- For the TNF-alpha inhibitor-experienced subgroup: ustekinumab and vedolizumab.

The company considered tofacitinib was not a relevant comparator because of safety concerns. The committee recalled the clinical experts' testimony that tofacitinib is used, although variably, across the NHS. It also recalled that a second TNF-alpha inhibitor may be used when there has been a secondary non-response to a first TNF-alpha inhibitor (see section 3.2). It also recalled that a highly individualised approach to management is adopted for ulcerative colitis. The committee was aware of the recently published NICE technology appraisal guidance on filgotinib for treating moderately to severely active ulcerative colitis (June 2022). It noted that filgotinib has not yet been routinely used in clinical practice and was not included in the scope of this appraisal. It concluded that although the order in which treatments are given may vary in practice, the relevant comparators are:

- For the TNF-alpha inhibitor-naive subgroup: TNF-alpha inhibitors (usually infliximab), vedolizumab and tofacitinib.

- For the TNF-alpha inhibitor-experienced subgroup: TNF-alpha inhibitors (usually adalimumab), ustekinumab, vedolizumab and tofacitinib.

Clinical evidence

The key clinical trial, TRUENORTH, shows that ozanimod improves clinical remission compared with placebo

3.5 The main clinical evidence for ozanimod came from a phase 3, double-blind, randomised, placebo-controlled, multicentre trial that included a 10-week induction phase and a 42-week maintenance phase. It included 1,012 adults (18 to 75 years) with moderately to severely active ulcerative colitis. This was defined by a 4-component Mayo score of between 6 and 12, and component subscores of at least 1 for stool frequency and rectal bleeding, and at least 2 for endoscopic findings. It had a re-randomised design and included 2 cohorts. Cohort 1 included 645 adults who were randomised to either ozanimod or placebo. Cohort 2 included an open-label group of 367 adults who had ozanimod. People taking corticosteroids maintained their dose during induction, and then tapered their dose on entering the maintenance phase. The key primary end point, the proportion of people in clinical remission at induction (week 10) and maintenance (week 52) used data from Cohort 1. The company presented the results based on the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced subgroups. The clinical experts confirmed that the most important clinical end point is clinical remission. For both the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced subgroups, a greater proportion of people who had ozanimod experienced clinical remission than those in the placebo group at the end of induction and maintenance. These findings were all statistically significant except for the TNF-alpha inhibitor-experienced subgroup at the end of induction. These results are considered academic in confidence by the company and cannot be presented here. The committee concluded that ozanimod

improved clinical remission compared with placebo for both the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced subgroups.

People in TRUENORTH are representative of people likely to have ozanimod in NHS clinical practice

3.6 The company confirmed that some people in the TNF-alpha inhibitor-experienced subgroup had received more than 1 biological treatment. The committee noted that the company had not further stratified the TNF-alpha inhibitor-experienced subgroup based on the number of previous biological treatments, that is, for second-line or third-line biological treatment. The ERG highlighted that an older group of adults may be missing in the trial. The clinical experts confirmed that people seen in the NHS are unlikely to be much older than people in the trial. They considered that the people in TRUENORTH are representative of people likely to have ozanimod in clinical practice. They explained that people in the TNF-alpha inhibitor-experienced subgroup are likely to have more severe ulcerative colitis and that any treatment is likely to be less effective at this stage. The committee concluded that the people in TRUENORTH are representative of people that would be treated in NHS clinical practice.

A high placebo response is commonly seen in trials of ulcerative colitis

3.7 The committee noted the high placebo response in TRUENORTH for both the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced subgroups. The clinical experts explained that high placebo responses are typically seen in these trials and that concomitant corticosteroid use may have a large impact on placebo response. The ERG noted that there was little detail on the use of concomitant medicines in the company submission. The committee noted that placebo response contributed to the heterogeneity across trials in the network meta-analysis.

The company's revised network meta-analysis is appropriate for decision making

3.8 Because there were no head-to-head trials, the company did network meta-analyses to compare the effectiveness of ozanimod with TNF-alpha inhibitors (adalimumab, infliximab, golimumab), vedolizumab, ustekinumab, and tofacitinib. The network meta-analyses included 25 trials stratified by TNF-alpha inhibitor experience (TNF-alpha inhibitor-naive compared with TNF-alpha inhibitor-experienced) and treatment phase (induction 6 to 14 weeks compared with maintenance 52 to 60 weeks). This was done using random effects ordinal models with a probit link to assess clinical remission and clinical response. The company assessed baseline risk in the placebo arm of its revised network meta-analyses using data from single trials in the network meta-analyses that it considered representative of UK clinical practice. This was in line with the ERG's approach. The ERG explained that overall, the company's revised network meta-analyses are in line with recommended practice and have accounted for some potential effect modifiers (mainly previous TNF-alpha inhibitor treatment and differences in trial design). But it considered that there is uncertainty as to whether the most suitable source of evidence had been used to estimate baseline placebo risk. The committee recognised that the company tried to address the limitation of identifying suitable data sources to estimate baseline placebo risk during technical engagement but was unsuccessful. It concluded that although the approach to estimate baseline placebo risk was suboptimal, overall the company's revised network meta-analyses were appropriate for decision making.

