Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2478

ozanimod 0.23mg, 0.46mg and 0.92mg hard capsules (Zeposia®)

Celgene Limited, a BMS Company

09 September 2022

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

ADVICE: following a full submission

ozanimod (Zeposia®) is accepted for use within NHSScotland.

Indication under review: 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.

In a randomised, double-blind, phase III study in patients with moderately to severely active UC, clinical remission was achieved by a significantly greater proportion of patients who received ozanimod compared with placebo after induction and maintenance treatment.

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

Chairman
Scottish Medicines Consortium

Indication

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. [1-3]

Dosing Information

The recommended dose of ozanimod is 0.92mg once daily taken orally with or without food.

An initial dose escalation regimen of ozanimod is required: 0.23mg (days 1-4); 0.46mg (days 5-7); 0.92mg (day 8 and thereafter).

Treatment should be initiated under the supervision of a physician experienced in the management of UC.

See the Summary of product characteristics (SPC) for further information. [1-3]

Product availability date

03 February 2022

Summary of evidence on comparative efficacy

Ozanimod is a selective sphingosine 1-phosphate (S1P) receptor modulator with a high affinity for S1P receptors $S1P_1$ and $S1P_5$. The mechanism by which ozanimod exerts therapeutic effects in UC is unknown, but may involve the reduction of the migration of lymphocytes (particularly those involved in the adaptive immune response) into the intestine.[1-3]

The key evidence comes from TRUENORTH, a randomised, double-blind, phase III study which comprised induction and maintenance periods. This study recruited adults (18 to 75 years) with moderately to severely active UC, defined as a complete Mayo score (the sum of four subscores [rectal bleeding, stool frequency, physician's global assessment, and endoscopy] each ranging from 0 to 3; overall score ranges from 0 to 12 with higher scores indicating greater activity) of 6 to 12, with an endoscopic score ≥2, a rectal bleeding score ≥1 and a stool frequency score ≥1. Patients were eligible if they had received stable doses of oral aminosalicylates (≥2.4g daily for at least 8 weeks) and/or prednisone (at a dose of ≤20mg per day) or equivalent, or budesonide for at least 2 weeks before screening endoscopy. [4, 5]

In cohort 1 of the induction period, patients were randomised in a 2:1 ratio to receive oral ozanimod (with a 7-day dose titration regimen of 0.23mg/day on days 1 to 4, 0.46mg/day on days 5 to 7, followed by 0.92mg/day) or placebo once daily for 10 weeks. Stratification factors were prior use of tumour necrosis factor inhibitor (TNFi) (yes or no) and use of corticosteroids (yes or no). In cohort 2, eligible patients received open-label ozanimod (dosed as described previously) to ensure sufficient responding patients for the maintenance period. [4, 5]

For the maintenance period, patients from cohorts 1 and 2 who achieved a clinical response to ozanimod at week 10 (defined as a reduction in the complete Mayo score of ≥3 points and ≥30% from baseline or in the three-component Mayo score [complete Mayo score excluding physician's global assessment] of ≥2 points and ≥35% from baseline, as well as a reduction in the rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of ≤1 point) during the induction period were randomised equally in a double-blind manner to ozanimod 0.92mg orally once daily or placebo for a further 42 weeks (until week 52). Stratification factors were clinical remission status (as defined below) at week 10 (yes or no) and corticosteroid use at week 10 (yes or no). Patients from cohort 1 who had been randomised to placebo and showed a clinical response at week 10 continued to receive placebo in the maintenance period in a double-blind manner.[4, 5]

Patients continued to receive oral aminosalicylates or corticosteroids at stable dose for the duration of the induction period; the corticosteroid dose had to be tapered once the patient entered the maintenance period.[5]

The primary outcome for the induction (at week 10) and maintenance (at week 52) periods was the proportion of patients in clinical remission. This was defined according to the three-component Mayo score (sum of the rectal bleeding, stool frequency and endoscopy subscores; each subscore ranging from 0 to 3 points with overall score ranging from 0 to 9). Clinical remission was defined as a rectal bleeding subscore of 0; a stool frequency subscore of ≤1, with a decrease of ≥1 point from baseline; and an endoscopy subscore of ≤1.[4, 5] Efficacy analyses were performed in the modified intention-to-treat population, which included all patients who underwent randomisation and received at least one dose of ozanimod or placebo.[5]

