National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Upadacitinib for treating moderately to severely active ulcerative colitis

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AbbVie	Yes; however, we recommend incorporating the following text: "Approximately 40% of ulcerative colitis patients are estimated to have moderately to severely active disease at any time post-diagnosis. Current treatments are unable to control the mucosal inflammation and associated symptoms of disease flares in all patients, and can be associated with adverse effects that limit their use (1-4). Approximately 52% of moderately to severely active patients do not respond to, or cannot tolerate conventional treatment and approximately 13% of patients are contraindicated to TNF-α inhibitors (5). Furthermore, while current biological therapies are beneficial, they may be associated with loss of response and serious adverse events, limiting the treatment options for clinicians and patients (6-8)."	Thank you for your comment. The background section of the scope is intended to provide a broad overview of the condition and its expected management. No action needed.
	Crohn's & Colitis UK	The NICE guideline on Ulcerative Colitis and quality standard on Inflammatory Bowel Disease are outdated and do not reflect current best practice and the experience of people with Ulcerative Colitis. We would ask that NICE update the guideline and quality standard urgently given it is the basis on which this drug will be appraised.	Thank you for your comment. Upadacitinib will be appraised independently of the NICE guideline on Ulcerative Colitis and the quality standard on Inflammatory Bowel

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			Disease. No action needed.
	Neonatal and Paediatric Pharmacists Group (NPPG)	Yes	Thank you for your comment. No action needed.
Wording	AbbVie	Yes. In addition to the current text, it would be useful to add the following text: "The anticipated licensed indication for upadacitinib is: [redacted]	Thank you for your comment. Details of the confidential anticipated marketing authorisation wording are not included in scopes. No action needed.
	Neonatal and Paediatric Pharmacists Group (NPPG)	Yes	Thank you for your comment. No action needed.
Timing Issues	AbbVie	There is a high unmet need for effective biologic therapies to treat moderately to severely active ulcerative colitis. As previously described, (in "Appropriateness") current treatments are unable to control the mucosal inflammation and associated symptoms of disease flares in all patients and can be associated with adverse effects that limit their use (1-4). Approximately 13% of patients are contraindicated to TNF α inhibitors (5). The use of current biological therapies is associated with loss of response and serious adverse events which limits the treatment options for clinicians and patients (6-8).	Thank you for your comment. No action needed.

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	Crohn's & Colitis UK	There are limited treatment options for this group of patients and new treatments are needed. It will increase treatment options for patients and support the delivery of personalised medicine. It would give people a treatment option to be taken at home, which will allow people to be treated at home and avoid hospital visits which is beneficial during a pandemic.	Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AbbVie	Where the draft scope states "Ulcerative colitis usually affects the rectum, and a variable extent of the colon proximal to the rectum", please can this be amended to "Ulcerative colitis can cause inflammation in the inner lining of the large intestine which is characteristically restricted to the mucosal surface with the disorder starting in the rectum and generally extending proximally in a continuous manner through the entire colon."	Thank you for your comment. The scope has been updated to reflect the suggested changes.
	Crohn's & Colitis UK	The number of people living with Ulcerative Colitis is incorrect based on recent and emerging evidence, which indicate an estimated 421,000 people with IBD living in England and 500,000 living in the UK. Based on three regional studies. Jones G, Lyons M, Plevris N, et al. (2019). IBD prevalence in Lothian, Scotland, derived by capture recapture methodology. Gut. 68: 1953–1960. 10.1136/gutjnl-2019-318936. Crohn's & Colitis UK (22 January 2021).	Thank you for your comments. The scope has been updated to reflect the suggested changes.

