

tofacitinib 5mg, 10mg film-coated tablets (Xeljanz®)

Pfizer Limited

11 January 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and 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

tofacitinib (Xeljanz®) is accepted for use within NHSScotland.

Indication under review: For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

In phase III studies, tofacitinib was superior to placebo in achieving and sustaining remission in adult patients with moderately to severely active ulcerative colitis who had treatment failure with, or were intolerant to, a conventional or biologic medicine.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of tofacitinib. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a 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 who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.¹

Dosing Information

The recommended dose is 10mg orally twice daily for 8 weeks for induction and 5mg twice daily for maintenance.

For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose can be extended for an additional 8 weeks (16 weeks total), followed by 5mg twice daily for maintenance. Tofacitinib induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

For some patients, such as those who have failed prior tumour necrosis factor (TNF) inhibitor therapy, consideration should be given to continuation of the 10mg twice daily dose for maintenance in order to maintain therapeutic benefit.

Patients who experience a decrease in response on tofacitinib 5mg twice daily maintenance therapy may benefit from an increase to tofacitinib 10mg administered twice daily.

In patients who have responded to treatment with tofacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.¹

Retreatment in ulcerative colitis

If therapy is interrupted, restarting treatment with tofacitinib can be considered. If there has been a loss of response, re-induction with tofacitinib 10mg twice daily may be considered. The treatment interruption period in clinical studies extended up to 1 year. Efficacy may be regained by 8 weeks of 10mg twice daily therapy.¹

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which tofacitinib is indicated.¹

Product availability date

01 August 2018

Summary of evidence on comparative efficacy

Tofacitinib is an inhibitor of the Janus Kinase (JAK) family. Inhibition of JAK1 and JAK3 by tofacitinib attenuates the response of multiple cytokines implicated in the pathogenesis of ulcerative colitis, resulting in modulation of the immune and inflammatory response.¹ Tofacitinib is the first JAK inhibitor licensed specifically for ulcerative colitis.

The evidence supporting the licensed indication is from two identical phase III, randomised, double-blind, placebo-controlled 8-week induction studies, OCTAVE Induction 1 and 2, and a

phase III, randomised, double-blind, placebo-controlled 52-week maintenance study, OCTAVE Sustain, that included patients who had completed and achieved a clinical response in the induction studies.²

OCTAVE Induction 1 and 2 included patients ≥ 18 years old with a confirmed diagnosis (endoscopic or radiographic and histological) of ulcerative colitis of ≥ 4 months duration and with moderately to severely active disease. Disease severity was centrally assessed using the Mayo scale which ranges from 0 to 12; where higher scores indicate increased severity. The total Mayo score comprises four subscores (stool frequency, rectal bleeding, endoscopic findings and physician’s global assessment) each graded 0 to 3. Eligible patients had total score ≥ 6 , rectal bleeding subscore ≥ 1 and endoscopic subscore ≥ 2 . They were required to have had an inadequate response, loss of response or intolerance to at least one of the following medicines: oral or intravenous corticosteroids, azathioprine, mercaptopurine, infliximab or adalimumab.²

Patients were randomised centrally in a 4:1 ratio to receive oral treatment with tofacitinib 10mg twice daily or placebo for eight weeks. Randomisation was stratified according to prior use of TNF inhibitors, use of corticosteroids at baseline and geographical region. Patients could receive concomitant treatment (if dose was stable throughout the study) with oral aminosalicylates and oral corticosteroids (maximum daily dose 25mg prednisone or equivalent).² Disallowed medication included TNF inhibitors, azathioprine, methotrexate and mercaptopurine.²

The primary outcome was remission at week 8, defined as total Mayo score ≤ 2 , with no subscore >1 and rectal bleeding subscore of 0. The Mayo endoscopic subscore was assessed centrally. The primary analysis was performed on all randomised patients.²

Remission at week 8 was achieved in significantly higher proportions of patients receiving tofacitinib than placebo in both OCTAVE Induction 1 and 2.²

Table 1: Primary outcome results at week 8 for OCTAVE Induction 1 and 2²

Outcome	OCTAVE Induction 1			OCTAVE Induction 2		
	Tofacitinib 10mg N=476	Placebo N=122	Treatment difference (95% CI)	Tofacitinib 10mg N=429	Placebo N=112	Treatment difference (95% CI)
Remission	88 (18%)	10 (8.2%)	10% (4.3 to 16) p=0.007	71 (17%)	4 (3.6%)	13% (8.1 to 18) p<0.001