Clinical remission was achieved by a significantly greater proportion of patients in the ozanimod group compared with the placebo group both at weeks 10 and 52. A hierarchical statistical testing strategy was applied in both study periods for key secondary outcomes, with no formal testing of outcomes after the first non-significant outcome in the hierarchy. All key secondary outcomes achieved statistical significance in favour of ozanimod over placebo at weeks 10 and 52. Results are detailed in Table 1 (for the induction period) and Table 2 (for the maintenance period); in each table, outcomes are presented in the hierarchical testing order used. [4, 5]

Table 1: TRUENORTH induction period – primary and key secondary outcomes at week 10 [4, 5]

	Ozanimod (n=429)	**Placebo (n=216)**	**Difference versus placebo in percentage points (95% CI)**	**Odds ratio (95% CI)**	**p-value**
Clinical remission, % (primary outcome)	18%	6.0%	12% (7.5 to 17)	3.59 (1.94 to 6.64)	<0.001
Clinical response, %	48%	26%	22% (14 to 29)	2.67 (1.86 to 3.84)	<0.001
Endoscopic improvement, %	27%	12%	16% (9.7 to 22)	2.88 (1.80 to 4.59)	<0.001
Mucosal healing, %	13%	3.7%	8.9% (4.9 to 13)	3.77 (1.76 to 8.07)	<0.001

Abbreviations: CI, confidential interval.

Table 2: TRUENORTH maintenance period – primary and key secondary outcomes at week 52 [4, 5]

	Ozanimod (n=230)	Placebo (n=227)	Difference versus placebo in percentage points (95% CI)	Odds ratio (95% CI)	p-value
Clinical remission, % (primary outcome)	37%	19%	19% (11 to 26)	2.76 (1.77 to 4.29)	<0.001
Clinical response, %	60%	41%	19% (10 to 28)	2.27 (1.54 to 3.33)	<0.001
Endoscopic improvement, %	46%	26%	19% (11 to 28)	2.48 (1.65 to 3.72)	<0.001
Clinical remission in the subset of patients who were in remission at week 10, %[a]	52% (41/79)	29% (22/75)	24% (9.1 to 39)	2.88 (1.45 to 5.74)	0.0025
Corticosteroid-free remission, %	32%	17%	15% (7.8 to 23)	2.56 (1.60 to 4.09)	<0.001
Mucosal healing, %	30%	14%	16% (8.2 to 23)	2.64 (1.64 to 4.26)	<0.001
Durable clinical remission, %	18%	9.7%	8.2% (2.8 to 14)	2.65 (1.38 to 5.06)	0.0030

Abbreviations: CI, confidential interval. [a] For this outcome, group sizes differ.

Exploratory analyses by prior TNFi use showed similar results. In TNFi-naive patients (n=450), clinical remission at the end of the induction period (week 10) was achieved by 22% (66/299) of patients receiving ozanimod compared with 6.6% (10/151) of patients in the placebo group. In TNFi-experienced patients (n=195), clinical remission at week 10 was achieved by 10% (13/130) of patients receiving ozanimod compared with 4.6% (3/65) of patients in the placebo group. In TNFi-naive patients (n=312), clinical remission at the end of the maintenance period (week 52) was achieved by 41% (63/154) of patients receiving ozanimod compared with 22% (35/158) of patients in the placebo group. In TNFi-experienced patients (n=145), clinical remission at week 52 was achieved by 29% (22/76) of patients receiving ozanimod compared with 10% (7/69) of patients in the placebo group. [4]Health-Related Quality of Life (HRQoL) was assessed using four questionnaires: Short Form 36 health survey (SF-36), EuroQol Quality of Life Scale (EQ-5D), Health Resource Utilization questionnaire, and Work Productivity and Activity Impairment Questionnaire for UC (WPAI-UC) V2.0.[4, 5] Overall, regulators considered that the descriptively assessed quality of life and work productivity outcomes showed some relevant improvements with ozanimod compared with placebo. Conclusions over health care utilisation could not be drawn due to the low number of events.[4]