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		Study shows over 50% more people in Wales have Crohn's or Colitis than previously recognised. www.crohnsandcolitis.org.uk/news/ study-shows-over-50-more-peoplein-wales-have-crohns-or-colitisthan-previo Hamilton B, Green H, Heerasing N, et al. (2020). Incidence and prevalence of inflammatory bowel disease in Devon, UK. Frontline Gastroenterology. Online: 24 June. doi:10.1136/flgastro-2019-101369. We would suggest amending 'colicky abdominal pain' to pain. Up to 50% will experience extraintestinal manifestations, involving different parts of their body, commonly joints, skin, bones, eyes, kidneys and liver (IBD UK). Of those who responded to the IBD UK Patient Survey, 70% (6,732) said they had experienced one or more flares during the previous 12 months, with 14% reporting more than five flares over this period. We would ask the Committee to review the initial paragraph – as it is unclear how it applies to this moderate to severe group.	
	Neonatal and Paediatric Pharmacists Group (NPPG)	Accurate and complete	Thank you for your comment. No action needed.
The technology/ intervention	AbbVie	Yes. It would be helpful to also include the following text: "Upadacitinib is a selective oral JAK inhibitor which has been engineered to have greater affinity for JAK1."	Thank you for your comment. The scope has been updated to include ustekinumab.

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		Please include ustekinumab where TNF-alpha inhibitors and vedolizumab are stated as biological treatments that patients have inadequate or loss of response to as the upadacitinib clinical trial population included patients who had previously received treatment with ustekinumab.	
	Neonatal and Paediatric Pharmacists Group (NPPG)	Yes	Thank you for your comment. No action needed.
Population	AbbVie	Where the evidence allows the following subgroups will be considered: • People who have been previously treated with 1 or more biologics • People who have not received a prior biologic.	Thank you for your comment. No action needed.
	Crohn's & Colitis UK	We would ask that the committee to more clearly distinguish between the experiences of people with mild disease and those with moderate to severe Ulcerative Colitis and the impact that this condition has on this group and their quality of life. Blood in stool, ulceration, frequent bowel movements, and fever not captured in the description of symptoms (Crohn's & Colitis UK and BSG guidelines on IBD) As currently written the background does not capture the significant unmet need within this patient cohort. Moderate to severe ulcerative colitis is defined as: Truelove and Witts define severe Ulcerative Colitis as six or more stools a day plus at least one of the features of systemic upset (marked with an *): visible blood; pyrexia*; pulse rate greater than 90 BPM*; erythrocyte sedimentation rate (mm/hour)* and anaemia.	Thank you for your comment. The background of the scope is intended to give a brief overview of the condition and treatment.

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		The Mayo Score defines severe Colitis as more than five stools a day, blood passed without stool, obvious blood with stools in most cases and severe disease (spontaneous bleeding, ulceration). It is estimated that refractory disease and moderate to severe disease that is uncontrolled affects about 5% of this population, which is significant in terms of the numbers of affected. This sub-group is likely to comprise <5% of patients with Ulcerative Colitis who experience more severe flares, weight loss, fever and constitutional symptoms and whose disease has not responded to other treatment options, are unable to tolerate these, and/or can benefit from this treatment in particular There should be a clear definition of acute severe Ulcerative Colitis included. The BSG Guidelines that state that 'acute severe colitis is a potentially life-threatening condition.' Acute severe colitis has a 1% mortality risk and a 29% chance of requiring emergency surgery to remove the inflamed bowel (colectomy). Between 15-25% of patients with Ulcerative Colitis will need to be hospitalised due to an acute severe flare up at some stage. Often this will be the first presentation of their disease. When a flare occurs in acute severe colitis, deterioration can occur rapidly. Patients will require close monitoring and review by appropriate specialists. It's also vitally important to make decisions quickly to avoid severe complications. The very real risks associated with acute severe colitis include: • Life-threatening haemorrhage • Toxic megacolon - can occur in up to 1 in 40 people with Colitis • Perforation of the bowel	

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	Neonatal and Paediatric Pharmacists Group (NPPG)	Is the population inclusive of <18yrs olds? Can they be considered as part of this review? Ideally use in trial setting or compassionate use prior to using in children <18yrs	Thank you for your comment. The technology will be appraised in line with the marketing authorisation and company's positioning.
Comparators	AbbVie	Yes, for most of the treatments listed; however, we recommend that filgotinib is not included as a comparator as it is currently being evaluated by NICE and therefore not approved for use in, or considered standard of care for, patients with moderately to severely active ulcerative colitis. We would also recommend that conventional therapy is not considered as a relevant comparator. Conventional therapy would typically be given earlier in the treatment pathway, compared with biological treatment, and prior to where upadacitinib will be placed. As treatment with upadacitinib would either be used alongside or follow treatment with conventional therapy, we believe conventional therapy is not a direct comparator to upadacitinib.	Thank you for your comment. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals have been included "(subject to ongoing NICE appraisal)" and conventional therapies have been retained. The company will have the opportunity during the full appraisal to outline which comparators it considers to be most relevant.

