

**7.07 TOFACITINIB,
Tablet 5mg, tablet 10mg,
Xeljanz[®],
Pfizer Australia Pty Ltd**

1 Purpose of submission

- 1.1 The resubmission requested the PBAC reconsider its March 2019 recommendation for a General Schedule, Authority Required listing for tofacitinib (TOF) for the treatment of moderate to severe ulcerative colitis (MSUC), in particular PBAC's recommendation that TOF be listed on a cost-minimisation basis against the least costly alternative biologic therapy currently PBS subsidised for this condition.

The resubmission requested listing on the basis of a cost-minimisation analysis versus a weighted comparator of infliximab (IFX), vedolizumab (VDZ), golimumab (GOL) and adalimumab (ADA).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the resubmission)

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.
Comparators	<ul style="list-style-type: none"> • Infliximab 5mg/kg IV infusion at 0, 2 and 6 weeks then Q8W thereafter. • Vedolizumab IV infusion, 300 mg at 0, 2 and 6 weeks then Q8W thereafter. • Adalimumab SC injection, 160 mg at week 0, 80 mg at week 2 then 40 mg Q2W thereafter. • Golimumab SC injection, 200 mg at week 0, 100 mg at week 2, then 100 mg Q4W thereafter.
Outcomes	<p>Indirect comparison of tofacitinib and comparators was conducted for the following outcomes, for induction and maintenance therapy taking into account differences in trial design:</p> <ul style="list-style-type: none"> • 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.
Clinical claim	<ul style="list-style-type: none"> • TNFi naïve patients: Tofacitinib is non-inferior in terms of efficacy to infliximab, <u>vedolizumab</u>, <u>adalimumab</u> and <u>golimumab</u>. • TNFi experienced: Tofacitinib is superior to adalimumab, and by extension golimumab*, and non-inferior to vedolizumab in terms of efficacy. <p>Tofacitinib is non-inferior to infliximab*, vedolizumab, adalimumab and golimumab in terms of safety, for both TNFi naïve and TNFi experienced patients.</p>

Source: Table 1.1.1, p3 of March 2019 submission; p75 of the resubmission.

Abbreviations: Q2W = once every 2 weeks; Q4W = once every 4 weeks; Q8W = once every 8 weeks; TNFi = tumour necrosis factor inhibitor. Shaded areas indicate data previously seen by the PBAC; Underlining refers to changes from the March 2019 submission.

*All the included infliximab and golimumab trials excluded patients with prior exposure to TNFi.

2 Background

Registration status

- 2.1 TOF was approved in September 2019 by the TGA for the following indication: treatment of adult patients with moderately to severely active ulcerative colitis (MSUC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.
- 2.2 In October 2019, the Product Information (PI) and Consumer Medicine Information (CMI) documents for TOF were updated to include information about an increased risk of blood clots and of death with the higher dose of TOF 10 mg twice daily¹, in response to results from an ongoing safety study of patients at least 50 years of age, with at least one additional cardiovascular risk factor.
- 2.3 TOF is currently PBS listed for the treatment of severe active rheumatoid arthritis (RA), and psoriatic arthritis (PsA).

¹ <https://www.tga.gov.au/alert/tofacitinib>

Previous PBAC consideration

- 2.4 A major submission requesting listing for MSUC was recommended by PBAC at the March 2019 PBAC meeting.
- 2.5 In March 2019, the PBAC considered that any of the currently listed agents for MSUC (IFX, VDZ, ADA and GOL) could be considered an alternative therapy to TOF for the treatment of MSUC, and recommended listing on a cost-minimisation basis with the least costly biologic therapy, which the resubmission identified as ADA on the basis of advice it received from the Department subsequent to the March 2019 recommendation.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Comparator	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 addition, the PBAC accepted any of the current PBS listed biologic therapies for MSUC could be an alternative therapy to TOF (Para 7.1, March 2019 PSD).	The resubmission nominated IFX, VDZ, ADA and GOL as the comparators, and presented a cost-minimisation analysis versus a weighted comparator of IFX, VDZ, ADA and GOL.
Clinical effectiveness	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 (Para 7.6, March 2019 PSD).	The resubmission claimed a significant improvement in efficacy for TOF compared to ADA and, by extension, GOL in TNFi experienced patients. The resubmission did not apply this superiority claim to a cost-effectiveness analysis, nor does the requested listing reflect a listing scenario that separates patients by prior TNFi treatment status.
Financial estimates	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 of TOF for MSUC should be cost-neutral to the PBS (Para 7.7, March 2019 PSD)	The resubmission presented a cost-minimisation analysis versus a weighted comparator of IFX, VDZ, ADA and GOL, and the resultant financial estimates showed cost savings to the Government of over \$█ million by Year 6 of listing.

Source: constructed during the evaluation based on the March 2019 Public Summary Document (PSD); TNFi = tumour necrosis factor inhibitor

The redacted value correspond to the following range:

1\$0 to <\$10 million

3 Requested listing

- 3.1 The Sponsor requested several restrictions for TOF 10 mg and TOF 5 mg to provide for initial treatment (1&2), continuing treatment, and grandfathered patients. The requested restrictions are the same as those recommended by the PBAC in the March 2019 consideration (para 8.1, TOF Public Summary Document (PSD), March 2019 PBAC Meeting). The requested restrictions were generally similar to that of currently PBS listed bDMARDs for MSUC. Below is an abbreviated version of the restrictions for Initial 1 and Continuing treatment.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TOFACITINIB 5 mg tablet	56	2 (induction) 5 (maintenance)	\$ [REDACTED] (Published) \$ [REDACTED] (Effective)	Xeljanz® Pfizer Australia
TOFACITINIB 10 mg tablet	56	3 (induction) 5 (maintenance)	\$ [REDACTED] (Published) \$ [REDACTED] (Effective)	Xeljanz® Pfizer Australia

Category / Program:	GENERAL – General Schedule (Section 85)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
PBS Indication:	Moderate to severe ulcerative colitis
Treatment phase:	Initial 1
Restriction:	<input checked="" type="checkbox"/> 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 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. A maximum of 16 weeks of treatment with this drug will be approved under this criterion. <u>The recommended dose is 10 mg twice daily for at least 8 weeks followed by 5 mg twice daily.</u>
Treatment phase:	Continuing
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
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: pp.22-29 of the March 2019 submission; Submission Summary Folder attached to the resubmission.

^a Requested DPMQs based on Table 3.4.11 of the submission.

3.2 The resubmission requested a Special Pricing Arrangement (SPA). The proposed published prices (DPMQ) for TOF 10 mg and TOF 5 mg are \$ [REDACTED] and \$ [REDACTED] respectively, per 56 tablets. The proposed effective prices (DPMQ) for both TOF 10 mg and TOF 5 mg are \$ [REDACTED].

3.3 The requested effective price is the same for both the 5 mg and 10 mg strengths, which represents a 13% decrease from the requested price in March 2019 for the 5 mg strength (\$ [REDACTED]) and a 40% decrease for the 10 mg strength (\$ [REDACTED]).

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

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. 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. Other PBS listed drugs for MSUC are:
- Tumour necrosis factor inhibitors (TNFi) - ADA, GOL and IFX
 - Integrin receptor antagonist – VDZ.
- 4.3 A key difference of TOF to the comparator drugs is that it is given orally whereas IFX and VDZ are administered by intravenous infusion (IV), and ADA and GOL are administered via subcutaneous injection (SC). The Pre-PBAC Response noted TOF represented a new therapeutic class for MSUC and argued there was a clinical need for additional treatments with new mechanisms of action available for patients.