TOUCHSTONE was a supportive double-blind, placebo-controlled phase II study in 197 adults with moderate to severe UC (82% of patients were TNFi-naive). Patients were randomised equally to receive ozanimod at a dose of 0.46mg (n=65) or 0.92mg (n=67) or placebo (n=65) daily for up to 32 weeks. The primary outcome was clinical remission (defined by Mayo Clinic score ≤2, with no subscore >1) at 8 weeks. More patients achieved clinical remission in the ozanimod group (16% in the ozanimod 0.92mg group) compared with the placebo group (6%); (p=0.048).[6, 7]

The submitting company presented Bayesian network meta-analyses (NMAs) for subpopulations of patients with and without prior use of TNFi (TNFi-naive and TNFi-experienced) and separate analyses for outcomes at the induction and maintenance periods. The NMAs compared ozanimod with adalimumab, infliximab (only compared in TNFi-naive subpopulation), golimumab (only compared in TNFi-naive subpopulation), ustekinumab, vedolizumab and tofacitinib using placebo as a common control. The NMAs were conducted in adults with moderately to severely active UC and included 22 studies. Outcomes assessed were clinical response and clinical remission. TRUENORTH four-component Mayo score results were used in the NMAs, since these outcomes' definitions were generally consistent with definitions used in the other included studies. For the induction period NMAs, in both subpopulations and for both outcomes, the results suggested no evidence of a difference between ozanimod and comparators, except against adalimumab in the TNFi-experienced patients when ozanimod appeared more effective. For the maintenance period NMAs, in both subpopulations and for both outcomes, the results suggested no evidence of a difference between ozanimod and comparators with the exception of intravenous vedolizumab and tofacitinib, which appeared to be more efficacious than ozanimod in the TNFi-naive subpopulation. In the few comparisons where evidence of a difference was seen between ozanimod and a comparator, the credible intervals of the odds ratios were wide.

Summary of evidence on comparative safety

Overall, regulators concluded that the safety profile of ozanimod in UC is considered to be manageable and overall in line with that seen in the multiple sclerosis (MS) indication.[4]

In TRUENORTH, in cohort 1 of the induction period, any treatment-emergent adverse event (AE) was reported by 40% (172/429) of patients in the ozanimod group and 38% (82/216) in the placebo group. In the ozanimod and placebo groups respectively, patients with a reported serious AE were 4.0% versus 3.2%, and these were considered treatment-related in one and two patients. Patients discontinuing therapy due to an AE were 3.3% versus 3.2%.[5]In the maintenance period, any treatment-emergent AE was reported by 49% (113/230) of patients in the ozanimod group and 37% (83/227) in the placebo group. In the ozanimod and placebo groups respectively, patients with a reported serious AE were 5.2% versus 7.9%, and these were considered treatment-related in only one patient in the placebo group. Patients discontinuing therapy due to an AE were 1.3% versus 2.6%.[5]

In TRUENORTH, the most frequently reported treatment-emergent AEs of any grade in the ozanimod group versus the placebo group were: anaemia (4.2% versus 5.6% in the induction period; 1.3% versus 1.8% in the maintenance period), nasopharyngitis (3.5% versus 1.4% in the induction period; 3.0% versus 1.8% in the maintenance period), headache (3.3% versus 1.9% in the induction period; 3.5% versus 0.4% in the maintenance period), alanine aminotransferase increased (2.6% versus 0 in the induction period; 4.8% versus 0.4% in the maintenance period), arthralgia (2.3% versus 1.4% in the induction period; 3.0% versus 2.6% in the maintenance period), γ-glutamyltransferase increased (1.2% versus 0 in the induction period; 3.0% versus 0.4% in the maintenance period).[5]

Frequency and type of cardiac AEs (mainly bradycardia during initiation and blood pressure effects with continued treatment) and hepatic effects (increase in liver function tests) appeared to be in line with the known safety profile of ozanimod. Before starting ozanimod, an ECG and recent transaminase and bilirubin levels are required. In patients with certain pre-existing conditions, first-dose monitoring is recommended. Blood pressure and transaminase and bilirubin levels should be regularly monitored during ozanimod treatment. Also consistent with the MS program, infection AEs in the UC program were mainly characterised by non-serious infections of the upper respiratory tract. During long-term treatment (pooled controlled and uncontrolled UC studies), the incidence of serious infections was 2.2% with ozanimod versus 1.4% with placebo. Opportunistic infections were more frequent with ozanimod compared with placebo with an incidence of 2.4% versus 0.4% and were predominantly reports of Herpes zoster. The SPC includes recommendations to measure blood cell counts prior to and during treatment with ozanimod, and advice to monitor patients at risk of infection. Varicella zoster virus (VZV) vaccination of patients without documented immunity to VZV is recommended prior to initiating treatment with ozanimod. [1-3]

