National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ozanimod for treating moderately to severely active ulcerative colitis

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	Yes, the topic is appropriate.	Thank you for your comment.
	Bristol-Myers Squibb	Yes, this topic is appropriate to refer to NICE for appraisal.	Thank you for your comment.
	Crohn's & Colitis UK	Yes. Currently, there are limited treatment options available in treating moderate to severe ulcerative colitis. It is important that patients have the widest possible options available to them, particularly given what we are increasingly coming to understand in terms of the importance of personalised treatments.	Thank you for your comment.

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Wording	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	The wording reflects the clinical issues. Method of administration, the oral route, should be taken into consideration when looking at the overall cost, no hospital costs for IV/ SC administration/ training patient to administer.	Thank you for your comment. The committee will consider all relevant costs and benefits when appraising this technology.
	Bristol-Myers Squibb	Yes, the wording of the remit is appropriate.	Thank you for your comment.
Timing Issues	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	TA publication by 2022	Thank you for your comment. This topic has been scheduled into the work programme.
	Bristol-Myers Squibb	The timings of this appraisal are appropriate.	Thank you for your comment. This topic has been scheduled into the work programme.
	Crohn's & Colitis UK	In light of Covid-19, there is a benefit to an additional treatment option which can be administered at home in reducing potential infection risk and pressure on the NHS.	Thank you for your comment. This topic has been scheduled

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			into the work programme.

Comment 2: the draft scope

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Background information	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	This is an accurate summary	Thank you for your comment.
	Bristol-Myers Squibb	The background information included is appropriate.	Thank you for your comment.
	Crohn's & Colitis UK	Based on emerging research, Crohn's & Colitis UK estimate that 1 in 133 people are living with Inflammatory Bowel Disease across the UK. The aim of treatment is for people to live their best-possible lives, not just achieve remission. A population-based study carried out in the county of Copenhagen[59] described the outcome in 1575 patients in the first 5 years following diagnosis of UC between 1962 and 2005. In the most recent period, the percentage of patients experiencing an 'indolent' course [no	Thank you for your comment. The information on the prevalence and aim of treatment in the background information section has been updated. This section is intended to provide a brief summary of the condition. This section

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		relapse during the first 5 years after diagnosis] was 13%, 74% had a 'moderate' course [two or more relapses within the first 5 years, but less than every year], and 13% had an 'aggressive' course [disease activity at least every year during the first 5 years]. Initial treatment may include surgery. The background information on Acute Severe Ulcerative Colitis is limited. According to the BSG guidelines 'Between 15% and 25% of patients with Ulcerative Colitis will require hospitalisation for an acute severe flare of disease at some stage in the natural history of their disease, often as the index presentation… A retrospective UK study (1950–2007) showed that the colectomy rate during first admission with Acute Severe Ulcerative Colitis (ASUC) was 19%, but after several admissions rose to 38.2%. In the biologics era, the colectomy rate after admission for ASUC in the CONSTRUCT trial was 23% during the inpatient stay, 200 and in another study was 19% at 2 years.' (Section 3.12) We would welcome further consideration about whether there may be circumstances in which a person with severe Ulcerative Colitis requiring intensive inpatient treatment may benefit from this treatment, in conjunction with other interventions. Biologics have played an increasing role in treatment over the past few years - consequently we would question the usefulness of the term 'conventional' treatment referenced throughout documentation.	notes that the scope of this appraisal does not include severe ulcerative colitis that is a medical emergency requiring intensive inpatient treatment.

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		We would also strongly advocate for a recognition within this section of the debilitating impact of the condition on the daily lives and quality of life of those affected, including its impact on education and employment - aligning with the 2019 IBD UK IBD Standards.	
The technology/ intervention *Is the description of the technology or technologies accurate?*	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	Yes	Thank you for your comment.
	Bristol-Myers Squibb	Please amend the description of the technology to the following: ***"Zeposia (ozanimod) is an oral, sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Zeposia reduces the capacity of lymphocytes to egress from lymph nodes, reducing the number of circulating lymphocytes in peripheral blood"*** Ozanimod has been investigated in adults only (18-75 years of age). The anticipated marketing authorisation is also expected to cover the adult population only. The label is expected to be worded as follows: ***"Zeposia (ozanimod) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have***	Thank you for your comment. The technology section has been updated.