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

5 Comparator

- 5.1 The resubmission nominated IFX, VDZ, ADA and GOL as a mixed comparator, and noted that IFX and VDZ are most widely prescribed in both the first- and later-line treatment of MSUC. The March 2019 submission nominated IFX as the main comparator. The PBAC previously recommended listing of TOF for MSUC on a cost-minimisation basis against 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 (paragraph 7.1, TOF PSD, March 2019 PBAC meeting).
- 5.2 The resubmission contended that TOF, due to its alternative mechanism of action, is a valuable alternative to VDZ for patients who have failed prior TNFi treatment.
- 5.3 The resubmission provided extensive discussion around the choice of comparator, specifically in a situation where there are a number of different alternative therapies which may have different prices. The resubmission stated (p13) that the PBAC's approach has been that new, non-inferior or therapeutically equivalent products should be based on a comparison with the price of the lowest cost product in a basket of products that have been considered by the PBAC to be either non-inferior or therapeutically equivalent to each other, regardless of the market share, or clinical utility/use of that lowest cost product. The resubmission added that the PBAC has defended this approach by referring to Section 101(3B) of the *National Health Act 1953* ('The Act'), which states that "where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is

substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee ... shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies.”

- 5.4 The resubmission stated (p13) that the Act did not provide a definition of the term ‘the alternative therapy or therapies’, and did not require this to be the therapy(ies) most likely to be replaced, which corresponds to the definition of comparator in the PBAC Guidelines, nor does it require it to be the lowest cost available therapy(ies). The Pre-Sub-Committee Response (PSCR) reiterated the Sponsor’s view that the PBAC Guidelines state the selection of comparators should be based on the current alternative therapies in Australia, and the therapies most likely to be replaced in clinical practice.
- 5.5 The PBAC noted that the “Key Factors Influencing PBAC Decision Making” section of the PBAC guidelines explicitly states that “PBAC is required, under the Act, to consider the effectiveness and cost of the proposed medicine compared with **existing therapies** [emphasis added]. PBAC therefore reaffirmed its previous advice that all biological therapies currently PBS listed for MSUC were potential alternative therapies.
- 5.6 To recommend TOF at a higher price than any less costly alternative, the PBAC must be satisfied, at a minimum, that TOF, for some patients, provides such a ‘significant improvement’ over that alternative therapy.
- 5.7 The PSCR and Pre-PBAC Response argued a weighted comparator approach was selected because a cost minimisation approach to the least costly comparator previously relied upon by the PBAC places no value on innovative advances in MSUC treatment, such as therapeutic agents with new mechanisms of action. The Pre-PBAC Response also argued that TOF provides, for some patients (namely in induction for those who are TNFi experienced) a significant improvement in efficacy over ADA (and by extension over GOL).
- 5.8 The PBAC noted the approach taken by the submission to separate the MSUC population into TNFi naïve and TNFi experienced patients was inconsistent with both the requested listing and the manner in which other biologic therapies for MSUC are PBS listed. Further, the submission did not identify any specific population(s) that could not use one or more of the potential alternative treatments; therefore, the PBAC considered the submission’s weighted comparator approach was not adequately justified.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (50), health care professionals (13) and Crohn's and Colitis Australia via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with TOF including improved symptom control, the ability to avoid life-changing surgery for ulcerative colitis, and the benefits of an oral therapy over the current intravenous or subcutaneous injection options. The PBAC specifically noted the advice from health care professionals and Crohn's and Colitis Australia that cited patient experiences of TOF being an effective treatment option when other biologics have failed and being useful for patients in rural and remote areas.

Clinical trials

6.3 There were no head-to-head trials of TOF vs. any of the alternative therapies for the treatment of MSUC. The resubmission presented a series of indirect comparisons using data from 17 randomised placebo-controlled trials:

- TOF vs. placebo (PBO) (three RCTs): OCTAVE 1, OCTAVE 2, OCTAVE sustain;
- IFX vs. PBO (five RCTs): ACT 1, ACT 2, Jiang 2015, REMICADE, Kobayashi 2018;
- GOL vs PBO (three RCTs): PURSUIT-SC, PURSUIT-M, PURSUIT-J;
- ADA vs. PBO (three RCTs): ULTRA 1, ULTRA 2, Suzuki 2014;
- VDZ vs. PBO (three RCTs): GEMINI-1, Motoya 2019, Sandborn 2020.

Two new trials of VDZ versus PBO (Motoya 2019, Sandborn 2020) were added in this resubmission and the PBAC had not previously considered data from these two trials.

6.4 Details of the trials presented in the resubmission are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

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.	<i>N Engl J Med.</i> 2017; 376 (18): 1723-1736
Infliximab trials		

Trial ID	Protocol title/ Publication title	Publication citation
ACT 1	Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis.	<i>N Engl J Med.</i> 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.	<i>J Clin Gastroenterol.</i> 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.	<i>J Gastroenterol</i> 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.	<i>Gut.</i> 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.	<i>Gastroenterology.</i> 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.	<i>J Gastroenterol.</i> 2014; 49:283-294.
Golimimumab 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	<i>Gastroenterology.</i> 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.	<i>Gastroenterology.</i> 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).	<i>J Gastroenterol.</i> 2017: 52(10):1101-1111
Vedolizumab trials		
GEMINI 1	Feagan B, Rutgeerts P, Sands B, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis.	<i>N Engl J Med.</i> 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.	<i>Clin Gastroenterol Hepatol.</i> 2017 Feb;15(2):229-239.e5.
Motoya 2019	Motoya S, Watanabe K, Ogata H, et al. Vedolizumab in Japanese patients with ulcerative colitis: A phase 3, randomized, double-blind, placebo-controlled study.	<i>PLOS ONE</i> February 2019; 14(2): e0212989.
Sandborn 2020	Sandborn W, Baert F, Danese S, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis.	<i>Gastroenterology</i> 2020; 158: 562-572.

Source: Table 2.2.1-2.2.5, pp. 25-30 of the resubmission.
Shaded areas indicate data previously seen by the PBAC.

6.5 The key features of the trials are summarised in Table 4.

Table 4: Key features of the included evidence

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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	1 ^{ary} : remission
OCTAVE 2 [Induction]	541		Low	TNFi-n & TNFi-e	2 ^{ary} : clinical remission, clinical response, mucosal healing
OCTAVE SUSTAIN [maintenance]	593	P3, MC, R, PC, DB (52wk), RWD, 3-arm.	High	Wk 8 responders in OCTAVE 1,2	1 ^{ary} : remission 2 ^{ary} : 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	1 ^{ary} : clinical response 2 ^{ary} : 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	1 ^{ary} : clinical response 2 ^{ary} : clinical remission, mucosal healing
Jiang 2015 [induction & maintenance]	123	MC, R, PC, DB (30wk), 3-arm	Low*	TNFi-n (Chinese)	1 ^{ary} : clinical response 2 ^{ary} : clinical remission, mucosal healing
REMICADE [induction & maintenance]	99	P3, MC, R, PC, DB (26wk)	Low*	Prior TNFi NR (Chinese)	1 ^{ary} : clinical response 2 ^{ary} : 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	1 ^{ary} : clinical response 2 ^{ary} : 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	1 ^{ary} : clinical response 2 ^{ary} : 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	1 ^{ary} : sustained clinical response 2 ^{ary} : 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	1 ^{ary} : sustained clinical response 2 ^{ary} : sustained clinical remission, sustained mucosal healing
ADA v PBO					
ULTRA 1 [induction]	390	P3, MC, R, PC, DB (8wk)	Low	TNFi-n	1 ^{ary} : clinical remission 2 ^{ary} : clinical response, mucosal healing
ULTRA 2 [induction & maintenance]	494	P3, MC, R, PC, DB (52wk)	Low*	TNFi-n & TNFi-e	1 ^{ary} : clinical remission 2 ^{ary} : clinical response, mucosal healing, IBDQ response, sustained clinical 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)	1 ^{ary} : clinical remission 2 ^{ary} : clinical response, mucosal healing
VDZ v PBO					
GEMINI 1 [induction & maintenance]	IP Ct1: 374 IP Ct2:	P3, MC, R, DB (58wk), RWD for maintenance (6wk induction, 52wk maintenance),	Low*	TNFi-n & TNFi-e Maintenance:	1 ^{ary} : clinical response