Ozanimod is likely to be as effective as some comparators

3.9 The results of the company's induction and maintenance network meta-analyses showed that ozanimod is likely to be as effective as some comparators in the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced subgroups. The results are considered academic in confidence by the company and cannot be presented here. The clinical

experts highlighted that different network meta-analyses may provide different rankings, and that it is difficult to choose a specific treatment based only on small differences in efficacy. They explained that this is because people respond differently, and no single treatment is very effective in terms of maintaining clinical remission. They emphasised that treatment choice is highly dependent on individual needs and preferences. The committee concluded that in the network meta-analyses, ozanimod did not stand out as being substantially more or less effective than the comparators.

The company's economic model

The company's economic model is appropriate for decision making

3.10 The company used a Markov model to estimate the cost effectiveness of ozanimod compared with adalimumab, golimumab, infliximab, tofacitinib, ustekinumab and vedolizumab for the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced subgroups. The company's model structure was similar to those used in previous ulcerative colitis technology appraisals. It included health states defined by the type of treatment and degree of disease control, to replicate the relapsing and remitting nature of ulcerative colitis. The types of treatment were active treatment (including both induction and maintenance phases), post-active treatment (including surgery and post-surgery), and best supportive care, comprising components of conventional treatment. Degrees of disease control were remission, response without remission, and active ulcerative colitis. The Markov model had a lifetime time horizon and a cycle length of 2 weeks and included clinical response, clinical remission and serious infections. The ERG agreed that the company captured all relevant health states and that its approach was appropriate. The committee concluded that the company's model was appropriate for decision making.

Assumptions in the model

Using subgroup-specific data to model efficacy estimates for best supportive care in the post-active treatment phase is preferred

3.11 To model efficacy estimates for best supportive care in the post-active treatment phase, the company used data from the TNF-alpha inhibitor-experienced subgroup to inform the transition probabilities for the TNF-alpha inhibitor-naive subgroup. The company considered that the data from the TNF-alpha inhibitor-experienced subgroup was more appropriate for the TNF-alpha inhibitor-naive subgroup because people in the post-active treatment phase had already had at least 1 TNF-alpha inhibitor. The ERG considered that subgroup-specific data should inform transition probabilities in the best supportive care arm. It considered that loss of response and loss of response (no remission) should be based on both the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced estimates. The committee noted that the 2 approaches resulted in only a modest difference in the incremental cost-effectiveness ratio (ICER), but considered that subgroup-specific data is preferred.

Cost-effectiveness estimates

Ozanimod is considered cost effective, except in comparison with infliximab in the TNF-alpha inhibitor-naive subgroup

3.12 The committee considered the cost effectiveness of ozanimod compared with adalimumab, golimumab, infliximab, tofacitinib, ustekinumab and vedolizumab for the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced subgroups. The company's and ERG's base case results included confidential commercial discounts, so they cannot be reported here. The committee considered that the ICERs are potentially unstable because of very small and uncertain differences in efficacy between the treatments that were used in the economic model. However, considering the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced subgroups separately, the committee concluded that overall, ozanimod

could be considered a cost-effective option when conventional or biological treatments are not tolerated or working well enough. The committee noted the exception that infliximab was more cost effective than ozanimod in the TNF-alpha inhibitor-naive subgroup. It concluded that ozanimod should only be offered to people in the TNF-alpha inhibitor-naïve subgroup if infliximab cannot be tolerated or is contraindicated.

Other factors

There are no equality issues relevant to the recommendations

3.13 The patient experts explained that for some religious groups the impact of active disease and the effects of surgery may interfere with religious practices and cause distress. The committee did not consider this an equality issue that could be resolved by this appraisal. No other equality or social value judgement issues were identified.

The benefits of ozanimod are adequately captured in the cost-effectiveness analysis

3.14 The company considered ozanimod to be innovative because it has a novel mechanism of action that uses sphingosine 1-phosphate (S1P) receptors to decrease circulating lymphocytes to reduce inflammation. Ozanimod addresses an unmet need by providing people with a new therapeutic oral option to treat symptoms and induce remission. The committee acknowledged the benefits offered by ozanimod and that people value an oral treatment. But it noted that it had not been presented with evidence of any additional benefits that were not captured in the quality-adjusted life year (QALY) measurements. The committee concluded that the benefits of ozanimod were adequately captured in the model.

4 Implementation

4.1 Section 7 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 moderately to severely active ulcerative colitis and the doctor responsible for their care thinks that ozanimod is the right treatment, it should be available for use, in line with NICE's recommendations.

Jane Adam
Chair, Appraisal committee
July 2022

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 A.

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.

Sharlene Ting
Technical lead

Alexandra Filby
Technical adviser

Jeremy Powell
Project manager

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