6.07 TOFACITINIB, Tablet 5mg, tablet 10mg, Xeljanz®, Pfizer Australia

1 Purpose of Application

1.1 Section 85 (General Schedule), Authority Required, listing for tofacitinib (TOF) for the treatment of moderate to severe ulcerative colitis (MSUC). The PBAC has not previously considered TOF for MSUC. TOF is PBS listed for rheumatoid arthritis (RA) and has been recommended for listing for psoriatic arthritis (PsA).

1.2 The requested basis for listing TOF was a cost-minimisation to infliximab (IFX). Other biological therapies currently listed on the PBS include adalimumab (ADA), vedolizumab (VDZ) and golimumab (GOL).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adult patients with moderate to severe ulcerative colitis who have had an inadequate response, lost response, or were intolerant to standard treatment.
Intervention	Tofacitinib 10 mg twice daily for at least 8 weeks for induction and then tofacitinib 5 mg twice daily (for maintenance) or tofacitinib 10 mg twice daily in a small proportion of patients who fail to maintain a response on tofacitinib 5 mg twice daily.
Comparator	Main comparator: Infliximab 5mg/kg IV infusion at 0, 2 and 6 weeks then Q8W thereafter. Other comparators: • Adalimumab SC injection, 160mg at week 0, 80mg at week 2 then 40mg Q2W thereafter. • Vedolizumab IV infusion, 300mg at 0, 2 and 6 weeks then Q8W thereafter. • Golimumab SC injection, 200mg at week 0, 100mg at week 2, then 100mg Q4W thereafter
Outcomes	Indirect comparison of tofacitinib and comparators was conducted for the following outcomes, for induction and maintenance therapy: • Clinical response, defined by a decrease from baseline in Mayo score of ≥3 and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥1 point or absolute subscore for rectal bleeding of 0 or 1; • Clinical remission, defined by a total Mayo score of ≤2, with no individual subscore exceeding 1. • Mucosal healing, defined by a Mayo endoscopic subscore of 0 or 1.
Clinical claim	Tofacitinib is non-inferior in terms of efficacy and safety to infliximab for induction and maintenance treatment of moderate to severe ulcerative colitis.

Source: Table 1.1.1, p3 of the submission.
Abbreviations: IV=intravenous, SC=subcutaneous; Q2W=every two weeks; Q4W=every four weeks; Q8W=every eight weeks

2 Requested listing

2.1 The Sponsor requested several restrictions for TOF 10 mg and TOF 5 mg to provide for initial treatment (1&2), continuing treatment, grandfathered patients and balance of supply. The requested restrictions were generally similar to that of currently PBS listed biological therapies for MSUC. Table 2 provides a summary of the restrictions for initial 1 and continuing treatment.

Table 2: Abbreviated version of requested restriction for TOF (Initial 1 and continuing therapy)

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Induction treatment					
TOFACITINIB 5 mg tablet	1	56	2	$[redacted] published $[redacted] effective	Xeljanz® Pfizer Australia
TOFACITINIB 10 mg tablet	1	56	3	$[redacted] published $[redacted] effective	
Maintenance treatment					
TOFACITINIB 5 mg tablet	1	56	5	$[redacted] published $[redacted] effective	Xeljanz® Pfizer Australia
TOFACITINIB 10 mg tablet	1	56	5	$[redacted] published $[redacted] effective	

Category:	General Schedule (Section 85)
PBS Indication:	Moderate to severe ulcerative colitis
Treatment criteria:	Must be treated by a gastroenterologist; OR Must be treated by a consultant physician (internal or general medicine specialising in gastroenterology)
Population criteria:	Patient must be aged 18 years or older
Treatment phase:	Initial treatment – new patient or recommencement of treatment after ≥5 years break in therapy (Initial 1)
Restriction:	☒Authority Required - In Writing
Clinical criteria:	Patient must have failed to achieve an adequate response (or intolerance) to standard medical management (5-aminosalicylate, azathioprine, 6-mercaptopurine, oral steroids); AND Patient must have a Mayo clinic score greater than or equal to 6; OR Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required).
Prescriber instructions	A partial Mayo clinic assessment of the patient's response to this initial course of treatment must be made up to 8 weeks after the first dose A maximum of 16 weeks of treatment with this drug will be approved under this criterion. The recommended dose is 10 mg twice daily for at least 8 weeks followed by 5 mg twice daily.
Treatment phase:	Continuing treatment
Restriction:	☒Authority Required - Telephone
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug.
Prescriber instructions	Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response.

Source: pp22-29 of the submission

2.2 The Sponsor requested PBS listing of the TOF 10 mg and 5 mg formulations for both induction and maintenance therapy. TOF 10 mg and TOF 5 mg are available in packs of 56 tablets, providing sufficient supply for 28 days (4 weeks). The submission stated that the requested number of repeats provided for 16 weeks of induction therapy and 24 weeks of maintenance therapy.

2.3 The PBAC noted the dosage section of the product information (PI) (3.1) included a recommendation to use the lowest effective dose of tofacitinib which may require clinicians to increase and decrease dosage depending on a patient's response to treatment. The PBAC considered patients treated with TOF 10 mg in the maintenance setting may require more frequent monitoring to assess response and adverse events (AEs). The PBAC considered it may be reasonable to include additional clarity around the recommended dose under 'prescriber instructions' for maintenance therapy.

2.4 The submission requested a Special Pricing Arrangement (SPA). The proposed published prices (Dispensed Price for Maximum Quantity) for TOF 10 mg and TOF 5 mg were $[redacted] and $[redacted] respectively, per 56 tablets. The proposed effective prices ($[redacted] and $[redacted] respectively) were based on a cost-minimisation analysis versus IFX.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

3.1 TGA status at time of PBAC advice: tofacitinib was approved by the TGA on 29 January 2019. The approved indication is 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 biological therapy.

3.2 The Sponsor made the submission under the TGA/PBAC Parallel Process. At the time of the submission, the TGA Clinical Evaluation Report was available. During evaluation, the TGA Delegate's Summary, Request for ACM advice and TGA approval letter also became available.

3.3 The dose section of the approved Product Information (PI) states:

'The recommended dose for adult patients with moderately to severely active ulcerative colitis is 10 mg twice daily for induction for 8 weeks and 5 mg twice daily for maintenance.

For patients who do not achieve adequate therapeutic benefit by week 8 (e.g. those with the greatest disease activity or those refractory to tumour necrosis factor (TNF)-inhibitors), the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Continued treatment is not recommended for patients who have not shown a clinical response by Week 16.

Use the lowest effective dose to maintain response. Following end of induction therapy, the choice of maintenance therapy should be based on individual consideration of the patient's clinical response and treatment history. For refractory patients, such as those who have failed prior TNF inhibitor therapy, consideration may be given to continuation of the 10 mg twice daily dose for maintenance in order to maintain therapeutic benefit.

Patients who fail to maintain therapeutic benefit on XELJANZ 5 mg twice daily may benefit from an increase to XELJANZ 10 mg administered twice daily for maintenance.'

3.4 The PI includes the following Special Warnings and Precautions for Use: dose-dependent adverse reactions seen in patients treated with Xeljanz 10mg twice daily, in comparison to 5mg twice daily include the following: herpes zoster infections, serious infections and non-melanoma skin cancer.

4 Population and disease

4.1 Ulcerative colitis is a life-long chronic relapsing and remitting inflammatory disease that involves ulceration of the mucosa of the colon. Patients with ulcerative colitis most commonly present with bloody diarrhoea, rectal bleeding, tenesmus (sensation of incomplete defecation), urgency, abdominal pain, and passage of mucus. Disease of moderate to severe activity may be associated with systemic symptoms, including fatigue, fever, anorexia, nausea, weight loss, and dehydration. The most serious complications of ulcerative colitis are bowel perforation and colorectal cancer.

4.2 TOF is an oral selective Janus-associated kinase (JAK) inhibitor. This leads to the inhibition of several cytokines, which contribute to the pathogenesis of autoimmune and inflammatory diseases.

4.3 The submission proposed TOF as an alternative to biological therapy in the treatment of adult patients with MSUC (as defined by a Mayo score ≥6) who have had an inadequate response or failure to standard medical management. The addition of TOF to the clinical management algorithm will not alter current practice, but will allow for an additional option with a different mechanism of action and an oral manner of administration.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated IFX as the main comparator. The argument provided in support of this nomination was that IFX is the most commonly prescribed biological therapy and the most likely to be replaced in practice. The submission also acknowledged that TOF would provide an alternative treatment option to any of the currently PBS-listed biological therapies for ulcerative colitis; i.e. ADA, GOL, and VDZ. Therefore, all of the biological therapies currently listed for MSUC were relevant comparators.

5.2 If treatment with TOF were substantially more costly than any of the relevant comparators the PBAC could only recommend listing of TOF if it was satisfied that TOF provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (National Health Act 1953, Section 101(3B)).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the limited treatment options for MSUC, the advantages of an additional treatment option with a new mechanism of action and the usefulness of having access to an oral therapy which avoids the need for injections or infusions and is particularly convenient for patients in rural and remote areas. The clinician also discussed the benefits of treatment with TOF including mucosal healing, which supports the restoration of normal bowel frequency and control of the primary symptoms of bleeding and urgency. The PBAC requested further clarification on the likely proportion of patients that would require dose escalation or ongoing use of the 10 mg dose in maintenance therapy, which the clinician estimated at approximately 10-20%. The clinician confirmed there are dose related adverse events (AE's) associated with the 10 mg dose with herpes zoster the most clinically relevant AE.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (7) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with TOF for MSUC including advantages of an oral therapy over currently available injected or infused treatment options, reduced reliance on other immunosuppressant medication, potential ability to return to work for patients with severe disease and the importance of additional treatment options with new modes of action for patients who have not responded or stopped responding to alternatives.

Clinical trials

6.3 There were no head-to-head trials of TOF vs. any relevant comparators for the treatment of MSUC. The submission presented a series of indirect comparisons using data from 12 randomised placebo-controlled trials:

- TOF vs. PBO (three RCTs): OCTAVE 1, OCTAVE 2, OCTAVE sustain;
- IFX vs. PBO (four RCTs): ACT 1, ACT 2, Jiang 2015, REMICADE;
- GOL vs PBO (two RCTs): PURSUIT-SC, PURSUIT-M;
- ADA vs. PBO (two RCTs): ULTRA 1, ULTRA 2;
- VDZ vs. PBO (one RCT): GEMINI-1.