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	Crohn's & Colitis UK	**We are concerned that the use of steroids as a comparator may imply that for those who cycle through available treatment options without success, steroids are an alternative treatment.** "Corticosteroids have no proven efficacy in maintaining remission in IBD and should not be used for this purpose." The BSG guidelines set out clear stipulations on the best practice of prescribing steroid therapies given their diminishing returns, harsh side effects and risk of dependency. Corticosteroids can induce remission, but they do not heal mucosa. There is no evidence to support the benefits of high-dose steroids and they have side effects. Approximately 50% of patients experience short-term corticosteroid-related adverse events such as acne, oedema, sleep and mood disturbance, glucose intolerance and dyspepsia. (BSG guideline on IBD)	Thank you for your comment. In order to keep the scope broad at this early stage, conventional therapies have been retained in the list of comparators. The company will have the opportunity during the full appraisal to outline which comparators it considers to be most relevant.
	Neonatal and Paediatric Pharmacists Group (NPPG)	Yes	Thank you for your comment. No action needed.
Outcomes	AbbVie	Yes. However, we recommend refining these to only include the outcomes considered in the model which were used to assess the most important health-related benefits. These outcomes are rates of remission, response, partial response w/o remission, and adverse events (as model inputs), as well as mortality (and life years gained), rates of surgical intervention, costs, and health-related quality of life (QALYs). With regards "mucosal healing (combines endoscopic and histological healing)", we recommend amending the description of this outcome to "Endoscopic remission combined with histological improvement".	Thank you for your comment. The wording of the outcome related to mucosal healing has been changed. The outcomes in the scope are broad and overarching, more specific outcomes relevant to these broader outcome

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			headings can be considered as part of the appraisal process.
	Crohn's & Colitis UK	Being able to retain work, training and education. We would ask that the Committee further **consider the complications of chronic, uncontrolled, active disease**. - Both osteoporosis and vitamin D deficiency are common in IBD. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity[1] - Anaemia is a common complication of IBD. Iron deficiency and anaemia of chronic disease are the commonest causes of anaemia in IBD[2] - Increased risk of cancer[3]	Thank you for your comment. Osteoporosis, anaemia and increased risk of cancer are all included in the background of the scope.
	Neonatal and Paediatric Pharmacists Group (NPPG)	Benefit of oral therapy will be welcome to families with frequent attendance at hospital as the alternative.	Thank you for your comment. No action needed.

[1] Mowat C, Cole A, Windsor A et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011; 60:571-607.
[2] Ibid
[3] BSG guideline (2019)

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Economic analysis	AbbVie	No issues have been identified.	Thank you for your comment. No action needed.
Equality and Diversity	AbbVie	No issues have been identified.	Thank you for your comment. No action needed.
	Crohn's & Colitis UK	Women who would like to avoid surgery to start a family. For religious groups such as Muslims, for whom this may impact on religious practices and cause distress.[4]	NICE is required by law to look at any protected characteristics and whether any recommendation could cause unlawful discrimination. The appraisal committee will consider any equality issues.
	Neonatal and Paediatric Pharmacists Group (NPPG)	Scope should be amended to include <18yr olds, if it does not already include this population.	Thank you for your comment. The technology will be appraised in line with the marketing authorisation and company's positioning.

[4] https://www.researchgate.net/publication/258203344_Quality_of_life_after_restorative_proctocolectomy_in_Muslim_patients