Summary of clinical effectiveness issues

Ulcerative colitis (UC) is a chronic inflammatory bowel disease, which affects the rectum and colon and is characterised by remissions and exacerbations. Symptoms include recurrent episodes of diarrhoea, rectal bleeding and abdominal pain, and patients are at an increased risk of perforated bowel, toxic megacolon and colorectal cancer.[4] The treatment goal for patients with active disease is to induce and maintain remission and mucosal healing. A significant number of patients with moderate to severe UC do not respond, lose response or are intolerant to currently available therapies.[4] Guidelines recommend that patients with moderately to severely active UC, who have an inadequate response or intolerance to conventional therapy, should be treated to induce and maintain remission with a TNFi (infliximab, adalimumab and golimumab), the α4β7 integrin antagonist vedolizumab, the interleukin 12/23 inhibitor ustekinumab or the Janus kinase (JAK) inhibitor tofacitinib.[8-10] These therapies have all been accepted for use in UC patients by SMC (SMC2276, SMC2250, SMC2122, SMC 1045/15, and MTA 329). In May 2022, SMC issued advice (SMC2467) that the JAK inhibitor filgotinib is accepted for use in UC. Ozanimod is the first selective S1P receptor modulator to be licensed for this indication.

In TRUENORTH, the primary outcome (clinical remission at weeks 10 and 52) and key secondary outcomes achieved statistical significance in favour of ozanimod over placebo. The difference between groups in clinical remission was only 12% at the end of the induction period and 19% at the end of the maintenance period; these seemingly small differences between groups may be explained by the strict outcome definition. Ozanimod benefits were demonstrated for both symptoms improvement (mainly diarrhoea and blood in stools) and outcomes relevant for long-term prognosis (such as endoscopic improvement, mucosal healing, and histological remission). Regulators concluded that ozanimod efficacy appears to be highly clinically relevant.[4]

Only patients responding to treatment with ozanimod during the induction period were randomised to study treatment in the maintenance period; this enriched design is likely to have

impacted the relative treatment effect at week 52, however this study design is commonly used for UC studies.

In TRUENORTH, patients were receiving stable doses of oral aminosalicylates and/or corticosteroids at baseline; but they were not required to have failed treatment to either conventional therapy or a biologic agent. Thus the population was wider than the licensed indication. However regulators were satisfied that most patients matched the indication. In all cohort 1 patients who received at least one dose of investigational medicine [n=645]: 75% of patients had previously used corticosteroids; 41% had failed to respond and/or were intolerant to immunomodulators; 30% of patients had an inadequate response, loss of response, or intolerance to TNFi; and 19% of patients had failed or were intolerant to non-TNFi biologics [such as vedolizumab]).

Subgroup analyses data to support the use of ozanimod both in TNFi-experienced and TNFi -naive patients were presented. These descriptive results suggest that the treatment effect size might be slightly smaller in TNFi-experienced patients compared with TNFi-naive patients. However, these results should be interpreted with caution as the TRUENORTH study was not powered for such analyses.

Available data supported maintenance of treatment effects for one year of treatment; however, long-term efficacy and safety data for ozanimod in the treatment of UC remain limited.[4]

Only patients ≤75 years old were eligible for TRUENORTH and only a small number of study patients were aged ≥65 years so available data in older patients are limited, introducing some uncertainty about the efficacy and safety in this population.[4]

No data are available to support the efficacy and safety of ozanimod in combination with any advanced therapy currently used in the indication under review (biologic therapy [TNFi, α4β7 integrin antagonist, interleukin 12/23 inhibitor] or Janus kinase inhibitor).

The submitting company considered that the relevant comparators in TNFi-naive patients are: infliximab, adalimumab, golimumab and vedolizumab; and in TNFi-experienced patients: vedolizumab and ustekinumab. There is some uncertainty about which treatments are the most relevant comparators; however, based on feedback received from clinical experts consulted by SMC, tofacitinib is also a relevant comparator in TNF experienced patients.