6.4 The submission's criteria for excluding trials were poorly justified and inconsistently applied. Three trials were inappropriately excluded: PURSUIT-J (GOL vs. PBO), Suzuki 2014 (ADA vs. PBO), and Kobayashi 2016 (IFX vs. PBO). The three excluded trials were included in the evaluation.

6.5 Details of the trials presented in the submission are provided in Table 3. With the exception of four trials (OCTAVE 1, 2, and Sustain, and Kobayashi 2016), the trials have been included in previous PBAC applications for biological therapies for MSUC.

Table 3 Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Tofacitinib trials		
OCTAVE 1	Study A3921094. A multicentre, randomized, double-blind, placebo-controlled, parallel-group study of oral CP-690,550 as an induction therapy in subjects with moderate to severe ulcerative colitis	Clinical study report – report date: 25 May 2016.
OCTAVE 2	Study A3921095. A multicentre, randomized, double-blind, placebo-controlled, parallel-group study of oral CP-690,550 as an induction therapy in subjects with moderate to severe ulcerative colitis.	Clinical study report – report date: 6 May 2016
OCTAVE SUSTAIN	Study A3921096. A multicentre, randomized, double-blind, placebo-controlled, parallel-group study of oral CP-690,550 as a maintenance therapy in subjects with ulcerative colitis.	Clinical study report – report date: 16 December 2016
*OCTAVE trials (1, 2, sustain)	Sandborn WJ, Chinyu S, Sands BE, et al; Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis	N Engl J Med. 2017; 376 (18): 1723-1736
Infliximab trials		
ACT 1	Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis.	N Engl J Med. 2005; 353:2462-2476.
ACT 2		
Jiang 2015	Jiang XL, Cui HF, Gao J, Fan H. Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis.	Journal of clinical gastroenterology. 2015, 49(7):582-588.
REMICADE	Jansen Research and Development. Clinical Study Report Synopsis. CNTO312 (infliximab). A Phase 3, multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of infliximab in Chinese subjects with active ulcerative colitis. REMICADEUCO3001.	NCT01551290
Kobayashi 2016	*Kobayashi T, Suzuki Y, Motoya S, Hirai F, Ogata H, Ito H, Sato N, Ozaki K, Watanabe M, Hibi T. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. Serum trough level as predictor of response.*	*Journal of Gastroenterology 2016; 51(3):241-51*
Adalimumab trials		
ULTRA 1	Reinisch W, Sandborn WJ, Hommes DW, *et al*. Adalimumab for induction of clinical remission in moderately to severely active UC: results of a randomised controlled trial.	Gut. 2011;60(6):780-787
ULTRA 2	Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate to severe UC.	Gastroenterology. 2012;142(2):257-65[e1-3]
Suzuki 2014	*Suzuki Y, Motoya S, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis.*	*J Gastroenterol. 2014; 49:283-294.*
Golimumab trials		
PURSUIT SC	Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis	Gastroenterology. 2014,146(1):85-95
PURSUIT M	Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis.	Gastroenterology. 2014,146(1):96-109
PURSUIT J	*Hibi T, Imai Y, Senoo A, Ohta K and Ukyo Y. Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: a phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study).*	*Journal of Gastroenterology.2017: 52(10):1101-1111*
Vedolizumab trial		
GEMINI 1	Feagan B, Rutgeerts P, Sands B, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis.	N Engl J Ned. 2013; 369(8):699-710.
	Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B, Sankoh S, James A, Smyth M. Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists.	*Clin Gastroenterol Hepatol. 2017 Feb;15(2):229-239.e5.*

Source: Table 2.2.1-5, pp35-39 of the submission
Italics = these trials/publications were excluded in the submission, but included in the evaluation.

6.6 Table 4 presents the key features of trials presented in the evaluation.

Table 4 Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
TOF v PBO					
OCTAVE 1 [Induction]	598	P3 MC, R, PC, DB (8wk).	Low	TNFi-n & TNFi-e	1ary: remission 2ary: clinical remission, clinical response, mucosal healing
OCTAVE 2 [Induction]	541		Low	TNFi-n & TNFi-e	
OCTAVE SUSTAIN [maintenance]	593	P3, MC, R, PC, DB (52wk), RWD, 3-arm.	High	Wk 8 responders in OCTAVE 1,2	1ary: remission 2ary: clinical remission, clinical response, sustained clinical remission, sustained clinical response, mucosal healing, corticosteroid-free remission
IFX v PBO					
ACT 1 [induction & maintenance]	364	P3 MC, R, PC, DB (52wk), 3-arm	Low*	TNFi-n	1ary: clinical response 2ary: clinical remission, mucosal healing, sustained clinical response, sustained clinical remission
ACT 2 [induction & maintenance]	364	P3 MC, R, PC, DB (30wk), 3-arm	Low*	TNFi-n	1ary: clinical response 2ary: clinical remission, mucosal healing
Jiang 2015 [induction & maintenance]	123	MC, R, PC, DB (30wk), 3-arm	Low*	TNFi-n (Chinese)	1ary: clinical response 2ary: clinical remission, mucosal healing
REMICADE [induction & maintenance]	99	P3 MC, R, PC, DB (26wk)	Low*	Prior TNFi NR (Chinese)	1ary: clinical response 2ary: clinical remission, mucosal healing, sustained clinical response, sustained clinical remission
Kobayashi 2016 [induction & maintenance]	IP: 208 MP:NR	P3 MC, R, PC, DB (30wk), RWD for maintenance (8wk induction, 22wk maintenance)	Low	TNFi-n (Japanese) Maintenance: Wk8 responders	1ary: clinical response 2ary: clinical remission, mucosal healing
GOL v PBO					
PURSUIT-SC [induction]	Pt1: 84 Pt2: 516	P2/3, MC, R, PC, DB (6wk), Part 1 cohort - 4arm dose ranging (6wk); Part 2 cohort - 3-arm dose confirming (6wk).	Low	TNFi-n	1ary: clinical response 2ary: clinical remission, mucosal healing, IBDQ change from baseline
PURSUIT-M [maintenance]	464	P3, MC, R, PC, DB (52wk), RWD, 3-arm (Included non-randomised cohort separately^)	High	Wk6 active responders in PURSUIT-SC & PURSUIT IV	1ary: sustained clinical response 2ary: sustained clinical remission, sustained mucosal healing, sustained clinical remission among patients with baseline clinical remission, corticoid-free clinical remission
PURSUIT-J [maintenance]	63	P3, MC, R, BD, PC, DB (54wk), RWD (included 6wk OL induction phase).	High	TNFi-n (Japanese) Wk6 responders to OL induction	1ary: sustained clinical response 2ary: sustained clinical remission, sustained mucosal healing
ADA v PBO					
ULTRA 1 [induction]	390	P3, MC, R, PC, DB (8wk)	Low	TNFi-n	1ary: clinical remission 2ary: clinical response, mucosal healing
ULTRA 2 [induction & maintenance]	494	P3, MC, R, PC, DB (52wk)	Low*	TNFi-n & TNFi-e	1ary: clinical remission 2ary: clinical response, mucosal healing, IBDQ response, sustained clinical

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
					remission, sustained clinical response, sustained mucosal healing
Suzuki 2014 [induction & maintenance]	273	P2/3, MC, R, PC, DB (52wk), 3-arm	Low*	TNFi-n (Japanese)	1ary: clinical remission 2ary: clinical response, mucosal healing
VDZ v PBO					
GEMINI 1 [induction & maintenance]	IP Ct1: 374 IP Ct2: 521 MP: 373	P3, MC, R, DB (58wk), RWD for maintenance (6wk induction, 52wk maintenance), 3-arm. Cohort 1 - randomised induction. Cohort 2- OL induction.	Low*	TNFi-n & TNFi-e Maintenance: Wk6 active responders in cohort 1 and 2.	1ary: clinical response 2ary: clinical remission, mucosal healing, sustained clinical response, sustained clinical remission, corticosteroid-free remission

Source: Compiled during the evaluation

* Low risk of bias in the induction phase, but high risk of bias during maintenance due to high attrition bias

^ Non-randomised cohort consisted of patients randomised to PBO or GOL without clinical response at Wk6 in PURSUIT-SC or -IV.

Abbreviations: ADA=adalimumab, bid=twice a day, DB=double blind; IFX=infliximab, IP=induction phase; MC=multi-centre; MP=maintenance phase; OL=open label; R=randomised, RWD=randomised withdrawal design; TOF=tofacitinib, TNFi-e=tumour necrosis factor inhibitor experience, TNFi-n= tumour necrosis factor inhibitor naïve, VDZ=vedolizumab,

6.7 The design of the trials differed considerably. Five trials investigated short-term induction therapy only (OCTAVE 1, OCTAVE 2, PURSUIT-SC, ULTRA 1, Kobayashi 2016). Six trials investigated induction and maintenance without re-randomisation of patients (ACT 1, ACT 2, Jiang 2015, REMICADE, ULTRA 2, Suzuki 2014). One trial investigated induction and then maintenance in responders to induction therapy using a randomised withdrawal design for maintenance therapy (GEMINI 1). Three trials investigated maintenance therapy only in responders to induction therapy using a randomised withdrawal design of responders to induction trials or open-label induction phases (OCTAVE Sustain, PURSUIT M, PURSUIT J).

6.8 Overall, the risk of bias in the induction studies was low. However, the maintenance studies had a high risk of attrition bias due to discontinuations and loss to follow-up. The methods to handle missing data were inconsistent across the studies; some trials did not report the methods applied, some trials used the last observation carried forward, and others used the non-responder imputation method.

6.9 There were no significant differences in baseline patient characteristics between the active treatment and placebo groups within the trials. However, there were some variations across the trials: duration of disease ranged from 4.4 to 8.8 years, extensive pancolitis at baseline was present in 33.6% to 80.8% of patients, and C-reactive protein concentrations varied from 0.7 mg/L to 35.8 mg/L.

6.10 The use of concomitant medications also differed across the trials. The proportion of patients treated with oral corticosteroids and immunomodulators (IMMs) ranged from 28.1%-66.3% and 12.1%-54.5%, respectively. Azathioprine and 6-mercaptopurine were the most commonly used IMMs, with the exception of the OCTAVE trials where these treatments (and methotrexate) were prohibited. The differences in the use of concomitant medications may influence exchangeability of the results.