N=number; CI=confidence interval

Subgroup analysis demonstrated a treatment effect in patients who had been refractory to TNF inhibitors. Rates of remission were significantly higher in patients receiving tofacitinib versus placebo in patients with and without prior failure of TNF inhibitors: 11% versus 1.6% in 307 (51%) patients with failure of TNF inhibitor and 26% versus 16% in 291 (49%) patients without failure of TNF inhibitor, respectively in OCTAVE Induction 1; and 12% versus 0 in 282 (52%) patients with failure of TNF inhibitor and 22% versus 7.7% in 259 (48%) patients without failure of TNF inhibitor,

respectively in OCTAVE Induction 2. Most patients without failure of TNF inhibitor were TNF inhibitor-naïve.²

The key secondary outcome was mucosal healing at week 8, defined as Mayo endoscopic subscore ≤ 1 . Other secondary outcomes included clinical response at week 8, defined as a decrease from induction study baseline in the total Mayo score of at least three points and at least 30%, with an accompanying decrease in rectal bleeding subscore of at least one point or absolute rectal bleeding subscore of 0 or 1; and endoscopic remission at week 8, defined as endoscopic subscore of 0.²

Table 2: Selected secondary outcome results at week 8 for OCTAVE Induction 1 and 2²

Outcome	OCTAVE Induction 1			OCTAVE Induction 2		
	Tofacitinib 10mg N=476	Placebo N=122	Treatment difference (95% CI)	Tofacitinib 10mg N=429	Placebo N=112	Treatment difference (95% CI)
Mucosal healing	149 (31%)	19 (16%)	16% (8.1 to 23) ^A	122 (28%)	13 (12%)	17% (9.5 to 24) ^A
Clinical response	285 (60%)	40 (33%)	27% (18 to 36) ^A	236 (55%)	32 (29%)	26% (17 to 36) ^A
Endoscopic remission	32 (6.7%)	2 (1.6%)	5.1% (1.9 to 8.3) ^B	30 (7.0%)	2 (1.8%)	5.2% (1.8 to 8.6) ^B

N=number; CI=confidence interval; ^Ap<0.001; ^Bp=0.04

Health related quality of life was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ), range 32 to 224, with higher scores signifying better quality of life. IBDQ remission is defined as a score of ≥ 170 . At week 8, in the tofacitinib group versus placebo group, IBDQ remission was achieved by 43% versus 26% of patients in OCTAVE Induction 1; and by 40% versus 18% of patients in OCTAVE Induction 2; p<0.001 for both studies. Significant benefits for tofacitinib over placebo were also reported for the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the short form 36 (SF-36), higher scores indicate better quality of life; least squares mean change from baseline for tofacitinib versus placebo in PCS was 6.8 versus 2.5 in OCTAVE Induction 1 and 6.8 versus 4.6 in OCTAVE Induction 2; the corresponding figures for MCS were 6.8 versus 3.5 and 7.6 versus 4.4, respectively.³ Benefits over placebo were also reported with the Euroqol-5 dimensions (EQ-5D) and the Work Productivity and Activity Impairment-Ulcerative Colitis (WPAI-UC) tools.⁴ The EQ-5D scale is 0 to 100, with higher scores denoting better quality of life.² There were significant improvements in change from baseline to week 8 in EQ-5D score for tofacitinib and placebo: 18 versus 9.5, respectively in OCTAVE Induction 1 and 17 versus 8.3, respectively in OCTAVE Induction 2; p<0.0001 in both studies.^{5, 6} The WPAI-UC questionnaire is a validated 6-item questionnaire designed to measure the ability to work and perform regular activities. It has four scores:

1. Absenteeism (work time missed).
2. Presenteeism (impairment at work/reduced on-the-job effectiveness).
3. Work productivity loss (overall work impairment/absenteeism plus presenteeism).
4. Activity impairment.²

There were significant improvements in OCTAVE Induction 1 in change from baseline to week 8 in WPAI-UC domain scores for tofacitinib versus placebo in presenteeism (difference from placebo: -