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
	521 MP: 373	3-arm. Cohort 1 - randomised induction. Cohort 2- OL induction.		Wk6 active responders in cohort 1 and 2.	2 ^{ary} : clinical remission, mucosal healing, sustained clinical response, sustained clinical remission, corticosteroid-free remission
Motoya 2019	246	P3, MC, R, DB, RWD for maintenance (10wk induction, 60wk maintenance). Randomised induction.	Low*	TNFi-n & TNFi-e	1 ^{ary} : clinical response 2 ^{ary} : clinical remission, mucosal healing
Sandborn 2020	383	P3, MC, R, DB, RWD for maintenance (6wk induction, 52wk maintenance). OL induction.	Low*	TNFi-n & TNFi-e	1 ^{ary} : clinical remission 2 ^{ary} : mucosal healing, sustained clinical response, sustained clinical remission, corticosteroid-free remission

Source: Compiled during the evaluation based on source reports and publications.

Shaded areas indicate data previously seen by the PBAC.

Abbreviations: ADA=adalimumab, bid=twice a day, DB=double blind; IFX=infliximab, IP=induction phase; MC=multi-centre; MP=maintenance phase; OL=open label; P3 = phase three; PC= placebo controlled R=randomised, RWD=randomised withdrawal design; TOF=tofacitinib, TNFi-e=tumour necrosis factor inhibitor experience, TNFi-n= tumour necrosis factor inhibitor naïve, VDZ=vedolizumab.

* 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.

6.6 The trials differed considerably by trial design:

- 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);
- Two trials investigated induction and then maintenance in responders to induction therapy using a randomised withdrawal design for maintenance therapy (GEMINI 1, Motoya 2019); and
- Four 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, Sandborn 2020).

6.7 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.

Comparative effectiveness

6.8 The clinically relevant outcomes were clinical remission and clinical response, as assessed using the Mayo score. Clinical remission was defined in the TOF trials as total Mayo score of ≤ 2 points with no individual subscore >1 point. Clinical response was defined in the trial 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.

6.9 The resubmission presented a series of indirect comparisons between TOF and all alternative therapies for induction and maintenance therapy using placebo as the common reference. Analyses were presented for the ITT population and for TNFi naïve and TNFi experienced subgroups.

- 6.10 To improve comparability across outcomes and trials, the following is detailed below: i) results for “clinical remission” 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, Week 6 and 52 in GEMINI-1 and Sandborn 2020, and Week 10 and 60 in Motoya 2019).
- 6.11 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. Indirect comparisons between TOF and IFX or ADA for maintenance therapy are not presented due to differences in trial design that favoured TOF.

Table 5: Clinical remission at Weeks 6/8/10 – induction therapy (relevant arms only)#

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI) ^a	RD (95% CI) ^a	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 (1.46, 5.95)	0.12 (0.08, 0.16)	8 (6, 12.5)
Meta, TNFi-n	100/417 (23.7)	13/104 (12.5)	1.86 (1.09, 3.18)	0.12 (0.05, 0.19)	8 (5, 20)
Meta, TNFi-e	60/488 (12.3)	1/130 (0.8)	10.25 (2.05, 51.19)	0.12 (0.08, 0.15)	8 (7, 12.5)
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)	2.72 (1.90, 3.88)	0.20 (0.12, 0.29)	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)	1.58 (1.05, 2.40)	0.05 (0.00, 0.11)	17 (10, 50)
Meta, TNFi-n	65/370 (17.5)	39/371 (10.5)	1.62 (1.02, 2.57)	0.06 (-0.01, 0.13)	14 (8, 50)
VDZ v PBO (Wk 6, 10)^b					
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)	NS
Motoya 2019, ITT	30/164 (18.3)	10/82 (12.2)	1.50 (0.77, 2.92)	0.06 (-0.03, 0.15)	NS
Motoya 2019, TNFi-n	22/79 (27.8)	6/41 (14.6)	1.90 (0.84, 4.32)	0.13 (-0.01, 0.28)	NS
Motoya 2019, TNFi-e*	8/85 (9.4)	4/41 (9.8)	0.96 (0.31, 3.02)	0.00 (-0.11, 0.11)	NS
Meta, ITT	68/389 (17.5)	18/231 (7.8)	2.14 (1.03, 4.43)	0.10 (0.05, 0.15)	10 (7, 20)
Meta, TNFi-n	52/209 (24.9)	11/117 (9.4)	2.51 (1.37, 4.60)	0.16 (0.08, 0.23)	6 (4, 13)
Meta, TNFi-e*	16/167 (9.6)	6/104 (5.8)	1.54 (0.50, 4.76)	0.04 (-0.02, 0.11)	NS
Indirect comparisons, ITT					
TOF (Meta ITT) v IFX (Meta ITT)			1.09 (0.49, 2.39)	-0.08 (-0.17, 0.01)	NS
TOF (Meta ITT) v IFX (Meta ITT/TNFi-n ACT1/2)			0.79 (0.27, 2.31)	-0.14 (-0.22, -0.06)	7 (4.5, 17)#
TOF (Meta ITT) v GOL (PURSUIT-SC ITT/TNFi-n)			1.06 (0.44, 2.57)	0.01 (-0.06, 0.08)	NS
TOF (Meta ITT) v ADA (Meta ITT)			1.87 (0.83, 4.22)	0.07 (0.002, 0.14)	14 (7, 502)
TOF (Meta ITT) v VDZ (Meta ITT)			1.38 (0.50, 3.80)	0.02 (-0.04, 0.08)	NA
Indirect comparisons, TNFi-n					
TOF (Meta TNFi-n) v IFX (Meta ITT/TNFi-n)			0.68 (0.36, 1.30)	-0.08 (-0.19, 0.03)	NS
TOF (Meta TNFi-n) v IFX (Meta ITT/TNFi-n ACT1/2)			0.50 (0.19, 1.32)	-0.14 (-0.24, -0.04)	7 (4, 25)#
TOF (Meta TNFi-n) v GOL (Meta ITT/TNFi-n)			0.67 (0.31, 1.43)	0.01 (-0.08, 0.10)	NS
TOF (Meta TNFi-n) v ADA (Meta TNFi-n)			1.15 (0.57, 2.33)	0.06 (-0.04, 0.16)	NS
TOF (Meta TNFi-n) v VDZ (Meta TNFi-n)			0.74 (0.33, 1.66)	-0.04 (-0.14, 0.06)	NS
Indirect comparisons, TNFi-e					
TOF (Meta TNFi-e) v ADA (ULTRA 2, TNFi-e)			7.71 (1.19, 49.96)	0.10 (0.02, 0.18)	10 (6, 50)
TOF (Meta TNFi-e) v VDZ (TNFi-e failure)			6.66 (0.93, 47.45)	0.08 (0.006, 0.15)	13 (7, 167)

Source: Tables 2.5.1, 2.5.3, 2.5.7, 2.5.9, pp.38-45 of resub. Shaded areas: data previously seen by the PBAC. Italics: results estimated during the evaluation. Blue line crossing zero. Bold typography: statistically significant. 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 naive, TNFi-e=TNFi exposed, VDZ=vedolizumab. ^a The more conservative primary outcome of remission was used by the submission. ^b GEMINI & Motoya 2019 outcomes at Week 6 & Week 10 respectively. ^a random effects meta-analysis using RevMan Ver5.4. *TNFi exposed+failure, TNFi exposed without failure were excluded. # Note that the redacted results presented in Table 5 were conducted during the evaluation specifically for the purposes of informing the PBAC consideration at the March 2019 PBAC meeting.