Comparative effectiveness

6.11 The clinically relevant outcomes were clinical remission and clinical response, as assessed using the Mayo score. Clinical remission was defined as total Mayo score of ≤2 points with no individual subscore >1 point. Clinical response was defined as a decrease from baseline in Mayo score of ≥3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥1 point or absolute subscore for rectal bleeding of 0 or 1.

6.12 The PBAC previously accepted these outcomes when considering biological therapies for MSUC (see Infliximab Public Summary Document (PSD) March 2014; Adalimumab PSD July 2014; Vedolizumab PSD July 2014). Adequate response on the PBS is defined as a partial Mayo clinic score ≤2, with no sub-score >1 (note: a partial Mayo score does not include the endoscopy findings).

6.13 The method used to calculate the Mayo score differed across the trials. The TOF, IFX, GOL and VDZ trials calculated the components of stool frequency and rectal bleeding as the average of the three most recent days prior to the actual day of the study visit, rounded to the nearest integer. If less than two days of data were available, the patient was categorised as a non-responder and the sub-score was considered missing. In contrast, the ADA trials calculated the Mayo score using the worst score of the last three days for stool frequency and rectal bleeding. These differences could have potentially led to lower Mayo scores in the ADA trials.

6.14 The submission presented a series of indirect comparisons between TOF and all relevant comparators for induction and maintenance therapy using placebo as common reference. However, interpretation of the indirect comparisons was problematic for a number of reasons.

6.15 For indirect comparisons of induction therapy, comparable data were available for outcomes at 6 and 8 weeks across the induction phases/trials for all comparators. However, for the outcome of clinical remission, the submission compared “remission” in the OCTAVE trials (a slightly more stringent definition of clinical remission) to “clinical remission” in the other trials.

6.16 For indirect comparisons in maintenance therapy, the submission included all trials regardless of trial design. As discussed above, some maintenance trials only included responders to induction therapy, re-randomised to active treatment or placebo (randomised withdrawal design), whereas other trials followed all randomised patients following induction therapy regardless of response (‘treat-through’ design). Indirect comparison for maintenance therapy was also limited due to differences in the outcomes reported and the timing of outcome assessment across trials.

6.17 To improve comparability across outcomes and trials, the evaluation presented i) results for “clinical remission” and “clinical response” following induction treatment, and ii) results for “sustained clinical remission” and “sustained clinical response” in maintenance therapy from trials that re-randomised patients with response to induction therapy consistent with the design of the TOF maintenance trial OCTAVE

Sustain. However, there were still some differences in the timing/frequency of the assessments for the outcomes of sustained clinical remission/response across trials (i.e. these outcomes were measured at Week 24 and 52 in OCTAVE sustain, Week 30 and 54 in the PURSUIT trials, and Week 6 and 52 in GEMINI-1).

6.18 Table 5 and Table 6 present results for clinical remission and clinical response, respectively, during induction. Table 7 and Table 8 present results for the outcomes of sustained clinical remission and sustained clinical response, respectively, for maintenance treatment. The evaluation did not undertake indirect comparisons between TOF and IFX or ADA for maintenance therapy due to differences in trial design that favoured TOF.

Table 5 Clinical remission at Weeks 6/8 – induction therapy (relevant arms only)

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)^	RD (95% CI)^	NNT (95%CI)
TOF 10mg v PBO (Wk 8)[a]					
OCTAVE 1, ITT	88/476 (18.5)	10/122 (8.2)	**2.26 (1.21, 4.21)**	**0.10 (0.04, 0.16)**	*10 (6, 25)*
OCTAVE 1, TNFi-n	56/222 (25.2)	9/57 (15.8)	1.60 (0.84, 3.03)	0.09 (-0.02, 0.20)	*NS*
OCTAVE 1, TNFi-e	32/254 (12.6)	1/65 (1.5)	**8.19 (1.14, 58.82)**	**0.11 (0.06, 0.16)**	*9 (6, 17)*
OCTAVE 2, ITT	72/429 (16.8)	4/112 (3.6)	**4.70 (1.75, 12.59)**	**0.13 (0.08, 0.18)**	*8 (5.5, 12.5)*
OCTAVE 2, TNFi-n	44/195 (22.6)	4/47 (8.5)	**2.65 (1.00, 7.01)**	**0.14 (0.04, 0.24)**	*7 (4, 25)*
OCTAVE 2, TNFi-e	28/234 (12.0)	0/65 (0)	16.01 (0.99, 258.73)	**0.12 (0.07, 0.17)**	*8 (6, 14)*
Meta, ITT	160/905 (17.7)	14/234 (6.0)	**2.95 (1.74, 5.00)**	**0.12 (0.08, 0.16)**	*8 (6, 12.5)*
Meta, TNFi-n					
Meta, TNFi-e					
IFX v PBO (Wk 8)					
ACT 1, ITT/TNFi-n	47/121 (38.8)	18/121 (14.9)	**2.61 (1.61, 4.23)**	**0.24 (0.13, 0.35)**	*4 (3, 8)*
ACT 2, ITT/TNFi-n	41/121 (33.9)	7/123 (5.7)	**5.95 (2.78, 12.75)**	**0.28 (0.19, 0.38)**	*4 (3, 5)*
Jiang 2015, ITT/TNFi-n	22/41 (53.7)	9/41 (22.0)	**2.44 (1.28, 4.65)**	**0.32 (0.12, 0.52)**	*3 (2, 8)*
REMICADE ITT/TNFi-n	11/50 (22.0)	5/49 (10.2)	2.16 (0.81, 5.75)	0.12 (-0.02, 0.26)	*NS*
Kobayashi 2016 ITT/TNFi-n	*21/104 (20.2)*	*11/104 (10.6)*	*1.91 (0.97, 3.76)*	*0.10 (-0.00, 0.19)*	*NS*
Meta, ITT/TNFi-n	*142/437 (32.5)*	*50/438 (11.4)*	***2.84 (2.13, 3.81)***	***0.21 (0.16, 0.26)***	*5 (4, 6)*
Meta (ACT1/2), ITT/TNFi-n	*88/242 (36.3)*	*25/244 (10.4)*	***3.74 (1.66, 8.45)***	***0.26 (0.19, 0.33)***	*4 (3, 5)*
GOL v PBO (Wk 6)					
PURSUIT-SC, ITT/TNFi-n	45/253 (17.8)	16/251 (6.4)	**2.79 (1.62, 4.80)**	**0.11 (0.06, 0.17)**	*9 (6, 17)*
ADA v PBO (Wk 8)					
ULTRA 1, ITT/TNFi-n	24/130 (18.5)	12/130 (9.2)	**2.00 (1.05, 3.83)**	**0.09 (0.01, 0.18)**	*11 (5.5, 100)*
ULTRA 2, ITT	41/248 (16.5)	23/246 (9.3)	**1.77 (1.10, 2.86)**	**0.07 (0.01, 0.13)**	*14 (8, 100)*
ULTRA 2, TNFi-n	*32/150 (21.3)*	*16/145 (11.0))*	**1.93 (1.11, 3.37)**	**0.10 (0.02, 0.19)**	*10 (5, 50)*
ULTRA 2, TNFi-e	*9/98 (9.2)*	*7/101 (6.9)*	*1.33 (0.51, 3.42)*	*0.02 (-0.05, 0.10)*	*NS*
Suzuki 2014, ITT/TNFi-n	9/90 (10.0)	11/96 (11.5)	*0.87 (0.38, 2.01)*	*-0.01 (-0.10, 0.07)*	*NS*
Meta, ITT	74/468 (15.8)	46/472 (9.7)	**1.62 (1.15, 2.29)**	***0.06 (0.00, 0.12)***	*17 (10, 50)*
Meta, TNFi-n	*65/370 (17.5)*	*39/371 (10.5)*	***1.66 (1.15, 2.41)***	***0.07 (0.02, 0.12)***	*14 (8, 50)*
VDZ v PBO (Wk 6)					
GEMINI 1, ITT	38/225 (16.9)	8/149 (5.4)	**3.15 (1.51, 6.55)**	**0.12 (0.05, 0.18)**	*8 (5.5, 20)*
GEMINI 1, *TNFi-n*	*30/130 (23.1)*	*5/76 (6.6)*	***3.51 (1.42, 8.66)***	***0.16 (0.07, 0.26)***	*6 (4, 14)*
GEMINI 1, *TNFi-e**	*8/82 (9.8)*	*2/63 (3.2)*	*3.07 (0.68, 13.97)*	*0.07 (-0.01, 0.14)*	*NA*
Indirect comparisons, ITT					
TOF (Meta ITT) v IFX (Meta ITT)					
TOF (Meta ITT) v IFX (Meta ITT/TNFi-n ACT1/2)					
TOF (Meta ITT) v GOL (PURSUIT-SC ITT/TNFi-n)					
TOF (Meta ITT) v ADA (Meta ITT)					
TOF (Meta ITT) v VDZ (GEMINI 1 ITT)					
Indirect comparisons, TNFi-n					
TOF (Meta TNFi-n) v IFX (Meta ITT/TNFi-n)					
TOF (Meta TNFi-n) v IFX (Meta ITT/TNFi-n ACT1/2)					
TOF (Meta TNFi-n) v GOL (Meta ITT/TNFi-n)					
TOF (Meta TNFi-n) v ADA (Meta TNFi-n)					
TOF (Meta TNFi-n) v VDZ (TNFi-n)					
Indirect comparisons, TNFi-e					
TOF (Meta TNFi-e) v ADA (ULTRA 2, TNFi-e)					
TOF (Meta TNFi-e) v VDZ (TNFi-e failure)					

Source: Table 2.5.2, Table 2.5.11-13, Table 2.6.1, pp79-109 of the submission; Attachment 1 of the submission (Tables 1.2.1-6, pp2-3); Faegan 2017, Kobayashi 2016, Sandborn 2012.

Abbreviations: ADA=adalimumab, CI=confidence interval, GOL=golimumab, ITT=intention to treat, NNT=number needed to treat, NS=not significant, RD=risk difference, RR=risk ratio, TOF=tofacitinib, TNFi=tumour necrosis factor inhibitor, TNFi-n=TNFi naïve, TNFi-e=TNFi exposed, VDZ=vedolizumab

Italics indicate results estimated during the evaluation. Bold typography indicate statistically significant differences. Blue line crossing zero.

[a] The submission used the primary outcome of "remission" instead of clinical remission, which is a more stringent criterion.

^ estimated during the evaluation using random effects meta-analysis using RevMan Version 5.3.