Since there are no direct comparative data, the submitting company performed NMAs comparing ozanimod with adalimumab, infliximab, golimumab, ustekinumab, vedolizumab and tofacitinib. There were some limitations that may affect the validity of the NMAs' results. Unlicensed doses were included for infliximab and ustekinumab; and for various comparators, multiple doses of the same treatment were pooled. There was clinical and methodological heterogeneity across the studies, including in terms of patient characteristics (such as race/ethnicity, disease extent, prior medication use, and concomitant steroid use), definition of TNFi subgroups, study design and outcome definitions. Sensitivity analyses were conducted to address some of these differences and the results were generally consistent. There was variability in the assessment point for induction (range 2 to 14 weeks) and maintenance treatments (range 32 to 60 weeks) and there was significant heterogeneity in placebo response rates across studies. The majority of comparisons were informed by single studies. Safety outcomes were not included in the NMAs.

Wide credible intervals were reported for some of the comparisons, indicating uncertainty. Given that the NMAs' results generally suggest that ozanimod is not likely to be superior or inferior to comparators, cost-minimisation analyses (CMA) in both subpopulations is relevant.

Ozanimod would provide an additional orally administered treatment option with a new mechanism of action to help manage UC in patients who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

Summary of comparative health economic evidence

The company submitted an economic case covering the full licensed indication for ozanimod. The company separated patients into TNFi-naive and TNFi-experienced populations and presented results for each group separately. The comparators differed between the two groups. Initially, ozanimod was compared to infliximab (or biosimilar), adalimumab (or biosimilar), golimumab and vedolizumab in the TNFi-naive population. Within the TNFi-experienced population, ozanimod was compared with vedolizumab and ustekinumab. Given uncertainty on where ozanimod would fit into clinical practice, the comparators were extended to include tofacitinib in both subgroups and ustekinumab in the TNFi-naive subgroup upon request.

The company provided two types of analysis, cost-utility analysis (CUA) and CMA. Both approaches utilised the same Markov model, which had a total of 12 states, over two phases. Within the Active Treatment phase, all patients started in the Induction state before entering a Remission state, a Response no Remission state or an Active UC state. The occupancy of each of these states was derived from a Bayesian NMA, which included the key, placebo controlled, phase III study of ozanimod, TRUENORTH.[5]

After entering the Active UC state, the simplifying assumption was made that active treatment was discontinued, and patients entered the Post-active treatment phase of the model. There, patients could still cycle between Remission and Response no Remission states, capturing the variable nature of the disease. Patients could also undergo surgery. The transition probabilities in the Post-active treatment phase were drawn from the literature.

Within the TRUENORTH study, participants completed EQ-5D questionnaires to capture their health related quality of life. The company noted several issues with the resulting data and opted to used values from the literature instead when conducting the CUA.

Medicine costs included in the model covered the acquisition costs, administration costs and AE costs associated with ozanimod, the comparators and components of conventional therapy. No subsequent treatments costs for active treatments were included once a patient had transitioned into the Active UC state. Only the cost of serious infections was included as an AE. Wider health state costs were based on patients using consultant visits, blood tests, emergency endoscopies, elective endoscopies, care without colectomy and post colectomy stoma care. Patients could undergo two rounds of surgery, which were assumed to cost £14,310 and £10,438 respectively.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

A PAS discount is in place for golimumab, ustekinumab, vedolizumab and tofacitinib and these were included in the results used for decision-making by using estimates of the comparator PAS price. SMC is unable to present the results provided by the company which used an estimate of the PAS price ozanimod and for the comparator medicines due to commercial confidentiality and competition law issues. Given this, results are presented using list prices for all medicines.

In light of the results of the NMA, which showed minimal difference between ozanimod and the comparators, the results focused on the CMA.

Table 3: Base-case pair-wise cost-minimisation results (list prices for all medicines)

Technologies	TNFi-naive population - Incremental costs for ozanimod vs comparator	TNFi-experienced population - Incremental costs for ozanimod vs comparator
Infliximab/biosimilar	£466	N/A
Adalimumab/biosimilar	£6,132	N/A
Golimumab	£2,386	N/A
Vedolizumab	£90	-£177
Ustekinumab	£1,718	£1,133
Tofacitinib	£5,216	£4,613

In addition to the baseline results, the company provided a selection of scenarios exploring areas of uncertainty. A selection of these are presented in Tables 4 and 5.