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		had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent". Please remove "children" from the following sentence *"It has been studied in clinical trials as oral induction and maintenance therapy compared to placebo in children and adults with moderately to severely active ulcerative colitis"*	
Population *1) Is the population defined appropriately? 2) Are there groups within this population that should be considered separately?*	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	1) Yes 2) people under the age of 18 years old.	Thank you for your comment. The population in the scope has been updated to only include adults in line with the anticipated licence wording.
	Bristol-Myers Squibb	Zeposia (ozanimod) is expected to be indicated for 1. adults, with 2. moderately to severely active ulcerative colitis (UC), who 3. have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. The scope currently covers all patients with moderately to severely active UC. This definition should be modified to add the wording at point 3. above. Biologic therapies that are currently licensed for the treatment of moderately to severely active UC are:	Thank you for your comment. The population in the scope has been updated in line with the anticipated licence wording.

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		• Tumour necrosis factor (TNF)-alpha inhibitors: adalimumab, golimumab, infliximab • Other biologics: tofacitinib, vedolizumab, ustekinumab Please amend the following "People with moderately to severely active ulcerative colitis" to ***"Zeposia (ozanimod) 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".***	
Comparators *1) Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	1) Yes 2) Yes	Thank you for your comment.
	Bristol-Myers Squibb	The list of comparators should be amended to take into account the population covered in the label (see label wording in item 'technology' above). Given that patients with moderately to severely active UC will be eligible for Zeposia if they "***have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent",***	Thank you for your comment. In order to keep the scope broad at this early stage, and for consistency with previous scopes in this disease area, conventional therapies have been retained as comparators in the

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		where, • Conventional therapy is oral corticosteroids and/or immunomodulators • Biologic agents are TNF-alpha inhibitors (including infliximab, adalimumab, golimumab), JAK inhibitors (tofacitinib), vedolizumab and ustekinumab. Conventional therapy is typically prescribed as a first-line treatment option for the vast majority of patients with moderate to severely active UC. As such, conventional therapy is not indicated as primary treatment in any of the treatment groups covered in the anticipated ozanimod label, as patients are eligible for ozanimod are anticipated to have failed on prior conventional therapy - for these patients further re-treatment with conventional therapy would not be appropriate and based on UK clinical expert feedback, these patients would instead receive treatment with a biologic. For patients who have failed on a biologic, treatment would typically comprise a second biologic of a different class. Further, all active comparators listed above are used after conventional therapy has failed. Therefore, conventional therapy should not be a comparator in this appraisal and should be removed. The list of relevant comparators should be as follows: • TNF alpha inhibitors (infliximab, adalimumab, golimumab) • Tofacitinib • Ustekinumab	scope. The company will have the opportunity to outline the comparators it considers to be most relevant in its submission.

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		• Vedolizumab	
	Crohn's & Colitis UK	We would ask the Committee to remove steroids. Steroids are not recommended for maintenance of remission and are associated with a range of side effects (BSG IBD Guideline)	Thank you for your comment. In order to keep the scope broad at this early stage, and for consistency with previous scopes in this disease area, conventional therapies have been retained as comparators in the scope. The company for this appraisal will have the opportunity to outline the comparators it considers to be most relevant in its submission.
Outcomes *Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	Yes	Thank you for your comment.
	Bristol-Myers Squibb	In the TRUE NORTH study, endoscopic improvement was defined as an (endoscopy subscore of ≤ 1 point).	Thank you for your comment. The outcomes in the scope

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		"Mucosal healing" was defined as a combination of endoscopic **improvement** and histological **remission (**defined as Endoscopic improvement (MES ≤ 1) and Geboes score <2 (no eosinophils, no neutrophils in lamina propria, no neutrophils in the epithelium, no erosion, no ulceration) Please amend the wording to include "endoscopic improvement" and "histological remission"	have been amended in the light of the comments.
	Crohn's & Colitis UK	Patient experience and outcomes. Improved medicine adherence and self-management. We are assuming that hospitalisation already takes into consideration readmissions or emergency admissions. Is this correct?	Thank you for your comment. Health-related quality of life is included as an outcome, which captures patient experience. The outcome list is not intended to be exhaustive. Where relevant and appropriate, all available data are welcomed and will be considered by the committee.
Economic analysis	Bristol-Myers Squibb	The proposed approach and wording are considered appropriate.	Thank you for your comment.