* TNFi-exposed+failure, TNF-exposed without failure were excluded. # *Favours IFX*

Table 6: Clinical response at Weeks 6/8 – induction therapy (relevant arms only)

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)^	RD [95% CI]^	NNT (95%CI)
TOF 10mg v PBO (Wk 8)					
OCTAVE 1, ITT	285/476 (59.9)	40/122 (32.8)	**1.83 (1.40, 2.38)**	**0.27 (0.18, 0.37)**	*4 (3, 5.5)*
OCTAVE 1, TNFi-n					
OCTAVE 1, TNFi-e					
OCTAVE 2, ITT	236/429 (55.0)	32/112 (28.6)	**1.93 (1.42, 2.61)**	**0.26 (0.17, 0.36)**	*4 (3, 6)*
OCTAVE 2, TNFi-n					
OCTAVE 2, TNFi-e					
Meta, ITT	521/905 (57.5)	72/234 (30.7)	**1.87 (1.53, 2.28)**	**0.27 (0.20, 0.34)**	*4 (3, 5)*
Meta, TNFi-n					
Meta, TNFi-e					
IFX v PBO (Wk 8)					
ACT 1, ITT/TNFi-n	84/121 (69.4)	45/121 (37.2)	**1.87 (1.44, 2.42)**	**0.32 (0.20, 0.44)**	*3 (2, 5)*
ACT 2, ITT/TNFi-n	78/121 (64.5)	36/123 (29.3)	**2.20 (1.62, 2.99)**	**0.35 (0.23, 0.47)**	*3 (2, 4)*
Jiang 2015, ITT/TNFi-n	32/41 (78.1)	15/41 (36.6)	**2.13 (1.38, 3.29)**	**0.41 (0.22, 0.61)**	*2 (2, 4.5)*
REMICADE ITT/TNFi-n	32/50 (64.0)	19/49 (38.8)	**1.65 (1.10, 2.48)**	**0.25 (0.06, 0.44)**	*4 (2, 17)*
Kobayashi 2016 ITT/TNFi-n	*57/104 (54.8)*	*37/104 (35.6)*	***1.54 (1.13, 2.10)***	***0.19 (0.06, 0.33)***	*5 (3, 17)*
Meta, ITT/TNFi-n	*283/437 (64.8)*	*152/438 (34.7)*	***1.87 (1.61, 2.16)***	***0.30 (0.24, 0.36)***	*3 (3, 4)*
Meta (ACT1/2), ITT/TNFi-n	*162/242 (66.9)*	*81/244 (33.2)*	***2.02 (1.65, 2.46)***	***0.34 (0.25, 0.42)***	*3 (2, 4)*
GOL v PBO (Wk 6)					
PURSUIT-SC, ITT/TNFi-n	129/253 (51.0)	76/251 (30.3)	**1.68 (1.35, 2.11)**	**0.21 (0.12, 0.29)**	*5 (3, 8)*
ADA v PBO (Wk 8)					
ULTRA 1, ITT/TNFi-n	71/130 (54.6)	58/130 (44.6)	1.22 (0.96, 1.57)	0.10 (-0.02, 0.22)	*NS*
ULTRA 2, ITT	125/248 (50.4)	85/246 (34.6)	**1.46 (1.18, 1.80)**	**0.16 (0.07, 0.24)**	*6 (4, 14)*
ULTRA 2, TNFi-n	*89/150 (59.3)*	*56/145 (38.6)*	***1.54 (1.20, 1.96)***	***0.21 (0.10, 0.32)***	*5 (3, 10)*
ULTRA 2, TNFi-e	*36/98 (36.7)*	*29/101 (28.7)*	*1.28 (0.86, 1.91)*	*0.08 (-0.05, 0.21)*	*NS*
Suzuki 2014, ITT/TNFi-n	45/90 (50.0)	34/96 (35.4)	**1.41 (1.00, 1.98)**	**0.15 (0.01, 0.29)**	*7 (3, 100)*
Meta, ITT	241/468 (51.4)	177/472 (37.5)	**1.37 (1.19, 1.59)**	**0.14 (0.08, 0.20)**	*7 (5, 12.5)*
Meta, TNFi-n	205/370 (55.4)	148/371 (39.8)	***1.39 (1.19, 1.62)***	***0.15 (0.08, 0.23)***	*7 (4, 12.5)*
VDZ v PBO (Wk 6)					
GEMINI 1, ITT	*106/225 (47.1)*	*38/149 (25.5)*	***1.85 (1.36, 2.51)***	***0.22 (0.12, 0.31)***	*4.5 (3, 8)*
GEMINI 1, *TNFi-n*	*69/130 (53.1)*	*20/76 (26.3)*	***2.02 (1.34, 3.04)***	***0.27 (0.14, 0.40)***	*4 (2.5, 7)*
GEMINI 1, *TNFi-e**	*32/82 (39.0)*	*13/63 (20.6)*	***1.89 (1.09, 3.29)***	***0.18 (0.04, 0.33)***	*5.5 (3, 25)*
Indirect comparisons, ITT					
TOF (Meta ITT) v IFX (Meta ITT)					
TOF (Meta ITT) v IFX (Meta ITT/TNFi-n ACT1/2)					
TOF (Meta ITT) v GOL (PURSUIT-SC ITT/TNFi-n)					
TOF (Meta ITT) v ADA (Meta ITT)					
TOF (Meta ITT) v VDZ (GEMINI 1 ITT)					
Indirect comparisons, TNFi-n					
TOF (Meta TNFi-n) v IFX (Meta ITT/TNFi-n)					
TOF (Meta TNFi-n) v IFX (Meta ITT/TNFi-n ACT1/2)					
TOF (Meta TNFi-n) v GOL (Meta ITT/TNFi-n)					
TOF (Meta TNFi-n) v ADA (Meta TNFi-n)					
TOF (Meta TNFi-n) v VDZ (TNFi-n)					
Indirect comparisons, TNFi-e					
TOF (Meta TNFi-e) v ADA (ULTRA 2, TNFi-e)					
*TOF (Meta TNFi-e) v VDZ (*TNFi-e failure)					

Source: Table 2.5.5, Table 2.5.11-13, Table 2.6.2, pp80-112 of the submission; Attachment 1 of the submission (Tables 1.2.13-18, pp6-7); Faegan 2017, Kobayashi 2016, Sandborn 2012.

Abbreviations: ADA=adalimumab, CI=confidence interval, GOL=golimumab, ITT=intention to treat, NNT=number needed to treat, NS=not significant, RD=risk difference, RR=risk ratio, TOF=tofacitinib, TNFi=tumour necrosis factor inhibitor, TNFi-n=TNFi naïve, TNFi-e=TNFi exposed, VDZ=vedolizumab

Italics indicate results estimated during the evaluation. Bold typography indicate statistically significant differences. Blue line crossing zero.

^estimated during the evaluation using random effects meta-analysis using RevMan Version 5.3.

*TNFi-exposed+failure, TNF-exposed without failure were excluded.

Table 7 Sustained remission or sustained clinical remission at 52/54 Weeks– maintenance therapy (relevant arms only)

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)^	RD [95% CI]^	NNT (95%CI)
TOF v PBO (Wk 24&52)*					
OCTAVE S, 5mg ITT	44/198 (22.2)	10/198 (5.1)	**4.40 (2.28, 8.49)**	**0.17 (0.11, 0.24)**	*6 (4, 9)*
OCTAVE S, 10mg ITT	50/197 (25.4)	10/198 (5.1)	**5.03 (2.62, 9.62)**	**0.20 (0.14, 0.27)**	*5 (4, 7)*
OCTAVE S, 5mg TNFi-n					
OCTAVE S, 5mg TNFi-e					
OCTAVE S, 10mg TNFi-n					
OCTAVE S, 10mg TNFi-e					
Pooled 5/10mg ITT	*94/395 (23.8)*	10/198 (5.1)	***4.71 (2.51, 8.84)***	***0.19 (0.14, 0.24)***	*5 (4, 7)*
Pooled 5/10mg TNFi-n					
Pooled 5/10mg TNFi-e					
GOL v PBO (Wk 30&54)					
PURSUIT-M, ITT/TNFi-n	*42/151 (27.8)*	*24/154 (15.6)*	***1.78 (1.14, 2.79)***	***0.12 (0.03, 0.21)***	*8 (5, 33)*
PURSUIT-J ITT/TNFi-n	*16/32 (50.0)*	*2/31 (6.5)*	***7.75 (1.94, 30.94)***	***0.44 (0.24, 0.63)***	*2 (2, 4)*
Meta	*58/183 (31.7)*	*26/185 (14.1)*	***2.25 (1.48, 3.43)***	***0.18 (0.09, 0.26)***	*5.5 (4, 11)*
VDZ v PBO (Wk 6&52)					
GEMINI 1, ITT	25/122 (20.5)	11/126 (19.8)	**2.35 (1.21, 4.56)**	**0.12 (0.03, 0.20)**	*8 (5, 33)*
GEMINI 1, *TNFi-n*	*16/72 (22.2)*	*10/79 (12.7)*	*1.76 (0.85, 3.62)*	*0.10 (-0.03, 0.22)*	*NS*
GEMINI 1, *TNFi-e**	*9/43 (20.9)*	*1/38 (2.6)*	***7.95 (1.06, 59.92)***	***0.18 (0.05, 0.31)***	*5.5 (3, 20)*
Indirect comparisons ITT					
TOF 5mg v GOL (Meta)					
TOF 10mg v GOL (Meta)					
TOF 5/10mg (Pooled) v GOL (Meta)					
TOF 5mg v VDZ					
TOF 10mg v VDZ					
TOF 5/10mg (Pooled) v VDZ					
Indirect comparisons, TNFi-n					
TOF/TNFi-n 5mg v GOL (Meta)					
TOF/TNFi-n 10mg v GOL (Meta)					
TOF/TNFi-n 5/10mg (Pooled) v GOL (Meta)					
TOF/TNFi-n 5mg v VDZ					
TOF/TNFi-n 10mg v VDZ					
TOF/TNFi-n 5/10mg (Pooled) v VDZ					
Indirect comparisons, TNFi-e					
TOF/TNF-e-n 5mg v VDZ					
TOF/TNFi-e 10mg v VDZ					
TOF/TNFi-e 5/10mg (Pooled) v VDZ					

Source: Table 2.5.6 (p81), Table 2.6.4 (p120) of the submission; Faegan 2013, Faegan 2017, Hibi 2017, Sandborn 2014

Abbreviations: CI=confidence interval, GOL=golimumab, ITT=intention to treat, NNT=number needed to treat, NS=not significant, RD=risk difference, RR=risk ratio, TOF=tofacitinib, TNFi=tumour necrosis factor inhibitor, TNFi-n=TNFi naïve, VDZ=vedolizumab

Italics indicate results estimated during the evaluation. Bold typography indicate statistically significant differences. Blue line crossing zero.