13, p=0.0003), work productivity loss (difference from placebo: -11, p=0.0143) and non-work activity impairment (difference from placebo: -14, p<0.0001).⁵ In OCTAVE Induction 2, there was only one significant change, improvement in non-work activity impairment (difference from placebo: -12, p<0.0001).⁶

OCTAVE Sustain included patients who had completed OCTAVE Induction 1 or 2 and had achieved a clinical response, as defined above. Eligible patients underwent re-randomisation in a 1:1:1 ratio to receive 52 weeks treatment with tofacitinib 5mg twice daily, tofacitinib 10mg twice daily or placebo. Randomisation was stratified by assigned group in the induction study and by the presence or absence of remission at OCTAVE Sustain baseline. Permitted concomitant medications were the same as for the induction studies and doses had to remain stable, except that any patients receiving corticosteroids had to taper these from the start of OCTAVE Sustain.²

The primary outcome was remission (as defined for the induction studies) at 52 weeks, with central assessment of the Mayo endoscopic subscore.²

Table 3: Primary outcome results at week 52 for OCTAVE Sustain²

Outcome	Tofacitinib 5mg N=198	Tofacitinib 10mg N=197	Placebo N=198	Treatment difference Tofacitinib 5mg versus placebo (95% CI)	Treatment difference Tofacitinib 10mg versus placebo (95% CI)
Remission	68 (34%)	80 (41%)	22 (11%)	23% (15 to 31) p<0.001	30% (21 to 38) p<0.001

N=number; CI=confidence interval

Remission rates at week 52 were significantly higher for tofacitinib 5mg twice daily and tofacitinib 10mg twice daily versus placebo for the subgroup that was in remission at baseline: 46% (30/65) and 56% (31/55) versus 10% (6/59) as well as the subgroup that had achieved clinical response but not remission at baseline: 29% (38/133) and 34% (49/142) versus 12% (16/139), p<0.001 for all comparisons with placebo.⁴

There were two key secondary outcomes: mucosal healing at 52 weeks, defined as Mayo endoscopic sub score ≤1 and, for the subgroup of 179 patients who were in remission at study entry, sustained remission, defined as remission that was present at both 24 and 52 weeks and occurred without the administration of corticosteroids for ≥4 weeks before the assessment.²

Table 4: Selected secondary outcome results at week 52 for OCTAVE Sustain²

Outcome	OCTAVE Sustain				
	Tofacitinib 5mg	Tofacitinib 10mg	Placebo	Treatment difference, tofacitinib 5mg versus placebo (95% CI)	Treatment difference tofacitinib 10mg versus placebo (95% CI)
Mucosal healing	37% (74/198)	46% (90/197)	13% (26/198)	24% (16 to 32) ^A	33% (24 to 41) ^A
Sustained corticosteroid-free remission	35% (23/65)	47% (26/55)	5.1% (3/59)	30% (17 to 43) ^A	42% (28 to 56) ^A
Clinical response	51% (102/198)	62% (122/197)	20% (40/198)	31% (22 to 40) ^A	42% (33 to 50) ^A

CI=confidence interval; ^Ap<0.001

Tofacitinib was efficacious in the subgroups of patients with and without prior TNF inhibitor failure. The former subgroup included patients who never achieved a response with TNF inhibitors as well as patients who achieved and then lost response. The size of treatment effect was similar with both doses of tofacitinib in the subgroups of patients without prior TNF inhibitor failure, but there was a clinically meaningful observed treatment difference between tofacitinib 10mg twice daily and 5mg twice daily doses in patients with prior TNF inhibitor failure.⁴

Table 5: Subgroup analysis according to TNF inhibitor failure of primary and key secondary outcomes at 52 weeks, OCTAVE Sustain⁴

Subgroup	Tofacitinib 5mg N=198	Tofacitinib 10mg N=197	Placebo N=198	Treatment difference, tofacitinib 5mg versus placebo (95% CI)	Treatment difference, tofacitinib 10mg versus placebo (95% CI)
Remission					
No prior TNFi failure	42% (48/115)	44% (46/104)	11% (12/109)	31% (20 to 42)	33% (22 to 44)
Prior TNFi failure	24% (20/83)	37% (34/93)	11% (10/89)	13% (1.6 to 24)	25% (14 to 37)
Prior TNFi failure due to primary non-response	23% (9/39)	31% (15/49)	11% (5/46)	12% (-3.8 to 28)	20% (4.0 to 36)
Prior TNFi failure due to secondary non-response	25% (9/36)	42% (17/41)	12% (4/34)	13% (-4.6 to 31)	30% (11 to 48)

