National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Tofacitinib for 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	Pfizer	It is appropriate for this topic to be referred to NICE.	Comment noted. No action required.
	British Society of Gastroenterology	No comments	Comment noted. No action required.
	MSD	Yes	Comment noted. No action required.
Wording	Pfizer	The wording is appropriate.	Comment noted. No action required.
	British Society of Gastroenterology	No comments	Comment noted. No action required.
Timing Issues	Pfizer	It is important that clinicians in England and Wales are provided with timely NICE Guidance on the use of tofacitinib in moderate to severe ulcerative colitis (UC) as this is a condition with a high unmet need	Comment noted. No action required.

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	British Society of Gastroenterology	No comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pfizer	Please can the italicised information be added to the background information in order to ensure accuracy and completeness. • Clinical remission of the disease is defined by a total Mayo score of 2 points or lower *with no individual sub-score exceeding 1* (Rutgeerts et al., 2015) • *If the disease progresses to moderate-severe UC then a tumour necrosis factor-alpha inhibitor (TNF-alpha inhibitor, such as infliximab, golimumab or adalimumab) or an anti-integrin (vedolizumab) may be considered* (NICE CG166, 2013).	Thank you for your comments. The scope has been updated to reflect this comment.
	British Society of Gastroenterology	No comments.	No action required.
	AbbVie	On page 2, paragraph 2 sentence two we note that calcineurin is not indicated for the treatment of ulcerative colitis (UC). On page 2, paragraph 2 sentence three we note that thiopurines are not indicated for the treatment of ulcerative colitis (UC)	Thank you for your comments. Calcineurin inhibitors (tacrolimus or ciclosporin) and surgical intervention have been removed as comparators. NICE clinical guideline 166 suggests that

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			thiopurines may be used for this indication.
The technology/ intervention	Pfizer	Please can the technology be described as follows: Tofacitinib (Xeljanz, Pfizer) is a Janus kinase (JAK) inhibitor and is a targeted synthetic small molecule that is taken orally.	Thank you for your comment. The technology has been updated to reflect this comment.
	British Society of Gastroenterology	No comments	No action required.
	MSD	Yes	Comment noted. No action required.
Population	Pfizer	The wording is appropriate.	Comment noted. No action required.
	British Society of Gastroenterology	No comments	No action required.
	AbbVie	Based on the tofacitinib trial programme as outlined in paragraph 4 on page two of the draft scope the anticipated licence for the drug and hence the appropriate population is: Adult people with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.	Thank you for your comment. As the marketing authorisation is currently unconfirmed, it is more appropriate to keep the population broad and avoid qualifying factors. No changes to the scope required.

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	MSD	Yes	Comment noted. No action required.
Comparators	Pfizer	The OCTAVE clinical trial programme included a patient population who had failed or had unacceptable side effects from treatment on conventional therapy (e.g. oral or intravenous glucocorticoids, azathioprine, mercaptopurine), or biologics (e.g..TNF inhibitors) (Sandborn 2017). This population is aligned with the populations appraised in NICE TA329 ("Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy") and NICE TA342 ("Vedolizumab for treating moderately to severely active ulcerative colitis"). Therefore Pfizer proposes that the decisions made by the NICE committees in those appraisals not to consider calcineurin inhibitors and surgery as comparators are applied to this appraisal. The rationales for the decision are provided below. The addition of calcineurin inhibitors (tacrolimus or ciclosporin), and surgical intervention as comparators is not appropriate. In UK clinical practice calcineurin inhibitor use is limited due to adverse events but according to NICE clinical guidance may be used to induce remission in mild to moderate disease, or for acute severe ulcerative colitis, neither of which are within the remit of this appraisal. Surgery may be an option according to disease history but is mostly reserved after failure of pharmacological treatments in this population. Surgery In patients with moderate-to-severe UC surgery is avoided as long as possible by clinicians and patients as it has potential complications and has long-term consequences on patient well-being. In this population, surgery is considered to be a last treatment option when all drug therapy has failed. Therefore for patients who are eligible for conventional or biologic treatment	Thank you for your comments. Calcineurin inhibitors (tacrolimus or ciclosporin) and surgical intervention have been removed as comparators.

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		in clinical practice surgery cannot be considered as a comparator. This is in line with published NICE guidance (NICE TA329, 2015; NICE TA342, 2015). Calcineurin inhibitors In UK clinical practice these may be used for inducing remission but not chronic treatment to maintain remission in the proposed population. This is in line with published NICE guidance (NICE TA342, 2015).	
	British Society of Gastroenterology	No comments	No action required.
	Napp Pharmaceuticals	Napp agree with inclusion of TNF-alpha inhibitors (infliximab, adalimumab and golimumab) as relevant comparators for tofacitinib in patients with moderate to severely active ulcerative colitis who have failed conventional therapy, as per TA329. Napp support the principal outlined by NICE that "the availability and cost of biosimilar products should be taken into account" when conducting technology appraisals. Napp would like to highlight the availability of biosimilar infliximab (Remsima®) as a relevant comparator for this appraisal.	Thank you for your comment. The scope has been updated to reflect that the availability and cost of biosimilars should be taken into account for the comparators.
	AbbVie	For the treatment of adult people with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to conventional therapy: • TNF-alpha inhibitors (infliximab, adalimumab and golimumab) • Vedolizumab	Thank you for your comments. The scope includes the comparators highlighted in your comment. The committee may consider whether there merit in considering separately subgroups