*TNFi-exposed+failure, TNF-exposed without failure were excluded.

* Sustained remission, as reported in the submission and OCTAVE sustain

^ estimated during the evaluation using random effects meta-analysis using RevMan Version 5.3.

Table 8: **Sustained Clinical response at 52/54 Weeks – maintenance therapy (relevant arms only)**

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)^	RD [95% CI]^	NNT (95%CI)
TOF v PBO (Wk 24&52)					
OCTAVE S, 5mg ITT	97/198 (49.0)	38/198 (19.2)	**2.55 (1.86, 3.51)**	**0.30 (0.21, 0.39)**	*3 (3, 5)*
OCTAVE S, 10mg ITT	117/197 (59.4)	38/198 (19.2)	**3.09 (2.27, 4.21)**	**0.40 (0.31, 0.49)**	*2.5 (2, 3)*
OCTAVE S, 5mg TNFi-n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCTAVE S, 5mg TNFi-e	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCTAVE S, 10mg TNFi-n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCTAVE S, 10mg TNFi-e	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled 5/10mg ITT	*214/395 (54.2)*	38/198 (19.2)	***2.82 (2.09, 3.81)***	***0.35 (0.28, 0.48)***	*3 (2, 4)*
Pooled 5/10mg TNFi-n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled 5/10mg TNFi-e	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL v PBO (Wk 30&54)					
PURSUIT-M, ITT/TNFi-n	*75/151 (49.7)*	*48/154 (31.2)*	***1.59 (1.20, 2.12)***	***0.19 (0.08, 0.29)***	*5 (3, 12.5)*
PURSUIT-J ITT/TNFi-n	*18/32 (56.3)*	*6/31 (19.4)*	***2.91 (1.33, 6.35)***	***0.37 (0.15, 0.59)***	*4 (2, 50)*
Meta	*93/183 (50.8)*	*54/185 (29.2)*	***1.74 (1.33, 2.28)***	***0.22 (0.12, 0.31)***	*4.5 (3, 8)*
VDZ v PBO (Wk 6&52)					
GEMINI 1, ITT	*69/122 (56.6)*	*30/126 (23.8)*	***2.38 (1.68, 3.37)***	***0.33 (0.21, 0.44)***	*3 (2, 5)*
GEMINI 1, *TNFi-n*	*47/72 (65.3)*	*21/79 (26.6)*	***2.46 (1.64, 3.68)***	***0.39 (0.24, 0.53)***	*3 (2, 4)*
GEMINI 1, *TNFi-e**	*20/43 (46.5)*	*6/38 (15.8)*	***2.95 (1.32, 6.56)***	***0.31 (0.12, 0.50)***	*1 (1, 2)*
Indirect comparisons ITT					
TOF 5mg v GOL (Meta)			[redacted]	[redacted]	[redacted]
TOF 10mg v GOL (Meta)			[redacted]	[redacted]	[redacted]
TOF 5/10mg (Pooled) v GOL (Meta)			[redacted]	[redacted]	[redacted]
TOF 5mg v VDZ			[redacted]	[redacted]	[redacted]
TOF 10mg v VDZ			[redacted]	[redacted]	[redacted]
TOF 5/10mg (Pooled) v VDZ			[redacted]	[redacted]	[redacted]
Indirect comparisons, TNFi-n					
TOF/TNFi-n 5mg v GOL (Meta)			[redacted]	[redacted]	[redacted]
TOF/TNFi-n 10mg v GOL (Meta)			[redacted]	[redacted]	[redacted]
TOF/TNFi-n 5/10mg (Pooled) v GOL (Meta)			[redacted]	[redacted]	[redacted]
TOF/TNFi-n 5mg v VDZ			[redacted]	[redacted]	[redacted]
TOF/TNFi-n 10mg v VDZ			[redacted]	[redacted]	[redacted]
TOF/TNFi-n 5/10mg (Pooled) v VDZ			[redacted]	[redacted]	[redacted]
Indirect comparisons, TNFi-e					
TOF/TNF-e-n 5mg v VDZ			[redacted]	[redacted]	[redacted]
TOF/TNFi-e 10mg v VDZ			[redacted]	[redacted]	[redacted]
TOF/TNFi-e 5/10mg (Pooled) v VDZ			[redacted]	[redacted]	[redacted]

Source: Table 2.5.10 (p85), Table 2.6.4 (p120) of the submission; Faegan 2013, Faegan 2017, Hibi 2017, Sandborn 2014
Italics indicate results estimated during the evaluation
. Bold typography indicate statistically significant differences. Blue line crossing zero.
^ estimated during the evaluation using random effects meta-analysis using RevMan Version 5.3.

6.19 The trial results demonstrated TOF and the relevant biological therapies were more effective than placebo for the outcomes of clinical remission and clinical response following induction therapy, and sustained clinical remission and sustained clinical response in maintenance therapy.

Indirect comparison: clinical remission at 6/8 Weeks

6.20 IFX was significantly more effective than TOF in the ITT population based on RD, and remained more effective than TOF when the primary outcome of "remission" (which is more conservative than clinical remission) reported in the OCTAVE trials was used (RD [redacted][95% CI [redacted]]). This finding was consistent in the TNFi-naïve subgroup but did not reach statistical significance (note small numbers). The Pre-PBAC Response argued there were differences in the definition of the Mayo endoscopic

subscore between the TOF and IFX studies that made it more difficult for the TOF studies to meet the criteria for clinical remission and mucosal healing, which favoured IFX in the indirect comparison.

6.21 There were no significant differences between TOF and GOL or VDZ.

6.22 TOF was marginally more effective than ADA in the ITT population and TNFi-experienced subgroup. This result should be interpreted with caution given the ADA trials used a more stringent method to calculate Mayo subscores, which may have influenced the results in favour of TOF. There was no difference between therapies in the TNFi-naïve subgroup.

Indirect comparison: clinical response at 6/8 Weeks

6.23 There were no significant differences between TOF and IFX, GOL or VDZ.

6.24 TOF was significantly more effective than ADA in the ITT population and TNFi-experienced subgroup, but not in TNFi-naïve patients. As discussed above, this result should be interpreted with caution given the ADA trials used a more stringent method to calculate Mayo subscores, which may have influenced the results in favour of TOF.

Indirect comparison: sustained clinical remission at 52/54 Weeks

6.25 There were generally no significant differences between TOF and GOL or VDZ. Subgroup analyses indicated that TOF 10 mg and TOF 5mg/10mg (pooled) was more effective compared to VDZ in TNFi-naïve patients, but this post-hoc analysis should be interpreted with caution due to very small numbers of patients.

Indirect comparison: sustained clinical response at 52/54 Weeks

6.26 There were generally no significant differences between TOF and GOL or VDZ. Subgroup analyses indicated that TOF 10 mg was more effective compared to GOL in the TNFi naïve patients, although this post-hoc analysis should be interpreted with caution due to very small numbers.

Other outcomes and analyses

6.27 The submission presented indirect comparisons of TOF and the biological therapies for the outcome of mucosal healing, with findings generally consistent with the induction results presented above; TOF was inferior to IFX (RD [redacted] [redacted]) but no significant differences were found with other biological therapies.

6.28 The direct comparison of TOF 5 mg and TOF 10 mg in maintenance therapy indicated that TOF 10 mg was significantly more effective at maintaining clinical response than TOF 5 mg (RD [redacted] [95% CI [redacted]]), but there was a non-significant difference between the two doses for the outcome of sustained clinical remission (RD [redacted] [95% CI [redacted]]).

6.29 Quality of life results from the OCTAVE trials demonstrated significant improvements associated with TOF treatment compared with placebo.

6.30 The PBAC agreed with the ESC and the Pre-Sub-Committee Response that relative risk (RR) may be a more appropriate measure than RD in the indirect treatment comparisons to assess the differences in treatments because placebo responses differed across the trials. The PBAC noted that based on RR, there were no significant differences for the induction outcomes between TOF and IFX in the ITT population.

Comparative harms

6.31 The submission presented safety data from the TOF trials, summarised in Table 9 and Table 10.

Table 9 Summary of key AEs in OCTAVE 1 and 2 (TOF 10mg vs. PBO) – induction therapy (Wk 8)