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Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 6: Clinical response at Weeks 6/8/10 – induction therapy (relevant arms only)#

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI) ^a	RD (95% CI) ^a	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	147/222 (66.2)	28/57 (49.1)	1.35 (1.02, 1.78)	0.17 (0.03, 0.31)	6 (3, 33)
OCTAVE 1, TNFi-e	138/254 (54.3)	12/65 (18.4)	2.94 (1.74, 4.97)	0.36 (0.25, 0.47)	3 (2, 4)
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	120/195 (61.5)	15/47 (31.9)	1.93 (1.25, 2.97)	0.30 (0.15, 0.45)	3 (2, 7)
OCTAVE 2, TNFi-e	116/234 (49.5)	17/65 (26.1)	1.90 (1.23, 2.91)	0.23 (0.11, 0.36)	4 (3, 9)
Meta, ITT	521/905 (57.5)	72/234 (30.7)	1.87 (1.53, 2.28)	0.27 (0.20, 0.33)	4 (3, 5)
Meta, TNFi-n	267/417 (64.0)	43/104 (41.3)	1.55 (1.09, 2.21)	0.23 (0.11, 0.35)	4 (3, 8)
Meta, TNFi-e	254/488 (52.0)	29/130 (22.3)	2.30 (1.49, 3.55)	0.30 (0.18, 0.42)	3 (3, 5)
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)	1.86 (1.61, 2.15)	0.30 (0.23, 0.37)	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)	1.36 (1.18, 1.58)	0.14 (0.08, 0.20)	7 (5, 12.5)
Meta, TNFi-n	205/370 (55.4)	148/371 (39.8)	1.38 (1.18, 1.61)	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)
Motoya 2019, ITT	65/164 (39.6)	27/82 (32.9)	1.20 (0.84, 1.73)	0.07 (-0.06, 0.19)	NS
Motoya 2019, TNFi-n	42/79 (53.2)	15/41 (36.6)	1.45 (0.92, 2.29)	0.17 (-0.02, 0.35)	NS
Motoya 2019, TNFi-e	23/85 (27.1)	12/41 (29.3)	0.92 (0.51, 1.67)	-0.02 (-0.19, 0.15)	NS
Meta, ITT	171/389 (44.0)	65/231 (28.1)	1.51 (0.99, 2.29)	0.15 (0.00, 0.29)	NS
Meta, TNFi-n	111/209 (53.1)	35/117 (29.9)	1.74 (1.26, 2.40)	0.23 (0.13, 0.34)	4 (3, 8)
Meta, TNFi-e	55/167 (32.9)	25/104 (24.0)	1.33 (0.66, 2.69)	0.09 (-0.12, 0.29)	NS
Indirect comparisons, ITT					
TOF (Meta ITT) v IFX (Meta ITT)			1.01 (0.79, 1.29)	-0.03 (-0.13, 0.07)	NS
TOF (Meta ITT) v IFX (Meta ITT/TNFi-n ACT1/2)			0.93 (0.70, 1.23)	-0.07 (-0.18, 0.04)	NS
TOF (Meta ITT) v GOL (PURSUIT-SC ITT/TNFi-n)			1.11 (0.83, 1.50)	0.06 (-0.05, 0.17)	NS
TOF (Meta ITT) v ADA (Meta ITT)			1.38 (1.07, 1.76)	0.13 (0.04, 0.22)	8 (4.5, 25)
TOF (Meta ITT) v VDZ (Meta ITT)			1.24 (0.78, 1.97)	0.12 (-0.04, 0.28)	NS
Indirect comparisons, TNFi-n					
TOF (Meta TNFi-n) v IFX (Meta ITT/TNFi-n)			0.83 (0.57, 1.22)	-0.07 (-0.21, 0.07)	NS
TOF (Meta TNFi-n) v IFX (Meta ITT/TNFi-n ACT1/2)			0.77 (0.51, 1.15)	-0.11 (-0.26, 0.04)	NS
TOF (Meta TNFi-n) v GOL (Meta ITT/TNFi-n)			0.92 (0.61, 1.40)	0.02 (-0.13, 0.17)	NS
TOF (Meta TNFi-n) v ADA (Meta TNFi-n)			1.12 (0.76, 1.65)	0.08 (-0.06, 0.22)	NS
TOF (Meta TNFi-n) v VDZ (Meta TNFi-n)			0.89 (0.55, 1.44)	0.00 (-0.16, 0.16)	NS
Indirect comparisons, TNFi-e					
TOF (Meta TNFi-e) v ADA (ULTRA 2, TNFi-e)			1.80 (1.00, 3.24)	0.22 (0.04, 0.40)	4.5 (3, 25)
TOF (Meta TNFi-e) v VDZ (TNFi-e failure)			1.73 (0.76, 3.95)	0.21 (-0.03, 0.45)	NS

Source: Tables 2.5.2, 2.5.4, 2.5.8, 2.5.10, pp.39-45 of resub. Shaded areas: data previously seen by the PBAC. Italics: results estimated during the evaluation. Bold typography indicates statistically significant differences. Blue line crossing zero. ^aestimated during the evaluation using random effects meta-analysis using RevMan Version 5.4. 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 naive, TNFi-e=TNFi exposed, VDZ=vedolizumab *TNFi exposed+failure, TNFi exposed without failure were excluded. # Note that the redacted results presented in Table 6 were conducted

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during the evaluation specifically for the purposes of informing the PBAC consideration at the March 2019 PBAC meeting. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 7: Sustained remission / clinical remission at 52/54/60 wks – maintenance therapy (relevant arms)#