Mucosal healing					
No prior TNFi failure	43% (49/115)	51% (53/104)	14% (15/109)	29% (18 to 40)	37% (26 to 49)
Prior TNFi failure	30% (25/83)	40% (37/93)	12% (11/89)	18% (5.8 to 30)	27% (15 to 40)
Prior TNFi failure due to primary non-response	28% (11/39)	37% (18/49)	11% (5/46)	17% (0.6 to 31)	26% (9.6 to 42)
Prior TNFi failure due to secondary non-response	33% (12/36)	42% (17/41)	15% (5/34)	19% (-0.8 to 38)	27% (7.5 to 46)
Sustained corticosteroid-free remission^A					
No prior TNFi failure	40% (19/47)	51% (19/37)	5.3% (2/38)	35% (19 to 51)	46% (28 to 64)
Prior TNFi failure	22% (4/18)	39% (7/18)	4.8% (1/21)	18% (-3.8 to 39)	34% (9.8 to 58)

^A Sustained corticosteroid-free remission analysed in patients who were in remission at baseline; TNFi=tumour necrosis factor inhibitor; CI=confidence interval

Table 6: IBDQ remission results at week 52 for OCTAVE Sustain²

Outcome	OCTAVE Sustain				
	Tofacitinib 5mg	Tofacitinib 10mg	Placebo	Treatment difference, tofacitinib 5mg versus placebo (95% CI)	Treatment difference tofacitinib 10mg versus placebo (95% CI)
IBDQ remission rate	38% (76/198)	48% (95/197)	15% (29/198)	24% (15 to 32) ^A	34% (25 to 42) ^A

IBDQ=Inflammatory Bowel Disease Questionnaire; CI=confidence interval; ^Ap<0.001

There were also improvements in the EQ-5D and WPAI-UC tools.⁴ There were significant improvements in change from baseline to week 52 in EQ-5D score for tofacitinib 5mg and 10mg versus placebo: 2.6 and 4.1 versus -11.⁷ There were also significant improvements in change from baseline to week 52 for WPAI-UC domain scores for tofacitinib 5mg and 10mg versus placebo in presenteeism, -3.6, -4.3 versus 7.2 and in non-work activity impairment, -2.8, -3.1 versus 11.3.⁷ Benefits for tofacitinib over placebo for the Physical Component Summary and Mental Component Summary of the SF-36 were maintained in OCTAVE Sustain.³

OCTAVE Open is an ongoing phase III, uncontrolled, open-label, long-term extension study, with the primary aim of evaluating safety. It enrolled patients who completed OCTAVE Induction 1 or 2 but did not achieve a clinical response and also patients who participated in OCTAVE Sustain (both completers and those who had treatment failure). Patients who were in remission at OCTAVE Open baseline were treated with tofacitinib 5mg twice daily and all others were treated with tofacitinib 10mg twice daily. Patients from the induction studies who did not respond after two months study treatment were withdrawn from the study. Data are available from an interim

report at 08 July 2016 cut-off when a total of 944 patients had been enrolled and assigned to study treatment and 914 of these patients had been assigned to treatment ≥ 2 months prior to cut-off and had received at least one dose of study medication. A total of 156 patients were assigned to the tofacitinib 5mg group and 758 patients to the tofacitinib 10mg group. By data cut-off, 42% (381/914) of patients had discontinued from the study; 11% in the tofacitinib 5mg group and 48% in the tofacitinib 10mg group.⁴

In the subgroup of patients who had been treated with tofacitinib in OCTAVE Sustain and were in remission on completion of that study (n=144), approximately three-quarters maintained this remission after one year in OCTAVE Open. The subgroup of patients who had received tofacitinib 10mg twice daily in the induction study and then failed on either tofacitinib 5mg twice daily (n=58) or placebo (n=99) in OCTAVE Sustain received tofacitinib 10mg in OCTAVE Open. In the prior tofacitinib 5mg group, after 2 months treatment, 34% (20/58) achieved remission and this increased to 52% (25/48) after 12 months. In the prior placebo group, after 2 months treatment, 40% (40/99) achieved remission and this increased to 43% (36/83) after 12 months.⁴ The subgroup of patients who did not achieve a clinical response after 8 weeks in the induction studies (receiving either tofacitinib 10mg or placebo) continued treatment with tofacitinib 10mg twice daily for a further 2 months in Octave Open and a clinical response was reported in 53% of these patients.⁴