Trial ID	TOF n/N (%)	PBO n/N (%)	RR (95% CI)	OR (95% CI)	RD (95% CI)
Any adverse event					
OCTAVE 1	269/476 (56.5)	73/122 (59.8)	0.94 (0.80, 1.11)	0.87 (0.58, 1.31)	-0.03 (-0.13, 0.06)
OCTAVE 2	232/429 (54.1)	59/112 (52.7)	1.03 (0.84, 1.25)	1.06 (0.70, 1.60)	0.01 (-0.09, 0.12)
Pooled Result	501/905 (55.4)	132/234 (56.4)	0.98 (0.86, 1.11)	0.96 (0.72, 1.28)	-0.01 (-0.08, 0.06)
Serious adverse event					
OCTAVE 1	16/476 (3.4)	5/122 (4.1)	0.82 (0.31, 2.19)	0.81 (0.29, 2.27)	-0.01 (-0.05, 0.03)
OCTAVE 2	18/429 (4.2)	9/112 (8.0)	0.52 (0.24, 1.13)	0.50 (0.22, 1.15)	-0.04 (-0.09, 0.02)
Pooled Result	34/905 (3.8)	14/234 (6.0)	0.62 (0.34, 1.14)	0.61 (0.32, 1.16)	-0.02 (-0.05, 0.01)
Discontinuation due to adverse event					
OCTAVE 1	18/476 (3.8)	2/122 (1.6)	2.31 (0.54, 9.81)	2.36 (0.54, 10.30)	0.02 (-0.01, 0.05)
OCTAVE 2	17/429 (4.0)	8/112 (7.1)	0.55 (0.25, 1.25)	0.54 (0.23, 1.28)	-0.03 (-0.08, 0.02)
Pooled Result	35/905 (3.9)	10/234 (4.3)	*0.91 (0.46, 1.80)*	*0.90 (0.44, 1.85)*	*-0.00 (-0.03, 0.02)*
Infections					
OCTAVE 1	111/476 (23.3)	19/122 (15.6)	1.50 (0.96, 2.33)	1.65 (0.97, 2.81)	**0.08 (0.00, 0.15)**
OCTAVE 2	78/429 (18.2)	17/112 (15.2)	1.20 (0.74, 1.94)	1.24 (0.70, 2.20)	0.03 (-0.05, 0.11)
Pooled Result	189/905 (20.9)	36/234 (15.4)	1.35 (0.97, 1.87)	1.44 (0.98, 2.13)	**0.05 (0.00, 0.11)**
Serious Infections					
OCTAVE 1	6/476 (1.3)	0	3.35 (0.19, 59.10)	3.38 (0.19, 60.50)	0.01 (-0.00, 0.03)
OCTAVE 2	1/429 (0.2)	0	0.79 (0.03, 19.22)	0.79 (0.03, 19.46)	0.00 (-0.01, 0.02)
Pooled Result	7/905 (0.8)	0/234 (0)	1.76 (0.21, 14.85)	1.76 (0.21, 15.06)	0.01 (-0.00, 0.02)
Herpes Zoster					
OCTAVE 1	*3/476 (0.8)*	*1/122 (0.8)*	*0.77 (0.08, 7.33)*	*0.95 (0.16, 5.81)*	*0.00 (-0.01, 0.02)*
OCTAVE 2	*2/429 (0.4)*	*0*	*1.31 (0.06, 27.18)*	*1.32 (0.06, 27.6)*	*0.00 (-0.01, 0.02)*
Pooled Result	*5/905 (0.5)*	*1/234 (0.4)*	*0.95 (0.16, 5.74)*	*0.95 (0.16, 5.81)*	*0.00 (-0.01, 0.01)*

Source: Table 2.5.18, p101 of the submission

Abbreviations: CI=confidence interval; n=number of participants with event; N=total participants in group, OR=odds ratio, RD=risk difference, RR=risk ratio, TOF=tofacitinib

Bold text=statistically significant

Table 10 Summary of key AEs in OCTAVE sustain (TOF 10mg / TOF 5mg vs. PBO) – maintenance therapy (Wk 52)

Time point	TOF n/N (%)	PBO n/N (%)	RR (95% CI)	OR (95% CI)	RD (95% CI)
TOF 5 mg					
Any AE	143/198 (72.2)	149/198 (75.3)	0.96 (0.85, 1.08)	0.86 (0.55, 1.34)	-0.03 (-0.12, 0.06)
Serious AE	10/198 (5.1)	13/198 (6.6)	0.77 (0.35, 1.71)	0.76 (0.32, 1.77)	-0.02 (-0.06, 0.03)
Discontinuation due to AE	18/198 (9.1)	37/198 (18.7)	**0.49 (0.29, 0.82)**	**0.44 (0.24, 0.79)**	**-0.10 (-0.16, -0.03)**
Infection	71/198 (35.9)	48/198 (24.2)	**1.48 (1.09, 2.01)**	**1.75 (1.13, 2.70)**	**0.12 (0.03, 0.21)**
Serious Infection	2/198 (1.0)	2/198 (1.0)	1.00 (0.14, 7.03)	1.00 (0.14, 7.17)	0.00 (-0.02, 0.02)
Herpes Zoster	*3/198 (1.5)*	*1/198 (0.5)*	*3.00 (0.31, 28.59)*	*3.03 (0.31, 29.39)*	*0.01 (-0.01, 0.03)*
TOF 10 mg					
Any AE	156/196 (79.6)	149/198 (75.3)	1.06 (0.95, 1.18)	1.28 (0.80, 2.06)	0.04 (-0.04, 0.13)
Serious AE	11/196 (5.6)	13/198 (6.6)	0.85 (0.39, 1.86)	0.85 (0.37, 1.94)	-0.01 (-0.06, 0.04)
Discontinuation due to AE	19/196 (9.7)	37/198 (18.7)	**0.52 (0.31, 0.87)**	**0.47 (0.26, 0.85)**	**-0.09 (-0.16, -0.02)**
Infection	78/196 (39.8)	48/198 (24.2)	**1.64 (1.22, 2.22)**	**2.07 (1.34, 3.18)**	**0.16 (0.06, 0.25)**
Serious Infection	1/196 (0.5)	2/198 (1.0)	0.51 (0.05, 5.53)	0.50 (0.05, 5.59)	-0.00 (-0.02, 0.01)
Herpes Zoster	*10/196 (5.1)*	*1/198 (0.5)*	***10.10 (1.31, 78.17)***	***10.59 (1.34, 83.55]***	***0.05 [0.01, 0.08]***
Indirect comparison TOF 10mg vs. TOF 5mg					
		Infections	*1.11 (0.72, 1.70)*	-	*0.04 (-0.09, 0.17)*
		Herpes Zoster	*3.37 (0.16, 71.02)*	-	***0.04 (0.00, 0.08)***

Source: Table 2.5.19, p101 of the submission
Abbreviations: CI=confidence interval; n=number of participants with event; N=total participants in group, OR=odds ratio, RD=risk difference, RR=risk ratio, TOF=tofacitinib
Bold text=statistically significant

6.32 Overall, the results of the OCTAVE trials indicated that treatment with TOF was associated with more infections (including Herpes Zoster, nasopharyngitis) compared to placebo. The TGA delegate raised the concern of a dose-dependent increase in herpes zoster infection following treatment with TOF; an indirect comparison between TOF 10 mg and TOF 5 mg conducted during the evaluation indicated a trend towards a greater risk of infection with TOF 10 mg than TOF 5 mg. In the open-label study, discontinuations due to AEs were also significantly higher in the TOF 10 mg group. The submission reported five patients on TOF 10 mg had hepatic injury and three died.

6.33 Results from an open-label study (A3921139) indicated TOF 10 mg was associated with more adverse events than TOF 5 mg, although the submission presented limited detail. The TGA delegate noted that TOF 10 mg was associated with increased risk of infections, malignancies, gastrointestinal perforations and dyslipidaemia compared with the TOF 5 mg in studies of rheumatoid arthritis.

6.34 The ESC noted that no data was provided on whether adverse drug withdrawal effects were experienced in the clinical trials. The ESC considered information regarding the occurrence of rebound inflammation on drug withdrawal or dose reduction may have helped inform the likely duration of treatment.

6.35 The submission did not present a formal comparison between TOF and any of the relevant comparators for safety outcomes. The Pre-PBAC Response provided a comparison of safety outcomes for TOF, GOL, IFX and ADA (based on data presented in the GOL November 2017 PSD) to support the claim that TOF appeared to be no worse with regards to comparative safety.

Clinical claim

6.36 For induction therapy, the submission described TOF 10 mg as non-inferior in terms of efficacy and safety when compared with IFX 5 mg/kg. For maintenance therapy, the submission described TOF 5 mg and 10 mg as non-inferior in terms of efficacy and safety when compared with IFX 5 mg/kg.

6.37 The submission did not make any clinical claim between TOF and the other relevant comparators (GOL, ADA and VDZ). Based on the evidence presented, TOF appeared to be no worse in terms of effectiveness than GOL or VDZ for induction and maintenance therapy. TOF appeared to be marginally more effective than ADA for induction, although this finding should be interpreted with caution due to differences in outcome measurement between the trials, which may favour TOF.

6.38 The pre-PBAC response noted a number of key differences between the TOF studies and IFX studies and considered that these differences in study design contributed to a bias against TOF and therefore the indirect comparison provided a conservative estimate of TOF's clinical benefit when compared with IFX.

6.39 The PBAC considered the claim of non-inferior comparative effectiveness to IFX in the induction phase may be reasonable. While there was a trend to TOF being inferior to IFX, there were differences in trial design that may bias against TOF and most of the outcomes were not significantly different. The PBAC considered the claim of non-inferior comparative effectiveness to IFX in the maintenance phase was uncertain given the differences in trial design. However, the PBAC recalled GOL and VDZ have previously been accepted as non-inferior to IFX in the maintenance phase, and noted that there was no significant difference in efficacy for TOF compared with GOL and VDZ in the maintenance phase.

6.40 The PBAC considered that it was difficult to assess the claim of non-inferior comparative safety compared to IFX and the other biologic therapies but overall considered it may be reasonable. The PBAC noted the 10 mg strength of TOF was associated with more infections that 5mg strength of TOF

Economic analysis

6.41 The submission presented a cost-minimisation analysis between TOF with IFX. The proposed equi-effective doses were based on the recommended doses: for induction TOF 10 mg BD orally = IFX 5 mg/kg IV Weeks 0, 2 and 6; for maintenance TOF 5 mg or 10 mg BD orally = IFX 5 mg/kg IV every 8 weeks from week 14.

6.42 The PBAC could only recommend listing of TOF at a higher cost if it was satisfied that TOF provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (National Health Act 1953, Section 101(3B)). Given no evidence has been provided to support TOF having a higher cost than alternative biological therapies, the ESC and PBAC considered TOF should be listed on the basis of a cost-minimisation analysis against the least expensive biological therapy.

6.43 The cost-minimisation analysis assumed:

- Equivalent total costs for TOF and IFX over the first two years (i.e. 104 weeks).
- Drug costs for IFX 5mg/kg based on the assumption of four vials per infusion (average patient weight of 80kg) and costed using the published DPMQ for public (4*$448.61) and private hospitals (4*$448.61 + $40.00 + $7.29), weighted by proportional use of each item. The PBAC noted the cost minimisation analysis should use effective AEMP rather than published DPMQ.
- The total cost for IFX over the first two years included the cost of administration, costed using MBS item 14245 ($97.95) per IV infusion.
- Patients receive TOF 10 mg for 8 weeks and then TOF 5 mg for 96 weeks over the first two years ([redacted]%); or remain on TOF 10 mg for induction and maintenance ([redacted]%). The proportional use of TOF 10 mg and TOF 5 mg scripts per patient (on average) corresponds to [redacted]% and [redacted]% over the first two years. This proportional use informs the relative differential pricing of the two formulations and the ESC considered it may not be reasonable. Furthermore, the requested restriction recommends induction therapy with TOF 10 mg for 8 to 16 weeks, whereas the submission has only accounted for 8-week induction treatment with TOF 10 mg in the cost-minimisation analysis. The ESC considered it was reasonable to assume a majority of patients would receive 16 weeks of induction therapy with TOF 10 mg. The ESC considered the proportion of use of TOF 10 mg and 5 mg in the maintenance setting to be uncertain but noted ~50% of patients treated with TOF 5 mg did not achieve a sustained clinical response in the SUSTAIN study (Table 8).
- The Pre-PBAC Response acknowledged the proportional split used in the CMA may not have been reasonable due to an erroneous calculation, and provided an updated estimated split of [redacted]% TOF 5 mg and [redacted]% TOF 10 mg.