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI) ^a	RD [95% CI] ^a	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	26/108 (24.1)	4/106 (3.8)	6.38 (2.31, 17.66)	0.20 (0.11, 0.29)	5 (3, 9)
OCTAVE S, 5mg TNFi-e	18/90 (20.0)	6/92 (6.5)	3.07 (1.28, 7.37)	0.13 (0.04, 0.23)	8 (4, 25)
OCTAVE S, 10mg TNFi-n	32/96 (33.3)	4/106 (3.8)	8.83 (3.24, 24.06)	0.30 (0.19, 0.40)	3 (2.5, 5)
OCTAVE S, 10mg TNFi-e	18/101 (17.8)	6/92 (6.5)	2.73 (1.13, 6.59)	0.11 (0.02, 0.20)	9 (5, 50)
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	58/204 (28.4)	4/106 (3.8)	7.53 (2.81, 20.19)	0.25 (0.17, 0.32)	4 (3, 6)
Pooled 5/10mg TNFi-e	36/191 (18.8)	6/92 (6.5)	2.89 (1.26, 6.61)	0.12 (0.05, 0.20)	8 (5, 20)
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)	3.22 (0.76, 13.63)	0.27 (-0.04, 0.57)	NS
VDZ v PBO (Wk 6/10&52/60^a)					
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)
Sandborn 2020, ITT	9/54 (16.7)	3/56 (5.4)	3.11 (0.89, 10.88)	0.11 (0.00, 0.23)	NS
Motoya 2019, ITT	11/41 (26.8)	7/42 (16.7)	1.61 (0.69, 3.74)	0.10 (-0.07, 0.28)	NS
Motoya 2019, TNFi-n	8/24 (33.3)	6/28 (21.4)	1.56 (0.63, 3.85)	0.12 (-0.12, 0.36)	NS
Motoya 2019, TNFi-e	3/17 (17.6)	1/14 (7.1)	2.47 (0.29, 21.21)	0.11 (-0.12, 0.33)	NS
Pooled ITT	45/217 (20.7)	21/224 (9.4)	2.16 (1.34, 3.50)	0.11 (0.05, 0.18)	9 (6, 20)
Pooled TNFi-n	24/96 (25.0)	16/107 (15.0)	1.68 (0.95, 2.95)	0.10 (-0.01, 0.21)	NS
Pooled TNFi-e	12/60 (20.0)	2/52 (3.8)	4.60 (1.06, 20.03)	0.16 (0.05, 0.28)	6 (4, 20)
Indirect comparisons ITT					
TOF 5mg v GOL (Meta)			1.37 (0.28, 6.67)	-0.10 (-0.41, 0.21)	NS
TOF 10mg v GOL (Meta)			1.56 (0.32, 7.61)	-0.07 (-0.38, 0.24)	NS
TOF 5/10mg (Pooled) v GOL (Meta)			1.46 (0.30, 7.06)	-0.08 (-0.39, 0.23)	NS
TOF 5mg v VDZ (ITT)			2.04 (0.90, 4.60)	0.06 (-0.04, 0.15)	NS
TOF 10mg v VDZ (ITT)			2.33 (1.04, 5.23)	0.09 (-0.00, 0.18)	NS
TOF 5/10mg (Pooled) v VDZ (ITT)			2.18 (0.99, 4.81)	0.08 (-0.00, 0.16)	NS
Indirect comparisons, TNFi-n					
TOF/TNFi-n 5mg v GOL (Meta)			1.98 (0.34, 11.58)	-0.07 (-0.39, 0.25)	NS
TOF/TNFi-n 10mg v GOL (Meta)			2.74 (0.47, 15.90)	0.03 (-0.29, 0.35)	NS
TOF/TNFi-n 5/10mg (Pooled) v GOL (Meta)			2.34 (0.41, 13.43)	-0.02 (-0.33, 0.29)	NS
TOF/TNFi-n 5mg v VDZ (Pooled)			3.80 (1.19, 12.17)	0.10 (-0.04, 0.24)	NS
TOF/TNFi-n 10mg v VDZ (Pooled)			5.26 (1.66, 16.62)	0.20 (0.05, 0.35)	5 (3, 20)
TOF/TNFi-n 5/10mg (Pooled) v VDZ (Pooled)			4.48 (1.44, 13.98)	0.15 (0.02, 0.28)	7 (4, 50)
Indirect comparisons, TNFi-e					
TOF/TNFi-e 5mg v VDZ (Pooled)			0.67 (0.12, 3.69)	-0.03 (-0.18, 0.12)	NS
TOF/TNFi-e 10mg v VDZ (Pooled)			0.59 (0.11, 3.29)	-0.05 (-0.20, 0.10)	NS
TOF/TNFi-e 5/10mg (Pooled) v VDZ (Pooled)			0.63 (0.12, 3.40)	-0.04 (-0.18, 0.10)	NS

Source: Table 2.5.3 of March 2019 Commentary; Sandborn 2020 publication. Shaded areas: data previously seen by the PBAC. Italics: results estimated during the evaluation. Bold typography indicate statistically significant differences. Blue line crossing zero. 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 naive, VDZ=vedolizumab. *TNFi exposed+failure, TNFi exposed without failure were excluded. * Sustained remission, as reported in the submission and OCTAVE Sustain ^aestimated during the evaluation using random effects meta-analysis using RevMan Version 5.4. ^a GEMINI measured outcomes at Week 6 for induction and Week 52 for maintenance; Motoya 2019 measured outcomes at Week 10 for induction and Week 60 for maintenance. # Note that the redacted results presented in Table 7 were conducted during the evaluation specifically for the purposes of informing the PBAC consideration at the March 2019 PBAC meeting. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 8: Sustained Clinical response at 52/54/60 Weeks – maintenance therapy (relevant arms only)#

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI) ^a	RD [95% CI] ^a	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	57/108 (52.8)	25/106 (23.6)	2.24 (1.52, 3.29)	0.29 (0.17, 0.42)	3 (2, 6)
OCTAVE S, 5mg TNFi-e	40/90 (44.4)	13/92 (14.1)	3.15 (1.81, 5.47)	0.30 (0.18, 0.43)	3 (3, 4)
OCTAVE S, 10mg TNFi-n	60/96 (62.5)	25/106 (23.6)	2.65 (1.82, 3.86)	0.39 (0.26, 0.52)	3 (2, 4)
OCTAVE S, 10mg TNFi-e	57/101 (56.4)	13/92 (14.1)	3.99 (2.35, 6.80)	0.42 (0.30, 0.54)	2 (2, 3)
Pooled 5/10mg ITT	214/395 (54.2)	38/198 (19.2)	2.82 (2.09, 3.81)	0.35 (0.28, 0.42)	3 (2, 4)
Pooled 5/10mg TNFi-n	117/204 (57.3)	25/106 (23.6)	2.43 (1.69, 3.49)	0.34 (0.23, 0.44)	3 (2, 4)
Pooled 5/10mg TNFi-e	97/191 (50.8)	13/92 (14.1)	3.59 (2.13, 6.06)	0.37 (0.27, 0.47)	3 (2, 4)
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)	1.92 (1.11, 3.32)	0.25 (0.08, 0.42)	4.5 (3, 8)
VDZ v PBO (Wk 6/10&52/60^a)					
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)
Sandborn 2020, ITT	39/54 (72.2)	16/56 (28.6)	2.53 (1.62, 3.95)	0.44 (0.27, 0.60)	2 (2, 4)
Motoya 2019, ITT	27/41 (65.9)	15/42 (35.7)	1.84 (1.16, 2.93)	0.30 (0.10, 0.51)	3 (2, 10)
Motoya 2019, TNFi-n	16/24 (66.7)	10/28 (35.7)	1.87 (1.05, 3.31)	0.31 (0.05, 0.57)	3 (2, 20)
Motoya 2019, TNFi-e	11/17 (64.7)	5/14 (35.7)	1.81 (0.83, 3.97)	0.29 (-0.05, 0.63)	NS
Pooled ITT	135/217 (62.2)	61/224 (27.2)	2.26 (1.79, 2.86)	0.35 (0.27, 0.44)	3 (2, 4)
Pooled TNFi-n	63/96 (65.6)	31/107 (29.0)	2.24 (1.61, 3.12)	0.37 (0.24, 0.50)	3 (2, 4)
Pooled TNFi-e	31/60 (51.7)	11/52 (21.2)	2.30 (1.31, 4.03)	0.30 (0.14, 0.47)	3 (2, 7)
Indirect comparisons ITT					
TOF 5mg v GOL (Meta)			1.33 (0.71, 2.50)	0.05 (-0.14, 0.24)	NS
TOF 10mg v GOL (Meta)			1.61 (0.86, 3.02)	0.15 (-0.04, 0.34)	NS
TOF 5/10mg (Pooled) v GOL (Meta)			1.47 (0.79, 2.74)	0.10 (-0.08, 0.28)	NS
TOF 5mg v VDZ (ITT)			1.13 (0.76, 1.67)	-0.05 (-0.17, 0.07)	NS
TOF 10mg v VDZ (ITT)			1.37 (0.93, 2.02)	0.05 (-0.07, 0.17)	NS
TOF 5/10mg (Pooled) v VDZ (ITT)			1.25 (0.85, 1.83)	0.00 (-0.11, 0.11)	NS
Indirect comparisons, TNFi-n					
TOF/TNFi-n 5mg v GOL (Meta)			1.17 (0.60, 2.28)	0.04 (-0.17, 0.25)	NS
TOF/TNFi-n 10mg v GOL (Meta)			1.38 (0.71, 2.68)	0.14 (-0.07, 0.35)	NS
TOF/TNFi-n 5/10mg (Pooled) v GOL (Meta)			1.27 (0.66, 2.44)	0.09 (-0.11, 0.29)	NS
TOF/TNFi-n 5mg v VDZ (Pooled)			1.00 (0.60, 1.66)	-0.10 (-0.29, 0.09)	NS
TOF/TNFi-n 10mg v VDZ (Pooled)			1.18 (0.72, 1.95)	0.00 (-0.19, 0.19)	NS
TOF/TNFi-n 5/10mg (Pooled) v VDZ (Pooled)			1.09 (0.66, 1.77)	-0.03 (-0.20, 0.14)	NS
Indirect comparisons, TNFi-e					
TOF/TNF-e-n 5mg v VDZ (Pooled)			1.37 (0.62, 3.01)	0.00 (-0.21, 0.21)	NS
TOF/TNF-e-n 10mg v VDZ (Pooled)			1.74 (0.80, 3.76)	0.12 (-0.08, 0.32)	NS
TOF/TNF-e-n 5/10mg (Pooled) v VDZ (Pooled)			1.56 (0.73, 3.36)	0.07 (-0.12, 0.26)	NS