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Equality	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	Can ozanimod be used as a 4th or 5th line biologic? Is it effective at this stage for resistant disease? Some CCGs refuse to fund 4th line biologic therapies so creating inequality of access to treatments based on postcodes. Adults over 55 years old and elderly population, can the manufactures provide more detailed information on how this population should be managed, monitored and reviewed?	Thank you for your comment. Where relevant and appropriate, the technology's position in the treatment pathway will be considered by the committee. Both the clinical- and cost-effectiveness of the technology will be considered before a recommendation is made and where appropriate, any relevant equality issues will be discussed. Information on managing this technology is outside the remit of this scope.
	Bristol-Myers Squibb	No comment	Thank you.
	Crohn's & Colitis UK	The mode of administration is a benefit for those with disabilities in terms of reducing the need for travel to hospital and could potentially improve adherence. This may also be a factor in cultures where it may be harder to speak openly about the condition or for those living in remote communities.	Thank you for your comment. Where appropriate, the committee will consider

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		Certain medications attract prescription costs in England. These costs can be prohibitive to groups of patients, acting as a barrier to well-being and adherence. The research can be read at: http://www.prescriptionchargescoalition.org.uk/	all relevant equality issues.
Other considerations	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	Funding applications forms for the CCGs to be made uniform across the UK. Dosing regimens both loading and maintenance should these be corrected for body weight? We have a number of patients with low body weight and Ozanimod has a high volume of distribution. When to review the therapy to ensure primary response to treatment? If a patient has altered Gastrointestinal anatomy or physiology how will the absorption of the ozanimod be altered? Will therapeutic drugs levels still be reached? Where is the site of absorption after oral admission?	Thank you for your comment. Information on managing this technology is outside the remit of this scope. Where relevant and appropriate, issues relating to dosing and monitoring of the treatment will be considered by the committee.
	Bristol-Myers Squibb	No comment	Thank you.
	Crohn's & Colitis UK	Biologics are administered via sub-cutaneous injection and/or infusion, which can be inconvenient and uncomfortable, so there is a clear benefit to patients from an additional treatment option which is an oral tablet.	Thank you for your comment. Where relevant and appropriate, benefits such as oral administration will be considered by the committee. No changes have been made to the scope.

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Innovation	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	This treatment is administered orally, will be a great help to patients who are not able to attend hospital for infusions of IV therapies due to lifestyle demands. Or those who struggle with SC administration due to the lack of ability to train for independent administration or have needle phobias. NHS centres prescribing will need to ensure they have robust systems in place to support the patient and work with the patient to ensure adherence to therapy.	Thank you for your comment. The innovative nature of this technology will be considered by the committee. No changes have been made to the scope.
	Bristol-Myers Squibb	Ozanimod offers a new mechanism of action in the treatment patients with moderately to severely active UC. It is a small molecule and a selective S1PR modulator that causes pro-inflammatory lymphocytes to remain in the lymph nodes preventing their migration to sites of inflammation, including the gastrointestinal tract Ozanimod is also administered orally, thereby reducing the treatment burden of patients, with the potential to persistence and compliance	Thank you for your comment. The innovative nature of this technology will be considered by the committee. No changes have been made to the scope.
	Crohn's & Colitis UK	There is also an advantage to a further treatment option which can be administered at home, which avoids the need for patients to take time off work or education and during the current pandemic also avoids any potential risks associated with travel to hospital.	Thank you for your comment. The innovative nature of this technology will be considered by the committee. No changes have been made to the scope.

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Questions for consultation	UK Clinical Pharmacy Association (UKCPA), Gastroenterology and Hepatology Committee	Are treatments given in combination in clinical practice, and if so, which combination treatments are used? Treatments are given in combination. Combinations include: aminosalicylates, corticosteroids, immunosuppressant and or biologics. Where do you consider ozanimod will fit into the existing NICE pathway, Ulcerative colitis overview? To induce and maintain remission. Can be used in both patients who have fail conventional therapies and are biologic naïve and those who biologic therapies have failed.	Thank you for your comment.
	Bristol-Myers Squibb	**Where do you consider ozanimod will fit into the existing NICE pathway, Ulcerative colitis overview?** As per proposed label, ozanimod is anticipated to be a treatment option for ***"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".*** Therefore, the anticipated positioning of Zeposia (ozanimod) in the NICE treatment pathway will be - Patients that have not previously received biologic therapy (a TNF alpha inhibitor or vedolizumab) or a JAK inhibitor (tofacitinib) or the IL 12/23 inhibitor ustekinumab	Thank you for your comment.

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		- Patients who have previously received one or more biologic therapy (a TNF-alpha inhibitor or vedolizumab) or a JAK inhibitor (tofacitinib) or the IL 12/23 inhibitor ustekinumab	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Abbvie

Amgen