Summary of evidence on comparative safety

There is no direct study evidence for tofacitinib versus active comparators in ulcerative colitis. The safety profile in ulcerative colitis was consistent with its use in rheumatoid arthritis and psoriatic arthritis. Based on current data, with the exception of a higher increased risk of herpes zoster, tofacitinib's safety profile was considered by the European Medicines Agency (EMA) to be similar to that of biologic medicines licensed to treat ulcerative colitis.⁴

In OCTAVE Induction 1 and 2, adverse events (AE) occurred in 56% (269/476) and 54% (232/429) of patients in the tofacitinib 10mg groups and in 60% (73/122) and 53% (59/112) of the placebo groups, respectively. Serious AE occurred in 3.4% and 4.2% of patients in the tofacitinib 10mg groups and in 4.1% and 8.0% in the placebo groups of the respective studies. AE (including worsening ulcerative colitis) led to study treatment discontinuation in 3.8% and 4.0% of patients in the tofacitinib 10mg groups and in 1.6% and 7.1% of patients in the placebo groups of the respective studies. In OCTAVE Sustain, AE occurred in 72% (143/198) of patients in the tofacitinib 5mg tofacitinib group, 80% (156/196) in the tofacitinib 10mg group, and 75% (149/198) in the placebo group. Serious AE occurred in 5.1%, 5.6% and 6.6% of patients in the respective groups. AE (including worsening ulcerative colitis) led to study treatment discontinuation in 9.1%, 9.7% and 19% of patients in the respective groups.² If AE related to worsening ulcerative colitis are excluded, the frequency of study discontinuation due to AE in the placebo-controlled studies was similar (<5%) of patients in the tofacitinib and placebo groups.⁴

Infection occurred in 23% and 18% of patients receiving tofacitinib 10mg in OCTAVE Induction 1 and 2 and in 16% and 15% of patients receiving placebo in the respective studies. Across both induction studies, serious infection occurred in 0.8% of patients receiving tofacitinib 10mg and in no patients receiving placebo and herpes zoster occurred in 0.6% of patients receiving tofacitinib 10mg and in 0.4% of patients receiving placebo. In OCTAVE Sustain infection occurred in 36% of patients receiving tofacitinib 5mg, 40% receiving tofacitinib 10mg and 24% receiving placebo; serious infection occurred in 1.0%, 0.5% and 1.0% in the respective groups and herpes zoster occurred in 1.5%, 5.1% and 0.5% in the respective groups. No cases of herpes zoster were classified as serious AE and none led to treatment discontinuation.²

Nasopharyngitis occurred in 7.1% and 4.9% of patients receiving tofacitinib 10mg in OCTAVE Induction 1 and 2 and in 7.4% and 3.6% of patients receiving placebo in the respective studies. In OCTAVE Sustain it occurred in 9.6% of patients receiving tofacitinib 5mg, 14% receiving tofacitinib 10mg and 5.6% receiving placebo.²

Across the two induction studies and the maintenance study, intestinal perforation occurred in one patient receiving tofacitinib 10mg and one receiving placebo; ductal breast carcinoma occurred in one patient receiving placebo; non-melanoma skin cancer occurred in five patients receiving tofacitinib 10mg and one receiving placebo; cardiovascular events occurred in one patient receiving tofacitinib 5mg and five patients receiving tofacitinib 10mg.²

A higher proportion of patients receiving tofacitinib than placebo across the induction and maintenance studies developed abnormal lipid and creatine kinase levels.²

Tofacitinib is contraindicated in pregnancy and breast-feeding.¹ It is metabolised by the enzyme CYP3A4, therefore interaction with medicines that inhibit or induce CYP3A4 is likely.¹