Source: Table 2.5.4 of March 2019 Commentary; Sandborn 2020 publication. Shaded areas: data previously seen by the PBAC. Blue line crossing zero.

^a estimated during the evaluation using random effects meta-analysis using RevMan Version 5.4.

^a GEMINI measured outcomes at Week 6 for induction and Week 52 for maintenance; Motoya 2019 measured outcomes at Week 10 for induction and Week 60 for maintenance.

Note that the redacted results presented in Table 8 were conducted during the evaluation specifically for the purposes of informing the PBAC consideration at the March 2019 PBAC meeting. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.12 The PSCR argued the TNFi naïve and experienced subgroup analyses were relevant to meeting the requirement of the Act to establish a population for whom TOF provides a significant improvement in efficacy or reduction in toxicity over the alternative therapies; specifically that TOF is more effective than ADA in TNFi experienced patients in achieving remission. The pre-PBAC Response also argued that as the evidence supported a conclusion that TOF is of non-inferior comparative efficacy to IFX in induction, it should follow that as ADA and GOL have previously been considered inferior to IFX in this treatment phase, TOF is also of superior comparative efficacy to these agents.
- 6.13 The PBAC considered the more appropriate analyses were those presented for the ITT population given both the requested listing for TOF and the current biologic therapy listings for MSUC are line-agnostic and allow for any sequence of therapies within a treatment cycle.

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

Comparative harms

- 6.14 The resubmission did not present a formal indirect comparison between TOF and any of the relevant alternative therapies for safety outcomes, due to differences in trial methodologies. The PBAC previously considered the claim of non-inferior comparative safety to IFX was uncertain but may be reasonable. The PBAC also previously considered the evidence presented did not support a conclusion that TOF provided a significant reduction in toxicity compared to any of the currently listed biologics for MSUC (paragraph 7.6, TOF PSD, March 2019 PBAC meeting).
- 6.15 Finally, the PBAC noted the 10mg strength of TOF was associated with more infections than the 5mg strength of TOF (paragraph 6.40, TOF PSD, March 2019 PBAC meeting). Results provided in the March 2019 submission provided an indirect comparison between TOF and IFX for safety outcomes, which showed significantly greater risk of infections with TOF compared to IFX. Given the above points, no new safety information has been provided to inform the comparison of TOF to IFX, ADA, GOL and VDZ.

Benefits/harms

- 6.16 Based on the non-inferiority results presented in the resubmission, no benefits and harms table was compiled.

Clinical claim

Sub-group analyses

- 6.17 Based on the results of the sub-group analysis undertaken for TNFi naïve patients, the resubmission described TOF as non-inferior in terms of effectiveness compared with IFX, VDZ, ADA and GOL. For TNFi experienced patients, the resubmission described

TOF as superior in terms of effectiveness compared with ADA and, by extension with GOL, and non-inferior in terms of effectiveness compared with VDZ. The resubmission did not make a claim in terms of effectiveness versus IFX for this sub-group of patients.

- 6.18 The resubmission described TOF as non-inferior in terms of safety compared to IFX, VDZ, ADA and GOL.

Intention to treat (ITT) analyses

- 6.19 Using results for the ITT populations on the basis that this may be the most relevant population to consider given TOF and any other biologic can be used in any order on the PBS, the evaluation considered that:

- TOF may be non-inferior to IFX: While TOF in induction was statistically significantly less effective than IFX for the outcome of clinical remission, it was only when the IFX trials were limited to ACT 1 and 2 and only using the RD statistic. There were no significant differences between TOF and IFX for the outcome of clinical response. Efficacy in maintenance treatment between TOF and IFX was however not able to be indirectly compared due to significant differences in trial designs.
- TOF may be non-inferior to VDZ: There were no significant differences between TOF and VDZ for induction, but in maintenance for sustained clinical remission the indirect comparison found TOF 10 mg, but not TOF 5 mg, was more effective than VDZ, using the RR statistic (RR=2.33, 95% CI: 1.04, 5.23) but the lower 95% CI was nearing one. However, there were no significant differences between TOF and VDZ on sustained clinical response.
- TOF may be non-inferior to GOL: There were no significant differences between the two drugs for any outcome in either induction or maintenance.
- TOF may be superior to ADA: TOF was significantly more effective than ADA for induction for the outcome of clinical response but not clinical remission. However, the result should be interpreted with caution: the ADA trials used a more conservative method to calculate Mayo subscores (using the worst score on any day in the measurement period vs. an average used in the TOF trials); but the TOF trials required a rectal bleeding subscore of 0, irrespective of other measurements, whilst the ADA trials did not. There may be biasing factors in both directions and their overall impact was uncertain. Efficacy in maintenance between TOF and ADA was not able to be indirectly compared due to significant differences in trial designs. Furthermore, the use of indirect comparisons to support this claim and the fact comparative outcomes results were mixed (i.e. statistically superior for response but not for remission) further highlights the uncertainty as to whether a claim of superior comparative efficacy to ADA is adequately supported.

- 6.20 Comparative evidence for safety was as previously seen by the PBAC, including demonstration of more infections observed with TOF compared to IFX, as well as the

10 mg strength of TOF being associated with more infections than 5 mg strength of TOF (paragraph 6.40, TOF PSD March 2019).