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		For the treatment of adult people with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumour necrosis factor-alpha (TNFα) antagonist. • TNF-alpha inhibitors (infliximab, adalimumab and golimumab) • Vedolizumab	based on the type of previous therapy received. No changes to the scope required.
	MSD	Yes	Comment noted. No action required.
Outcomes	Pfizer	Yes we agree with the outcomes listed in the draft scope. In addition we would like to include 'steroid free remission' in the list of proposed outcomes. It is recommended that steroid use in all patients is kept to a minimum as the use of steroids in the long-term has undesirable long term consequences (RCP, 2016).	Thank you for your comment. The effect of treatment on steroid-free remission may be presented in the context of the rate and duration of remission which are included among the outcomes in the scope.
	British Society of Gastroenterology	Long-term safety should be considered – taking into account the 8 year safety data from use in Rheumatology and Dermatology (eg J Rhematology 2014;41:837; Arthritis Res Ther 2016;18:34; Br J Dermatol 2015;172:1395; Lancet 2015;386:552)	Thank you for your comments. Adverse effects of treatment has been included in the scope. No changes to the scope required.
	MSD	Yes	Comment noted. No action required.
	Pfizer	No comments.	No action required.

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Economic analysis	British Society of Gastroenterology	No comments	No action required.
	Napp Pharmaceuticals	Currently the draft scope for this appraisal does not suggest that "the availability and cost of biosimilar products should be taken into account" when conducting the economic analysis. As biosimilars are available for some comparators listed in this appraisal (e.g. infliximab), Napp would suggest that this wording is added to the scope. Napp would recommend that in order to accurately reflect the true NHS acquisition cost of biosimilar medicines that actual tender prices are included for biosimilar medicines, and not just the list price. If information relating to actual tender prices is not available, Napp would suggest that uncertainty related to acquisition cost could be handled as a sensitivity analysis covering a range of discounts (i.e. 10%, 20%, 30%, 40%, 50%, etc.).	Thank you for your comment. The scope has been updated to reflect that the availability and cost of biosimilars should be taken into account for the comparators.
Equality and Diversity	Pfizer	No comments.	No action required.
	British Society of Gastroenterology	No comments	No action required.
Innovation	Pfizer	There is an unmet need in patients with UC as many patients do not achieve long term remission on currently available treatments. Furthermore patients who fail on conventional therapy and biologics have limited treatment options. Tofacitinib is innovative and is a step-change in the management of moderate to severe UC as it is an oral therapy that has a different mode of action to	Comment noted. You are encouraged to describe the innovative nature of the technology in your submission to

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		currently available treatments. Tofacitinib provides an additional option for patients with moderate to severe UC. UC is highly symptomatic, which often means that patients are unable to work and suffer loss of productivity. This measure is not currently captured in the QALY calculation and therefore the benefit of tofacitinib in prolonging remission in patients with UC cannot be fully captured. Tofacitinib offers an oral alternative to the current standard of care which is intravenously or subcutaneously administered. The benefits of an oral therapy cannot be captured fully in the QALY calculation. The benefits include ease of disease management for the patient, and also providing a solution to those patients who have difficulties with intravenous administration. Furthermore, the addition of tofacitinib to the treatment pathway may delay surgery and reduce steroid use in patients, both of which are known to have a negative impact on patient quality of life.	NICE. No changes to the scope required.
	British Society of Gastroenterology	No comments	No action required.
Other considerations	Pfizer	No additional comments.	No action required.
	British Society of Gastroenterology	Consider subgroup with UC proctitis if data available	Comment noted. No action required.
Questions for consultation	Pfizer	**Where do you consider tofacitinib will fit into the existing NICE pathway** It is expected that tofacitinib would be included in NICE CG 166 (2013) as a treatment option for patients with moderate-to-severe UC after treatment failure or intolerance to conventional therapies, OR after failure or intolerance to biologic agents. **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?**	Thank you for your comments. This topic will be recommended for appraisal as a single technology appraisal.

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		The Phase 2/3 clinical programme did not include active comparator studies, therefore head to head data do not exist. In order to estimate relative efficacy adjusted indirect comparison analyses will be conducted and presented in the submission. Tofacitinib is an oral therapy therefore is likely to have lower resource use than current treatments that require hospital visits in order to receive treatments via IV infusion. Additionally, as a synthetic small molecule tofacitinib is likely to avoid the clinical consequences of immunogenicity such as therapeutic drug monitoring and dose escalation. **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 primary outcome in the OCTAVE clinical studies is clinically relevant. The outcome was remission (defined as a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0) at 8 weeks (Sandborn et al., 2017). This defined measure of remission is more stringent than for studies for biologic therapies in UC which do not include rectal bleeding scores in their primary outcome definitions of clinical remission. The European Medicines Agency's draft guideline advocates the inclusion of a rectal bleeding measure in trials evaluating new medications for UC (EMA, 2016). The OCTAVE clinical studies also included clinical remission as defined in comparator studies as a secondary outcome so that comparisons on efficacy will be possible. **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?** Important ongoing tofacitinib clinical trials: **1.** OCTAVE open label long term extension study (NCT01470612). The objective of this study is to assess the safety and tolerability of long-	

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		term tofacitinib therapy in subjects with UC. The estimated study completion date July 2018. **2.** A Study of Tofacitinib in Patients With Ulcerative Colitis in Stable Remission (NCT03281304). This study is a follow up study for subjects with Ulcerative Colitis (UC) in stable remission designed to evaluate flexible dosing of Tofacitinib (5mg vs 10mg). The estimated study completion date is November 2018.	
	British Society of Gastroenterology	No comments	No action required.
Additional comments on the draft scope	Pfizer	None	No action required.
	British Society of Gastroenterology	See above	Comment noted.

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

- Department of Health