Summary of clinical effectiveness issues

Ulcerative colitis is a chronic inflammatory disease of the colon that follows a relapsing, remitting course. Patients commonly have diarrhoea, rectal bleeding, abdominal pain, urgency, and may also experience fatigue, fevers, weight loss, dehydration and potentially fatal fulminant colitis. The main objectives of treatment are the induction and maintenance of symptomatic and endoscopic remission.⁴ Clinical experts consulted by SMC advised that current treatment options for the indication under review are TNF inhibitors (adalimumab, golimumab or infliximab) or vedolizumab, an anti-integrin, gut-selective, immunosuppressant biologic agent. After failure on TNF inhibitors, options include surgery for selected patients, although this is associated with short- and long-term adverse effects and complications; switching to an alternative TNF inhibitor in patients who had initially responded and then lost response; or vedolizumab. All current biologic treatments are administered parenterally. Clinical experts consulted by SMC considered that tofacitinib fills an unmet need in this therapeutic area, namely for patients who have failed on biologic treatment or as an oral alternative to biologic treatments, all of which are administered parenterally.

The OCTAVE induction studies demonstrated that tofacitinib is superior to placebo across relevant outcomes including remission, mucosal healing and endoscopic remission. OCTAVE Sustain demonstrated that tofacitinib is superior to placebo in maintaining remission, mucosal healing and sustained corticosteroid-free remission in responders for one year. Draft updated EMA guidance now advises that the primary outcome in ulcerative colitis studies should be the number of patients in clinical and endoscopic remission in whom steroids could be withdrawn.¹² Therefore the key secondary outcome of sustained corticosteroid-free remission may be the most clinically relevant outcome. A treatment effect was present in patients who had treatment failure on TNF inhibitors as well as TNF inhibitor-naïve patients, but it should be noted that, in patients with prior TNF inhibitor failure, the treatment effect with 5mg twice daily maintenance dose is substantially lower than with 10mg twice daily. The summary of product characteristics notes that “For some patients, such as those who have failed prior TNF inhibitor therapy, consideration should be given to continuation of the 10mg twice daily dose for maintenance in order to maintain therapeutic benefit.”¹

Limitations of the evidence include the lack of controlled evidence beyond one year of maintenance treatment.⁴ Also, there is no direct clinical evidence versus an active comparator.

Bayesian network meta-analyses (NMAs) were performed to compare tofacitinib with adalimumab, golimumab, infliximab and vedolizumab in TNF inhibitor-naïve patients and with adalimumab and vedolizumab in TNF inhibitor-experienced patients, using placebo as the common comparator. However, a sensitivity analysis comparing tofacitinib 10mg twice daily with vedolizumab in patients with TNF inhibitor failure may have particular relevance to practice but due to the scarcity of evidence the sensitivity analysis could not be undertaken. Included studies were in adults with moderate to severe active ulcerative colitis with previous treatment failure on conventional therapies, with some studies also including patients who had received TNF inhibitors. Efficacy outcomes (clinical response, clinical remission and mucosal healing) were assessed in both the induction and maintenance phases. Safety outcomes (discontinuation due to AE, serious AE and serious infections) were assessed in the induction phase only. Analyses were performed for the intention to treat (ITT) population, TNF inhibitor-naïve patients and TNF inhibitor-exposed patients. As clinical remission was commonly reported in the NMA studies, it was used instead of remission, which was the primary outcome in the OCTAVE studies. Clinical remission is defined as total Mayo score ≤ 2 , with no individual subscore >1 and is less stringent than remission as it does not require a rectal bleeding subscore of 0. Results for remission and clinical remission in the OCTAVE Induction studies were very similar,² therefore the use of clinical remission in the NMA is acceptable. Limitations of the NMAs included heterogeneity, particularly in the maintenance networks; outcome data for treat-through studies in the maintenance setting were adjusted to be analysed as re-randomised responder studies, and this is another source of uncertainty; and fewer studies contributed to the networks for the population of patients with prior TNF inhibitor exposure and in the maintenance setting. However, taking these limitations into consideration, the NMAs suggested that tofacitinib had comparable efficacy and safety to TNF inhibitors and vedolizumab.

Clinical experts consulted by SMC considered that tofacitinib is a therapeutic advancement due to having comparable clinical effectiveness to the TNF inhibitors and vedolizumab and because it is administered orally. They advised that its place in therapy would be after the failure of TNF inhibitors, especially when an oral option is preferred. They considered that the introduction of this oral medicine may be more convenient for the patient and may reduce the impact on the service.