6.44 The cost-minimisation analysis did not include additional costs for monitoring or management of adverse events. The dosage section of the PI emphasises that patients should be treated with the "lowest effective dose to maintain response" in maintenance. Given the difference in safety profile between the two strengths, the PBAC considered TOF 10 mg may be associated with additional costs due to increased monitoring of adverse events and increased medical visits to assess response for potential dose reduction.

6.45 The Sponsor requested differential pricing for TOF 5 mg (DPMQ of $[redacted]) and 10 mg (DPMQ of $[redacted]) tablets [1]. There is uncertainty associated with the proportional use of TOF 10 mg and TOF 5 mg for maintenance therapy which is relevant for the cost-minimisation analysis and budget impact to the PBS.

[1] Assuming [redacted]% of patients are treated with 8 weeks of TOF 10 mg followed by 96 weeks of TOF 5 mg and [redacted]% of patients are treated with 104 weeks of TOF 10 mg.

Drug cost/patient/year:

6.46 $[redacted], assuming 8 weeks on TOF 10 mg and 44 weeks on TOF 5 mg; or $[redacted], assuming 52 weeks on TOF 10 mg.

Estimated PBS usage & financial implications

6.47 This submission was not considered by DUSC. The budget impact analysis used a market share approach to estimate the financial implications of the proposed listing to the PBS/RPBS, summarised in Table 11. The analysis used PBS claims data to estimate the growth of the biologic market and proportional use of treatment for initial and maintenance therapy. The analysis assumed that the listing of TOF will not affect current market growth and that TOF will substitute for all listed biological therapies (except GOL, which the analysis excluded due to limited claims data). The results presented below account for errors corrected during the evaluation.

Table 11: **Estimated net cost of TOF to the PBS/RPBS**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
4.2 Estimation of use and financial impact of the proposed medicine						
Total scripts PBS/RPBS TOF 10mg TOF 5 mg	[redacted]					
Net Cost PBS/RPBS (less co-pay), TOF	[redacted]					
4.3 Estimation of changes in use and financial impact of other biologic therapies						
Other biologic therapy scripts ADA IFX (public) IFX (private) VDZ (public) VDZ (private)	[redacted]					
Net cost PBS/RPBS (less co-pay), biological therapies ADA IFX (public) IFX (private) VDZ (public) VDZ (private)	[redacted]					
4.4 Estimated financial implications for the PBS/RPBS						
Net Cost PBS/RPBS (less co-payment)	[redacted]					
4.5 Estimated financial implications for the health budget						
VDZ infusions	[redacted]					
Net cost MBS	[redacted]					
Net cost to health budget (less co-payment)	[redacted]					

Source: Compiled during the evaluation from Section 4 workbook "Utilisation and cost-model"
Abbreviations:, TOF=tofacitinib, VDZ=vedolizumab. IFX=infliximab

The redacted table shows that at year 6, the estimated number of total scripts is less than 10,000, and the net cost to the health budget would be a saving of less than $10 million.

6.48 The predicted use and financial impacts of the proposed listing were not reliable for the following reasons:

- The proportional use of TOF 5 mg and 10 mg was uncertain.
- The proportional fixed rates of substitution across comparators were poorly justified and uncertain; the submission assumed the highest substitution would be for ADA because it is administered SC, which contradicted the rationale for the nomination of IFX as the comparator.
- The submission estimated the reduction in scripts for IFX, ADA and VDZ based on assumed fixed proportional use across induction and maintenance treatment for IFX and VDZ, and estimated script relativities versus TOF based on 8-week induction periods (rather than the full initial treatment period of 16 weeks).
- The submission estimated the costs associated with TOF based on the requested effective price but the reduction in costs to the PBS for IFX, ADA and VDZ based on the published DPMQs (rather than effective indication-specific prices). This is the main driver in the estimated net savings to the PBS/RPBS.
- The submission estimated the reduction in costs to the MBS for IV administration associated with VDZ, but not IFX.

Quality Use of Medicines

6.49 The submission identified a number of potential barriers to the appropriate, effective and safe use of TOF and proposed a range of strategies to manage them.

6.50 The ESC noted that, unlike other medicines for MSUC, TOF requires dosage adjustment in patients taking concomitant CYP3A4/ CYP2C19 inhibitors, those with renal impairment, hepatic impairment or cytopaenias. The ESC considered this will require education and training for prescribers and could impact on the relative safety of TOF.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required listing of tofacitinib (TOF) for moderate to severe ulcerative colitis (MSUC) on a cost minimisation basis with the least costly biologic therapy currently PBS listed for MSUC. In making this recommendation, the PBAC accepted any of the current PBS listed biologic therapies for MSUC could be an alternative therapy to TOF.

7.2 The PBAC considered the equi-effective doses of TOF and alternative biologic therapies could be derived with reference to the Product Information and the previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets. For the purpose of achieving an equi-effective cost, the PBAC considered that patients would likely receive 16 weeks of TOF 10 mg in the induction phase, and that in the maintenance phase a split of [redacted]% TOF 5 mg and [redacted]% TOF 10 mg use should apply. The PBAC noted this was consistent with the proportion of use between the two strengths proposed in the pre-PBAC response.

7.3 The PBAC noted that any increase in efficacy for TOF 10 mg compared to TOF 5 mg in the maintenance setting was at the expense of a higher rate of AEs.

7.4 The PBAC noted that there are four alternative biologic therapies listed on the PBS for the treatment of MSUC. The PBAC noted that TOF had a different mechanism of action and mode of administration (oral) compared with the alternative therapies. The PBAC considered an oral therapy would provide a new treatment option for some patients, particularly those in rural or remote areas.

7.5 The PBAC considered infliximab (IFX) was an appropriate comparator but noted that as an intravenous therapy with a rapid response, IFX has a specific place in practice for the treatment of MSUC, particularly in the induction setting. The PBAC considered any of the currently listed biologics for MSUC (infliximab, vedolizumab, adalimumab and golimumab) could be considered an alternative therapy to TOF for the treatment of MSUC. As described in paragraph 5.2 above, tofacitinib could only be recommended for listing with a higher price than alternative therapies if the PBAC is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction in toxicity.

7.6 The PBAC considered the claim of non-inferior comparative effectiveness to IFX in the induction and maintenance phases may be reasonable. The PBAC considered the claim of non-inferior comparative effectiveness to IFX in the maintenance phase was uncertain given the differences in trial design. However, the PBAC recalled GOL and VDZ have previously been accepted as non-inferior to IFX in the maintenance phase, and noted that there was no significant difference in efficacy for TOF compared with GOL and VDZ in the maintenance phase. The PBAC considered the claim of non-inferior comparative safety to IFX was uncertain but may be reasonable. The PBAC considered the evidence presented in the submission did not support a conclusion that TOF provided a significant improvement in efficacy or reduction in toxicity compared to any of the currently listed biologics for MSUC.

7.7 The PBAC noted the financial estimates provided in the submission were highly uncertain but considered that based on a cost minimisation basis with the least costly biologic therapy the listing TOF for MSUC should be cost-neutral to the PBS.

7.8 The PBAC considered it would be appropriate to align the listing of TOF with the other written authority biologic therapies for MSUC, including the requested grandfather restriction and that flow-on changes to notes in the other listings to include TOF in the list of therapies would be required to facilitate the listing. The PBAC advised that grandfathered patients will be required to meet the PBS eligibility criteria and noted the grandfather restriction will be removed from the listing after 12 months (unless otherwise negotiated with the Department), in line with standard procedure.

7.9 The PBAC noted the sponsor requested consideration of a special pricing arrangement and agreed that, under criterion 2 of the Special Pricing Arrangement (SPA) criteria, tofacitinib has unique characteristics compared to other available therapies for the treatment of MSUC as the only oral agent.

7.10 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* that tofacitinib may be treated as interchangeable on an individual patient basis with infliximab, adalimumab, vedolizumab and golimumab for MSUC.

7.11 The PBAC advised that it remained of the view that tofacitinib is not suitable for prescribing by nurse practitioners.

7.12 The PBAC recommended that the Early Supply Rule should apply.

7.13 The PBAC noted the flow-on restriction changes to the other biological therapies PBS listed for MSUC (noted in Section 8 below).

7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
TOFACITINIB				
Tablet 5mg, 56	1	3	Xeljanz®	Pfizer Australia Pty Ltd
Tablet 10mg, 56	1	3		

Program	Section 85 (General Schedule)
Prescriber Types:	☒Medical Practitioners
Severity:	Moderate to severe
Condition:	Ulcerative colitis
PBS Indication:	Moderate to severe ulcerative colitis
Treatment phase:	Initial treatment (new patient or Recommencement of treatment after more than 5 years break in therapy - Initial 1)
Restriction:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].

Clinical criteria:	Patient must have failed to achieve an adequate response to a 5-aminosalicylate oral preparation in a standard dose for induction of remission for 3 or more consecutive months or have intolerance necessitating permanent treatment withdrawal, AND Patient must have failed to achieve an adequate response to azathioprine at a dose of at least 2 mg per kg daily for 3 or more consecutive months or have intolerance necessitating permanent treatment withdrawal; OR Patient must have failed to achieve an adequate response to 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more consecutive months or have intolerance necessitating permanent treatment withdrawal; OR Patient must have failed to achieve an adequate response to a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period or have intolerance necessitating permanent treatment withdrawal, and followed by a failure to achieve an adequate response to 3 or more consecutive months of treatment of an appropriately dosed thiopurine agent, AND Patient must have a Mayo clinic score greater than or equal to 6; OR Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).
Population criteria:	Patient must be aged 18 years or older.