- 6.21 The ESC considered that while there were limitations with the indirect comparisons due to exchangeability issues with the trials, the presented analyses may support a conclusion that TOF has superior efficacy to ADA and is non-inferior to IFX for induction (noting TOF could not be reliably compared to these therapies in the maintenance phase due to differences in trial designs); and may be non-inferior in terms of efficacy to GOL and VDZ for both induction and maintenance in MSUC. The ESC noted the indirect comparison with GOL had the least exchangeability issues.
- 6.22 The tables below provide a summary of the PBAC’s previous conclusions for each VDZ, ADA and GOL versus INF (the first biological therapy PBS listed by MSUC) and with each other. The TOF comparisons were added during the evaluation of the resubmission.

Table 9: Summary of clinical claims across the biologic therapies for MSUC for induction phase

Drug versus	IFX	VDZ	ADA	GOL	TOF
IFX		Non-inferior	Superior	Superior	Non-inferior ^a
VDZ	Non-inferior		Superior	Non-inferior	Non-inferior ^b
ADA	Inferior	Inferior		Non-inferior	May be inferior ^c
GOL	Inferior	Non-inferior	Non-inferior		Non-inferior
TOF	Non-inferior ^a	Non-inferior ^b	Superior ^c	Non-inferior	

Source: Compiled during the evaluation.

ADA=adalimumab, IFX=infliximab, GOL=golimumab, TOF=tofacitinib, VDZ=vedolizumab

^a Only when the IFX trials were limited to the ACT 1 and ACT 2 trials, using the clinical remission outcome, and using the RD statistic, was when TOF was found to be statistically significantly inferior to IFX.

^b Focusing on the ITT population, TOF was non-inferior to VDZ in the induction phase. .

^c Focusing on the ITT population in induction, overall TOF appears superior to ADA for the clinical response outcome. For the clinical remission outcome, the RR risk statistic was not significant and the RD risk statistic was marginally significant.

Table 10: Summary of clinical claims across the biologic therapies for MSUC for maintenance phase

Drug versus	IFX	VDZ	ADA	GOL	TOF
IFX		Non-inferior	Superior	Non-inferior	Uncertain ^a
VDZ	Non-inferior		Superior	Non-inferior	Non-inferior ^b
ADA	Inferior	Inferior		Non-inferior	May be inferior ^c
GOL	Non-inferior	Non-inferior	Non-inferior		Non-inferior
TOF	Uncertain ^a	Non-inferior ^b	Uncertain ^c	Non-inferior	

Source: Compiled during the evaluation.

ADA=adalimumab, IFX=infliximab, GOL=golimumab, TOF=tofacitinib, VDZ=vedolizumab

^a Formal indirect comparisons of TOF versus IFX in the maintenance phase were unable to be made.

^b In the maintenance phase, overall TOF appears to be non-inferior to VDZ, with the exception of the sustained remission outcome for TOF 10 mg vs VDZ, using the RR risk statistic.

^c Formal indirect comparisons of TOF versus ADA in the maintenance phase were unable to be made.

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

Economic analysis

- 6.23 The resubmission presented a cost-minimisation analysis between TOF with a weighted comparator of IFX, VDZ, ADA and GOL. The March 2019 submission presented a cost-minimisation analysis between TOF and IFX.

6.24 As discussed earlier in this PSD (paragraph 5.8), the PBAC considered the weighted comparator approach followed in the resubmission was not adequately justified.

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

Tofacitinib cost/patient/year

6.25 The submission’s estimated cost is \$ [REDACTED] with TOF 10mg for induction and TOF 5mg/10mg in maintenance over 52 weeks assuming full compliance.

Estimated PBS usage & financial implications

6.26 This resubmission was not considered by DUSC.

6.27 The resubmission stated that a market share approach was used to estimate the financial implications of the proposed listing to the PBS/RPBS, however, the analysis indicated that a mixed epidemiological and market share approach was used instead (see Table 11).

Table 11: Key inputs for financial estimates

Step	Data	Values applied in the resubmission					Comments
1	Individual bDMARD annual growth rates		ADA	GOL	IFX	VED	Uncertain. The source of these rates was reported to be the Pfizer Xeljanz UC patient forecast model (epidemiological approach), but this was not provided during the evaluation and it is unclear how these were calculated. These growth rates were applied to PBS scripts in 2019 (market share approach) to estimate future bDMARD scripts.
		2020	%	%	%	%	
		2021	%	%	%	%	
		2022	%	%	%	%	
		2023	%	%	%	%	
		2024	%	%	%	%	
		2025	%	%	%	%	
2	Substitution rates for all bDMARDs	Year 1:	%				Uncertain. Based on sponsor’s assumptions. It was assumed that TOF will substitute equally for all PBS listed bDMARDs. Substitution rates did not distinguish the initiation and maintenance treatment phases. It is highly unlikely that TOF would substitute all listed bDMARDs equally. These rates were applied to the estimated number of bDMARD scripts (calculated with growth rates in Step 1) to estimate the number of annual TOF scripts.
		Year 2:	%				
		Year 3:	%				
		Year 4:	%				
		Year 5:	%				
		Year 6:	%				
3	Additional market growth due to TOF	Yr 1:	%				TOF scripts (Step 2) were then added to the bDMARD scripts (from Step 1), and the resulting percent difference was interpreted as the additional market growth due to TOF listing. This is not reasonable. If the resubmission estimates an increasing number of scripts for patients who are not yet treated with bDMARDs and are not accounted for in the annual growth rates, these cannot be derived from current scripts using fixed substitution rates. Also, any additional growth due to TOF listing beyond current market trends is uncertain.
		Yr 2:	%				
		Yr 3:	%				
		Yr 4:	%				
		Yr 5:	%				
		Yr 6:	%				
4	Total bDMARD annual growth rate (including growth due to TOF)	Yr 1:	%				The revised annual market growth (including the additional growth due to TOF – Step 3) was derived from the percentage difference between the total scripts (bDMARDs+TOF) and initial bDMARD scripts (calculated in Step 1). These rates are presented in Table 4.1.2, p92 of the resubmission, but are not used in the model.
		Yr 2:	%				
		Yr 3:	%				
		Yr 4:	%				
		Yr 5:	%				
		Yr 6:	%				