Summary of comparative health economic evidence

The company submitted a lifetime cost- minimisation analysis (CMA) comparing tofacitinib to infliximab, adalimumab, golimumab and vedolizumab for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy or biologic agent. Based on SMC expert responses, the comparators seem reasonable. Several experts have noted that vedolizumab is likely to be the comparator displaced in Scotland.

A Markov model was provided which consisted of nine health states (key health states included active ulcerative colitis, remission and response no-remission). Patients entered the model on active treatment and began in the active ulcerative colitis health state. After eight weeks, responders to treatment entered the remission or response no-remission health states. Patients who did not achieve a response were assumed to continue on standard therapy. The clinical data used to underpin the assumption of comparable efficacy were taken from the NMA for the ITT population. The key clinical parameters within the model were probability of response and remission. As the base case analysis was a CMA, the company assumed no difference in these clinical parameters between treatments. That is, the efficacy of tofacitinib was assumed to apply to all treatments.

Medicine costs for both induction and maintenance periods were included for treatments as well as administration costs for medicines which required intravenous infusion. Within the analysis 100% of patients responding to tofacitinib were assumed to continue receiving a maintenance dose of 5mg twice daily. The company did provide scenario analyses which varied the proportion of patients assumed to receive a 10mg twice daily dose as maintenance treatment. Health state costs and costs associated with post-elective surgery and post-emergency surgery were also included although these were assumed to be the same for all treatments. The company has included differential costs associated with the probability of serious infection for each medicine.

A patient access scheme (PAS) was submitted for tofacitinib and was assessed as acceptable for implementation by the Patient Access Scheme Assessment Group (PASAG). Under the PAS, a discount is offered on the price of the medicine. A PAS discount is in place for vedolizumab and this was included in the results used for decision-making by SMC by using estimates of the comparator PAS price.

Table 5: Base case results using list price for all medicines including tofacitinib

Treatment	Total cost	Incremental costs/savings
Tofacitinib	£137,554	-
Adalimumab	£137,283	£271
Golimumab	£138,221	-£667
Infliximab	£141,707	-£4,153
Vedolizumab	£146,279	-£8,725

A negative figure denotes incremental savings

The results presented do not take account of the PAS for vedolizumab or the PAS for tofacitinib but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for vedolizumab due to commercial confidentiality and competition law issues.

There were a number of limitations with the analysis which include the following;

- There is a lack of direct data comparing tofacitinib to active comparators, therefore clinical data used within the economic model were taken from NMAs which had some limitations as noted above. However, despite these limitations comparable efficacy was considered to have been demonstrated.
- As noted, the company provided sensitivity analysis to show the impact of assuming a 10mg twice daily dose of tofacitinib in different proportions of patients (30%, 50%, 75% and 100%). These analyses provided reassurance around the cost-effectiveness of tofacitinib when used at a higher maintenance dose.
- The base case CMA does include differences in adverse events (probability of serious infection) and thus costs, which may not be consistent with CMA methodology. However, as tofacitinib is associated with the highest probability of serious infection (and therefore results in the highest adverse event costs), the inclusion of this difference may be conservative given the conclusion from the NMA noted above of comparable safety between treatments.

Despite the uncertainties outlined above, the economic case has been 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% pharmaceutical company funding in the past two years, with none from 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.
- Current treatments available in NHS Scotland remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to medical treatments and may face the prospect of surgery with considerable anxiety.
- There is value to an additional treatment option, which being orally administered, offers greater convenience and acceptability to patients, as well as a good side effect profile and reduced likelihood of loss of response (immunogenicity). Due to tofacitinib's different mode of action, those who have had little or no success with currently available medical treatment options and wish to avoid or delay surgery will be particularly likely to benefit.

Additional information: guidelines and protocols

The British Society of Gastroenterology guidance on ulcerative colitis refers to the National Institute for Health and Care Excellence (NICE) clinical guideline CG166 which was published in 2013.¹³ An update of this guideline is planned.

The European Crohn's and Colitis Organisation (ECCO) published the Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management in 2017.¹⁴ ECCO receives support from the pharmaceutical industry; the organisation maintains a database of potential conflicts of interest of contributing authors. This consensus guideline includes the following advice concerning the use of biologic agents in ulcerative colitis:

Initial recommended treatment for severe active ulcerative colitis is intravenous steroids. Monotherapy with intravenous ciclosporin is an alternative especially in cases of serious adverse events due to steroids. In patients with severe colitis who do not respond to intravenous steroids, treatment options including ciclosporin, infliximab, tacrolimus or surgery should be considered. Patients with steroid-dependent disease should be treated with a thiopurine, TNF inhibitor, preferably combined with thiopurines (at least for infliximab), vedolizumab, or methotrexate. In case of treatment failure, second-line medical therapy with an alternative TNF inhibitor, vedolizumab, or colectomy should be considered.