Prescriber Instructions	Application for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed Ulcerative Colitis PBS Authority Application - Supporting Information Form which includes the following: (i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition; and (ii) details of prior systemic drug therapy [dosage, date of commencement and duration of therapy]; and (iii) the signed patient acknowledgement. The most recent Mayo clinic or partial Mayo clinic score must be no more than 1 month old at the time of application. Patients who fail to achieve a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 or have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug. A partial Mayo clinic assessment of the patient's response to this initial course of treatment must be made up to 12 weeks after the first dose for patients administered doses at weeks 0, 2, 6 and 10 so that there is adequate time for a response to be demonstrated. All tests and assessments should be performed preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior conventional treatment. A maximum of 16 weeks of treatment with this drug will be approved under this criterion. Patients receive 8 weeks therapy of 10mg tofacitinib twice daily, and either change to 5mg tofacitinib twice daily for weeks 8-16 or continue on 10mg tofacitinib twice daily from weeks 8-16. Patients must have signed a patient acknowledgement indicating they understand and acknowledge that the PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment. If treatment with any of the above-mentioned drugs is contraindicated according to the relevant TGA-approved Product Information, details must be provided at the time of application. If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application.

Administrative Advice	Note: Details of accepted toxicities including severity can be found on the Department of Human Services website at www.humanservices.gov.au. Note: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 No increase in the maximum number of repeats may be authorised.

Program	Section 85 (General Schedule)
Prescriber Types:	☒Medical Practitioners
Severity:	Moderate to severe
Condition:	Ulcerative colitis
PBS Indication:	Moderate to severe ulcerative colitis
Treatment phase:	Change or Re-commencement of treatment after a break in therapy of less than 5 years (Initial 2)
Restriction:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].

Clinical criteria:	Patient must have previously received PBS-subsidised treatment with adalimumab, golimumab, infliximab, tofacitinib or vedolizumab for this condition in this treatment cycle, AND Patient must not have failed PBS-subsidised therapy with tofacitinib for this condition in the current treatment cycle.
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions	To demonstrate a response to treatment the application must be accompanied by the results of the most recent course of this drug within the timelines specified in the relevant restriction. If the response assessment to the previous course of this drug is not submitted as detailed in the relevant restriction, the patient will be deemed to have failed therapy with this drug. A maximum of 16 weeks of treatment with this drug will be approved under this criterion. Patients receive 8 weeks therapy of 10mg tofacitinib twice daily, and either change to 5mg tofacitinib twice daily for weeks 8-16 or continue on 10mg tofacitinib twice daily from weeks 8-16. Application for authorisation of change or recommencement treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed Ulcerative Colitis PBS Authority Application - Supporting Information Form which includes the following: (i) Mayo clinical assessment (to demonstrate response to prior treatment).
Administrative Advice	Note: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 No increase in the maximum number of repeats may be authorised.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
TOFACITINIB				
Tablet 5mg, 56	1	5	Xeljanz®	Pfizer Australia Pty Ltd
Tablet 10mg, 56	1	5		

Program	Section 85 (General Schedule)
Prescriber Types:	☒Medical Practitioners
Severity:	Moderate to severe
Condition:	Ulcerative colitis
PBS Indication:	Moderate to severe ulcerative colitis
Treatment phase:	Continuing treatment
Restriction:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug.
Population criteria:	Patient must be 18 years or older.
Prescriber Instructions	Patients who have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug. Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response. At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.

Administrative Advice	Note: Authority approval for sufficient therapy to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Program	Section 85 (General Schedule)
Prescriber Types:	☒Medical Practitioners
Severity:	Moderate to severe
Condition:	Ulcerative colitis
PBS Indication:	Moderate to severe ulcerative colitis
Treatment phase:	Initial 3 (Grandfathered patients)
Restriction:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].

Clinical criteria:	Patient must have previously received non-PBS-subsidised therapy with this drug for this condition prior to <<listing date>>, AND Patient must have had a Mayo clinic score greater than or equal to 6 prior to commencing treatment with this drug; or Patient must have had a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores were both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo score) prior to commencing treatment with this drug; or Patient must have a documented history of moderate to severe refractory ulcerative colitis prior to having commenced treatment with this drug where a Mayo clinic, partial Mayo clinic baseline assessment is not available, AND Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 after 16 weeks treatment with this drug.
Population criteria:	Patient must be 18 years or older.
Prescriber Instructions	Patients who have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug. Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response. At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.
Administrative Advice	Note: Authority approval for sufficient therapy to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Administrative advice common to all MSUC listings (with flow-on changes to include tofacitinib in the list of approved therapies)

Administrative Advice	TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of adalimumab, golimumab, infliximab, tofacitinib and vedolizumab for adult patients with ulcerative colitis. Patients are eligible for PBS-subsidised treatment with either adalimumab, golimumab, infliximab, tofacitinib or vedolizumab at any one time. Where the term 'biological medicine' appears in notes and restrictions, it refers to adalimumab, golimumab, infliximab, tofacitinib and vedolizumab only. From 1 June 2018, under the PBS, all adult patients will be able to commence a treatment cycle where they may trial PBS-subsidised adalimumab, golimumab, infliximab, tofacitinib or vedolizumab without having to experience a disease flare when swapping to one of the alternate agents. Under these arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with adalimumab, golimumab, infliximab or vedolizumab while they continue to show a response to therapy. A patient who received PBS-subsidised adalimumab, infliximab, vedolizumab treatment prior to 1 June 2018 is considered to start their first cycle as of 1 June 2018. Within the same treatment cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised adalimumab, golimumab, infliximab, tofacitinib or vedolizumab more than once. Once a patient has either failed or ceased to respond to treatment 3 times, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 5-year break in PBS-subsidised therapy before they are eligible to commence the next cycle. The 5-year break is measured from the date of the last approval for PBS-subsidised adalimumab, golimumab, infliximab, tofacitinib or vedolizumab treatment in the most recent cycle to the date of the first application for initial treatment with adalimumab, golimumab, infliximab, tofacitinib or vedolizumab under the new treatment cycle. A patient who has failed fewer than 3 trials of either adalimumab, golimumab, infliximab, tofacitinib or vedolizumab in a treatment cycle and who has a break in therapy of more than 5 years, may commence a new treatment cycle. (1) How to prescribe PBS-subsidised treatment with adalimumab, golimumab, infliximab, tofacitinib and vedolizumab after 1 June 2018. (a) Initial treatment. Applications for initial treatment should be made where: (i) an adult patient has received no prior PBS-subsidised treatment with adalimumab, golimumab, infliximab, tofacitinib or vedolizumab in this treatment cycle and wishes to commence such therapy (Initial 1 - New patient or recommencement of treatment after more than 5 years break in therapy); or (ii) an adult patient has received prior PBS-subsidised (initial or continuing) adalimumab, golimumab, infliximab, tofacitinib or vedolizumab therapy and wishes to trial an alternate agent (Initial 2 - Change or Re-commencement of treatment after a break in therapy of less than 5 years) [further details are under 'Swapping therapy' below]; or (iii) an adult patient wishes to re-commence treatment with adalimumab,

	golimumab, infliximab, tofacitinib or vedolizumab following a break in PBS-subsidised therapy with the same agent (Initial 2 - Change or Re-commencement of treatment after a break in therapy of less than 5 years). Treatment authorisations under Initial 1 and Initial 2 will be limited to provide for a maximum of 16 weeks of therapy for adalimumab, 14 weeks of therapy for golimumab, infliximab and vedolizumab. A patient must be assessed for response to a course of initial PBS-subsidised treatment following a minimum of 12 weeks of treatment for adalimumab and up to 12 weeks after the first dose (6 weeks following the third dose) for golimumab, infliximab and vedolizumab. For second and subsequent courses of PBS-subsidised biological medicine treatment, it is recommended that a patient is reviewed in the month prior to completing their current course of treatment. (b) Continuing treatment. Following the completion of an initial treatment course with adalimumab, golimumab, infliximab, tofacitinib or vedolizumab a patient may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response. It is recommended that a patient be reviewed in the month prior to completing their current course of treatment. (2) Swapping therapy. Once initial treatment with the first PBS-subsidised treatment is approved, a patient may swap if eligible to the alternate adalimumab, golimumab, infliximab, tofacitinib or vedolizumab treatment within the same treatment cycle without having to requalify with respect to the indices of disease severity (i.e. Mayo clinic score or partial Mayo clinic score), or the prior corticosteroid therapy and immunosuppressive therapy. A patient may trial an alternate treatment at any time, regardless of whether they are receiving therapy (initial or continuing) with adalimumab, golimumab, infliximab, tofacitinib or vedolizumab at the time of the application. However, they cannot swap to a particular therapy if they have failed to respond to prior treatment with that drug once within the same treatment cycle. To ensure a patient receives the maximum treatment opportunities allowed under these arrangements, it is important that they are assessed for response to every course of treatment. (3) Re-commencement of treatment after a 5-year break in PBS-subsidised therapy. A patient who wishes to trial a second or subsequent course of treatment following a break in PBS-subsidised adalimumab, golimumab, infliximab, tofacitinib or vedolizumab therapy of at least 5 years, must requalify for initial 1 treatment with respect to the scores of disease severity. A patient must have received treatment with a 5-aminosalicylate oral preparation in a standard dose for induction of remission for a minimum of 3 consecutive months, and, either azathioprine or 6-mercaptopurine for a minimum of 3 consecutive months or a tapered course of oral steroids over a 6 week period followed by an appropriately dosed thiopurine agent for a minimum of 3 consecutive months (unless intolerance develops necessitating permanent treatment

	withdrawal to these agents). These above prior treatments must have been received immediately prior to the time the scores of disease severity being used to trial a second or subsequent course are measured. (4) Patients 'grandfathered' onto PBS-subsidised treatment with golimumab. A patient who commenced treatment with golimumab for moderate to severe ulcerative colitis prior to 1 June 2018 and who continues to receive treatment at the time of application, may qualify for treatment under the initial 3 'grandfather' treatment restriction. A patient may only qualify for PBS-subsidised treatment under this criterion once. A maximum of 24 weeks of treatment will be authorised under this criterion. Following completion of the initial PBS-subsidised course, further subsidised treatment must be prescribed under the continuing treatment restriction of the relevant drug. 'Grandfather' arrangements will only apply for the first treatment cycle. For the second and subsequent cycles, a 'grandfather' patient must qualify for continuing treatment under the criteria that apply to a continuing patient.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Pfizer Australia welcomes the PBAC recommendation to list tofacitinib (Xeljanz®) on the PBS as the first oral bDMARD option for the treatment of moderate to severe ulcerative colitis, offering these patients another effective and convenient treatment alternative.