Table 4: Cost-minimisation scenario analyses, TNFi-naive patients (list prices for all medicines)

			Incremental costs					
#	**Scenario description**	**Base case description**	**Adali.**	**Inflix.**	**Vedo.**	**Golim.**	**Ustek.**	**Tofa.**
1	1% Spontaneous response/remission	0.5% Spontaneous response/remission	£6,137	£471	£98	£2,395	£1,722	£5,221
2	0% Spontaneous response/remission		£6,128	£462	£80	£2,377	£1,713	£5,212
3	Include extended induction	Standard induction length	£6,132	£464	-£798	£1,779	£792	£4,851
4	0% dose escalation in maintenance phase	30% dose escalation in maintenance phase	£8,015	£2,561	£1,752	£4,655	£2,781	£7,266
5	50% dose escalation in maintenance phase		£4,877	-£930	-£1,019	£874	£1,009	£3,850

6	25% treatment waning after 2 years	No treatment waning	£5,910	£357	£18	£2,222	£1,497	£5,022
7	Include vial sharing	Exclude vial sharing	£6,132	£1,965	£90	£2,386	£2,042	£5,216
8	40 year time horizon	58 year time horizon	£6,133	£467	£90	£2,387	£1,719	£5,217

Abbreviations: *Adali.: adalimumab, Inflix.: infliximab, Vedo: vedolizumab, Golim.: golimumab, Ustek.: ustekinumab, Tofa.: tofacitinib*

Table 5: Cost-minimisation scenario analysis, TNFi-experienced patients (list prices for all medicines)

			Incremental costs		
#	**Scenario description**	**Base case description**	**Vedo.**	**Ustek.**	**Tofa.**
1	1% Spontaneous response/remission	0.5% Spontaneous response/remission	-£169	£1,138	£4,617
2	0% Spontaneous response/remission		-£187	£1,129	£4,608
3	Include extended induction	Standard induction length	-£1,244	£24	£4,176
4	0% dose escalation in maintenance phase	30% dose escalation in maintenance phase	£1,265	£2,055	£6,391
5	50% dose escalation in maintenance phase		-£1,139	£519	£3,428
6	25% treatment waning after 2 years	No treatment waning	-£237	£944	£4,447
7	Include vial sharing	Exclude vial sharing	-£177	£1,348	£4,613
8	40 year time horizon	58 year time horizon	-£176	£1,134	£4,613

Abbreviations: *Adali.: adalimumab, Inflix.: infliximab, Vedo: vedolizumab, Golim.: golimumab, Ustek.: ustekinumab, Tofa.: tofacitinib*

The strengths of the economic case were assessed as being:

- The model appeared clear, well structured and well aligned with those used in previous submissions in this clinical area.
- The company reports having matched many of the assumptions and inputs with previous NICE submissions for other medicines in the clinical area. However, for unknown reasons there were often discrepancies between the NICE submission and the corresponding SMC submission for the same indication.

The weaknesses of the economic case were assessed as being:

- The key study, TRUENORTH, compared ozanimod with placebo. Results from a Bayesian NMA were uncertain, but indicated that the outcomes for ozanimod patients were largely comparable to those for patients treated with the comparators. Based on this, the CMA results were the central results considered in the appraisal, rather than the CUA results favoured by the submitting company.

- There was some uncertainty on where ozanimod would fit into clinical care, and what the most appropriate comparator should be. Additional comparisons with other relevant treatment options were provided on request.

Despite these limitations, the economic case was demonstrated.