Moderate disease refractory to oral steroids should be treated either with intravenous steroids or a TNF inhibitor preferably combined with thiopurines (at least for infliximab), vedolizumab, or tacrolimus. Second-line medical therapy with a different TNF inhibitor or vedolizumab may be an option; colectomy should also be considered. Patients with moderate colitis refractory to thiopurines should be treated with a TNF inhibitor, preferably combined with thiopurines (at least for infliximab), or vedolizumab. In case of treatment failure, a different TNF inhibitor or

vedolizumab should be considered, and colectomy recommended if further medical therapy does not achieve a clear clinical benefit.

The goal of maintenance therapy is to maintain steroid-free remission. Options for a stepwise escalation of maintenance therapy include dose escalation of oral/rectal aminosalicylates, the addition of thiopurines, and TNF inhibitor therapy or vedolizumab. In patients responding to a TNF inhibitor, maintaining remission by continuing TNF inhibitor therapy with or without thiopurines is appropriate. The use of thiopurine maintenance is an alternative option. A TNF inhibitor or vedolizumab may be used as first-line biological therapy. Vedolizumab is effective in patients failing a TNF inhibitor. In patients responding to vedolizumab, maintenance therapy with vedolizumab is appropriate. In thiopurine-naïve patients with severe colitis responding to steroids, ciclosporin or tacrolimus, thiopurines are appropriate to maintain remission. Patients responding to infliximab should continue infliximab with or without thiopurines; thiopurine maintenance is an alternative option. In view of limited evidence, no recommendation can be given for the duration of treatment with TNF inhibitors or vedolizumab, although prolonged use of these medications may be needed.¹⁴

Additional information: comparators

Relevant comparators are adalimumab, golimumab, infliximab and vedolizumab.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Tofacitinib	Orally, 10mg twice daily for 8 or 16 weeks induction, then maintenance dose of 5mg twice daily or 10mg twice daily.^A	First year costs: 5mg twice daily maintenance dose: 10,350 to 11,731 10mg twice daily maintenance dose: 17,990 Subsequent years costs: 8,995 to 17,990
Golimumab	By subcutaneous injection. For body weight <80kg: 200mg at week 0 and 100mg at week 2; If response is adequate: 50mg at week 6 and every 4 weeks thereafter. If response is inadequate: 100mg at week 6 and every 4 weeks thereafter.	13,733 to 22,889 in first year 9,919 to 19,837 in subsequent years

	For body weight ≥80kg: 200mg at week 0 and 100mg at week 2, then 100mg every 4 weeks thereafter.	
Vedolizumab	By intravenous infusion, 300mg at weeks 0, 2 and 6, then every 8 weeks or every 4 weeks thereafter, depending on response to treatment.	16,400 to 28,700 in first year 13,325 to 26,650 in subsequent years
Infliximab	By intravenous infusion, 5mg/kg at weeks 0, 2 and 6 and every 8 weeks.	12,064 in first year 10,556 in subsequent years ^B
Adalimumab	By subcutaneous injection, 160mg at week 0, 80mg at week 2, then 40mg every 2 weeks or every week thereafter, depending on response to treatment.	9,821 to 17,741 in first year 8,237 to 16,474 in subsequent years ^B

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online for infliximab and from eVadis for other medicines on 01.11.18. Cost of infliximab based on 70kg body weight. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. ^ASummary of product characteristics notes that consideration of 10mg twice daily maintenance dose for some patients, such as those who have failed prior tumour necrosis factor inhibitor therapy.¹ This is the patient population in which clinical experts consulted by SMC expect tofacitinib to be used. ^BCost of biosimilars.

Additional information: budget impact

The submitting company estimated there would be 1,154 patients eligible for treatment with tofacitinib in year 1 rising to 1,173 in year 5.

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.

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

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This assessment is based on data submitted by the applicant company up to and including 14 December 2018.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.