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Other considerations	AbbVie	As previously discussed, (in “Population”), relevant subgroups will be considered where the evidence allows for this.	Thank you for your comment. No action needed.
Innovation	AbbVie	Yes, as described in questions 4 through 6.	Thank you for your comment. No action needed.
Questions for consultation	AbbVie	***Q1.*** *Have all relevant comparators for upadacitinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for ulcerative colitis? It may be appropriate to ask whether a specific comparator should be included or not.* Yes, all relevant comparators have been included in the scope. However, as previously discussed, (in “Comparators”), we recommend that filgotinib is not included as a comparator as it is currently being evaluated by NICE and therefore not recommended for use in, or considered standard of care for, patients with moderately to severely active ulcerative colitis. Furthermore, we also recommend that conventional therapy is not included as a comparator as this is provided earlier in the treatment pathway, compared with biological treatment, and prior to where upadacitinib will be placed. As treatment with upadacitinib would either be used alongside or follow treatment with conventional therapy, we believe conventional therapy is not a direct comparator to upadacitinib. *Q2.* ***Are the outcomes listed appropriate?*** Yes, as previously discussed in the text in “Outcomes”. Furthermore, with regards “mucosal healing (combines endoscopic and histological healing)”, we recommend amending the description of this outcome to “Endoscopic remission combined with histological improvement”.	Thank you for your comment. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals have been included "(subject to ongoing NICE appraisal)” and conventional therapies have been retained. The outcomes in the scope are broad and overarching, more specific outcomes relevant to these broader outcome

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		Q3. ***Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom upadacitinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** Yes, the subgroups suggested are appropriate and there are no additional subgroups that should be examined separately. *Q4.* ***Where do you consider upadacitinib will fit into the existing NICE pathway, Ulcerative colitis: management?*** We consider upadacitinib as an option to biological treatments in people with moderately to severely active ulcerative colitis with inadequate response, loss of response, or intolerance to corticosteroids, immunosuppressive agents, and/or other biologic therapies. As such, upadacitinib would be placed in the existing NICE pathway, *"Ulcerative colitis: management (NG130)"* under Section 1.2 *"Inducing remission in people with ulcerative colitis"*, specifically under Section 1.2.14 *"Biologics and Janus kinase inhibitors for moderately to severely active ulcerative colitis: all extents of disease"* as a treatment option for patients who have an inadequate response or are intolerant to conventional therapy, and in patients who have an inadequate response to biological therapy or are contraindicated to TNF-alpha treatment. *Q5.* ***Do you consider upadacitinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?*** Upadacitinib is a selective oral JAK inhibitor which has been engineered to have greater affinity for JAK1.	headings can be considered as part of the appraisal process.

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		Advice sought by AbbVie UK indicates upadacitinib has a substantial opportunity to provide clinical outcomes valued highly by people living with moderate to severe UC. *Q6.* ***Do you consider that the use of upadacitinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*** Substantial improvements in outcomes for people living with moderate to severe UC may positively influence the health-related quality of life of their carers or next-of-kin. In addition, upadacitinib is licensed in a range of inflammatory conditions that respond to selective JAK inhibition. Therefore, we consider it likely that some health-related benefits are not fully captured by the QALY calculation. *Q7.* ***To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.*** No issues or barriers to adoption of upadacitinib are expected. *Q8.* ***NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. Would it be appropriate to use the cost comparison methodology for this topic?*** We believe NICE's intention to assess upadacitinib in patients with moderately to severely active ulcerative colitis through the STA process to be appropriate. We look forward to engaging with NICE on the appropriate appraisal process.	

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		Q9. ***Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?*** It is anticipated that upadacitinib will offer improved clinical outcomes and similar resource use compared with the comparators listed. *Q10.* ***Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?*** Yes. The best-known disease activity instrument for ulcerative colitis is the Mayo Score. The Mayo Score is a composite instrument comprised of four categories: bleeding, stool frequency, physician global assessment, and endoscopic appearance which are each rated from 0–3 and summed to give a total score that ranges on a scale from 0–12. The primary endpoint for upadacitinib (proportion of subjects who achieved clinical remission) was assessed by Adapted Mayo Score which is a Mayo Score without the physician global assessment category. The primary outcome is considered clinically relevant and has been validated as relevant by Experts in an advisory board conducted in November 2021. *Q11.* ***Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?*** We are not aware of any substantial new evidence for the comparator technology/ies that has/have not been considered, or if any important ongoing trials are due to report in the next 12 months.	
	Neonatal and Paediatric	*Where do you consider upadacitinib will fit into the existing NICE pathway, Ulcerative colitis: management?* – At the same stage as tofacitinib is	Thank you for your comment. No action required.

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	Pharmacists Group (NPPG)	considered. It is good to have another choice with a different mode of action for those who have failed other therapies prior to surgery.	

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

Takeda, Janssen