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

Summary of patient and carer involvement

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

- We received a patient group submission from Crohn's and Colitis UK, which is a registered charity.
- Crohn's and Colitis UK has received 5.23% pharmaceutical company funding in the past two years, including from the submitting company.
- The symptoms of ulcerative colitis, and their unpredictable nature can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, abdominal pain and fatigue, anaemia, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships. Emotional well-being can be significantly affected, stigma and lack of understanding of the condition exacerbate the impact.
- There is unmet need within the moderate to severe cohort of patients. Current treatments remain far from optimal for some patients, a substantial number of whom experience a lack of response (primary or secondary) and/or adverse reactions to medical treatments and may face the prospect of surgery, with considerable anxiety.
- Ozanimod offers a novel treatment option, administered by patients orally at home without the need to travel to hospital for infusions or to self-inject; this increases therapeutic choice for both clinicians and patients (in the context of shared decision making). The availability of an additional treatment option may delay or prevent surgery for some patients. This can be particularly important for patients who have exhausted all other treatment options.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published NICE Clinical Guideline 130, Ulcerative colitis: management in May 2019. The current NICE guidance make recommendation based on the severity of the condition. The guidance highlights that the use of biologics and Janus kinase inhibitors for moderately to severely active UC (all extents of disease) should be informed by the technology assessments for specific agents: infliximab, adalimumab, golimumab,

vedolizumab and tofacitinib. This guidance predates the availability of filgotinib, ustekinumab and ozanimod for UC.[8]

The British Society of Gastroenterology produced consensus guidelines on the management of inflammatory bowel disease in adults in 2019. This guideline recommends that in patients with ulcerative colitis who have failed treatment with high dose mesalazine (or 5-aminosalicylic acid), treatment options for induction and maintenance include thiopurine, TNFi, vedolizumab or tofacitinib. After mesalazine failure, it does not recommend methotrexate in the maintenance of remission in UC. Vedolizumab and tofacitinib are recommended when TNFi treatment has failed. The choice of drug should be determined by clinical factors, patient choice, cost, likely adherence and local infusion capacity. This guideline predates the availability of filgotinib, ustekinumab and ozanimod for UC.[10]

The European Crohn's and Colitis Organisation (ECCO) published the ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment in 2022. This guideline recommends that patients with moderately to severely active UC, who have an inadequate response or intolerance to conventional therapy, should be treated with TNFi agents to induce and maintain remission (infliximab, adalimumab and golimumab). Vedolizumab, ustekinumab and tofacitinib are also recommended as a treatment option (same treatment which induced remission should be used for maintenance) for these patients.[9]

Additional information: comparators

Adalimumab, infliximab, golimumab, tofacitinib, ustekinumab or vedolizumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Ozanimod	**Year 1** **Days 1 to 4: 0.23mg orally once daily.** **Days 5 to 7: 0.46mg orally once daily.** **Day 8 onwards: 0.92mg orally once daily.** **Year 2 onwards** **0.92mg orally once daily.**	**17,849** **17,849**

Costs from eMC Dictionary of Medicines and Devices Browser on 01/07/2022. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

References

1. Bristol-Myers Squibb Pharmaceuticals limited. Ozanimod 0.23 mg hard capsules (Zeposia®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk. Last updated: 07 Apr 2022.

2. Bristol-Myers Squibb Pharmaceuticals limited. Ozanimod 0.46 mg hard capsules (Zeposia®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk. Last updated: 07 Apr 2022.

3. Bristol-Myers Squibb Pharmaceuticals limited. Ozanimod 0.92 mg hard capsules (Zeposia®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk. Last updated: 07 Apr 2022.

4. The European Medicines Agency (EMA) European Public Assessment Report. Ozanimod (Zeposia®). 14 October 2021, Procedure No. EMEA/H/C/004835/II/0002/G. www.ema.europa.eu.

5. Sandborn WJ, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB*, et al.* Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine. 2021;385(14):1280-91.

6. Sandborn WJ, Feagan BG, Wolf DC, D'Haens G, Vermeire S, Hanauer SB*, et al.* Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis. New England Journal of Medicine. 2016;374(18):1754-62.

7. Clinicaltrials.gov. Efficacy and Safety Study of Ozanimod in Ulcerative Colitis (Touchstone). ClinicalTrials.gov Identifier: NCT01647516. Last Update Posted: May 19, 2021. Available at https://www.clinicaltrials.gov/ct2/show/NCT01647516.

8. National Institute for Health and Care Excellence. Ulcerative colitis: management. (NG130). 2019. Available at: https://www.nice.org.uk/guidance/ng130.

9. Raine T, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, Bachmann O, Bettenworth D, Chaparro M, Czuber-Dochan W, Eder P. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. Journal of Crohn's and Colitis. 2022 Jan;16(1):2-17.

10. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK*, et al.* British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1.

This assessment is based on data submitted by the applicant company up to and including 12 August 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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

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

Advice context:

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

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