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Step	Data	Values applied in the resubmission	Comments																																			
5	Individual bDMARD growth (incl.growth due to TOF)	<table border="1"> <thead> <tr> <th></th> <th>ADA</th> <th>GOL</th> <th>IFX</th> <th>VED</th> </tr> </thead> <tbody> <tr> <td>2019-2021</td> <td>█%</td> <td>█%</td> <td>█%</td> <td>█%</td> </tr> <tr> <td>2022</td> <td>█%</td> <td>█%</td> <td>█%</td> <td>█%</td> </tr> <tr> <td>2023</td> <td>█%</td> <td>█%</td> <td>█%</td> <td>█%</td> </tr> <tr> <td>2024</td> <td>█%</td> <td>█%</td> <td>█%</td> <td>█%</td> </tr> <tr> <td>2025</td> <td>█%</td> <td>█%</td> <td>█%</td> <td>█%</td> </tr> <tr> <td>2026</td> <td>█%</td> <td>█%</td> <td>█%</td> <td>█%</td> </tr> </tbody> </table>		ADA	GOL	IFX	VED	2019-2021	█%	█%	█%	█%	2022	█%	█%	█%	█%	2023	█%	█%	█%	█%	2024	█%	█%	█%	█%	2025	█%	█%	█%	█%	2026	█%	█%	█%	█%	<p>These rates (decimals were rounded) were the result of combining rates in Step 1 with additional growth due to TOF (Step 3). In this way, the model includes TOF uptake in the market and the additional growth due to TOF. The estimated growth rates for injectable bDMARDs are high particularly in 2021. These were then applied to the number of PBS scripts in 2019 for each bDMARD, along with the annual substitution rates (Step 2), to estimate the number of injectable bDMARD scripts that will be replaced by TOF.</p> <p>The number of TOF scripts was derived from each of these multiplied by the conversion factors used for each bDMARD (Step 6 below) and the compliance rate (Step 7 below). The scripts of injectable bDMARDs replaced by TOF were later estimated as cost offsets for TOF in the financial estimates. This was inappropriate. Any increased utilisation of injectable bDMARDs as a result of TOF listing should instead be counted as additional cost to government rather than deductions.</p>
	ADA	GOL	IFX	VED																																		
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6	Conversion factors used	<table border="1"> <thead> <tr> <th>Induction scripts</th> <th>TOF</th> <th>Factor</th> </tr> </thead> <tbody> <tr> <td>ADA 80/160mg=2</td> <td rowspan="4">10mg =2</td> <td>1</td> </tr> <tr> <td>VDZ 300mg= 3</td> <td>0.67</td> </tr> <tr> <td>IFX 400mg= 3</td> <td>0.67</td> </tr> <tr> <td>GOL 100mg=2</td> <td>1</td> </tr> <tr> <th>Maintenance scripts</th> <th>TOF</th> <th>Factor</th> </tr> <tr> <td>ADA 20/40mg= 13/yr</td> <td rowspan="4">(5/10mg) = 13/yr</td> <td>1</td> </tr> <tr> <td>VDZ 300mg= 7.1/yr</td> <td>1.83</td> </tr> <tr> <td>IFX 400mg= 6.5/yr</td> <td>2</td> </tr> <tr> <td>GOL 100mg=13/yr</td> <td>1</td> </tr> </tbody> </table>	Induction scripts	TOF	Factor	ADA 80/160mg=2	10mg =2	1	VDZ 300mg= 3	0.67	IFX 400mg= 3	0.67	GOL 100mg=2	1	Maintenance scripts	TOF	Factor	ADA 20/40mg= 13/yr	(5/10mg) = 13/yr	1	VDZ 300mg= 7.1/yr	1.83	IFX 400mg= 6.5/yr	2	GOL 100mg=13/yr	1	<p>The resubmission used a conversion factor for VDZ of 1.83, instead of 2 in the March 2019 submission. The 1.83 conversion factor (13 scripts TOF 5 mg: 7.1 scripts VDZ 300 mg) was based on average doses in a 24 month period, given the VDZ PBS item codes do not differentiate between initiation or continuation usage. The resubmission explained this was because VDZ scripts could not be separated into initiation and continuation usage. This was appropriate.</p>											
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7	Compliance with TOF	89%	<p>Based on the 2019 average of TOF scripts per patient per month when used for Rheumatoid Arthritis. Compliance was reduced from 100% compliance presented in the March 2019 submission to 89% in the resubmission. This is uncertain. As an oral agent, TOF would potentially lead to higher compliance than ADA (93%) or GOL (91%). The ESC agreed this change in the resubmission was poorly justified.</p>																																			
8	TOF cost (Effective)	DPMQ for both TOF 5mg and 10mg= \$█	<p>There was a reduction in effective price from the March 2019 submission (TOF 10mg= \$█ and TOF 5mg=\$█). Also, the differential pricing between the two doses was removed. This was appropriate.</p>																																			
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10944B, 11127P, 10955N, 10960W, 11121H, 10961X	\$█																																					
10972L, 10945C, "	\$█																																					

Step	Data	Values applied in the resubmission		Comments
11	VDZ cost (effective)	PBS items	Cost applied	Estimated effective costs applied to the corresponding PBS scripts. VDZ services were not split into initiating or continuing, so the resubmission assumed all substitution of VDZ by TOF would be in the continuation phase. This was not reasonable, as the conversion factor for VDZ for maintenance treatment is double that in the initiation phase.
		10384M	\$ [REDACTED]	
		10398G	\$ [REDACTED]	
12	GOL cost (effective)	PBS items	Cost applied	Estimated effective costs applied to the corresponding PBS scripts.
		11382C	\$ [REDACTED]	
		11502J, 11381B	\$ [REDACTED]	
13	Patient co-payment	\$32.01 PBS; 4.18 RPBS		Weighted average of ADA and GOL. The resubmission explained these are Section 85 listed medicines, the same category as that proposed for PBS listing of TOF. This was appropriate.
14	MBS costs	\$99.50 MBS item 14245		Applied to IFX and VDZ injections. MBS cost at 80% rebate would have been more appropriate for the financial estimates as it more accurately reflects cost to government.

Source: Compiled during the evaluation from Section 4 workbook "Utilisation and cost-model"

Abbreviations: ADA=adalimumab, bDMARDs=biological disease modifying antirheumatic drug, GOL=golimumab, IFX=infliximab, TOF=tofacitinib, VDZ=vedolizumab.

- 6.28 The resubmission assumed that the listing of TOF would increase current annual market growth of all bDMARDs for MSUC. This was a change from the March 2019 submission, which assumed the listing of TOF would not increase annual market growth. The resubmission explained that additional growth due to TOF is expected due to the lack of alternate options in MSUC, with the majority of patients still being treated with their first biologic (excluding those who have discontinued treatment altogether). The resubmission stated (p95) that TOF being the first JAK inhibitor and the first oral therapy for MSUC is likely to be embraced by the gastroenterology community, particularly for patients who may have ceased previous biologic treatment due to an inability to achieve long-term remission or disease control, and/or for whom injectable therapy is inconvenient or undesirable.
- 6.29 The evaluation considered that while the assumption of additional market growth due to the availability of an oral agent for MSUC may be reasonable, the estimates used in the model are high and uncertain. This has downstream impacts in the financial estimates as increased scripts for injectable biologic therapies due to TOF are then deducted as cost offsets for TOF. The PSCR argued that both the market share and epidemiological approaches predicted sufficiently similar financial implications to the PBS (cost saving in both instances) and were more reliable than the March 2019 estimates due to the availability of additional historical data. The ESC considered the assumption that the listing of TOF would grow the MSUC market was poorly justified and considered that while an oral agent may grow the market, the level of growth was uncertain.
- 6.30 Table 12 presents the estimated net financial implications for the proposed listing of TOF for MSUC over the first 6 years.

Table 12: Estimated use and financial implications (based on effective prices)

	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	1	2	2	3	3	3
TOF 10mg	4	4	1	1	1	1
TOF 5 mg	4	1	2	2	2	2
<i>Total scripts PBS/RPBS March 2019 submission</i>	5	4	4	4	4	4
Net Cost PBS/RPBS (less co-pay), TOF	\$ 6	\$ 7	\$ 7	\$ 7	\$ 8	\$ 7
4.3 Estimation of changes in use and financial impact of other bDMARDs						
bDMARD scripts substituted by TOF	4	2	2	2	2	2
ADA	4	4	4	4	4	4
GOL	5	4	4	4	4	4
IFX	4	4	1	1	1	1
VDZ	4	4	1	1	1	1
Net cost PBS/RPBS (less co-pay), bDMARDs	-\$ 6	-\$ 7	-\$ 7	-\$ 8	-	-
ADA	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
GOL	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
IFX	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
VDZ	-\$ 6	-\$ 6	-\$ 6	-\$ 7	-	-\$ 7
4.4 Estimated financial implications for the PBS/RPBS						
Net Cost PBS/RPBS (less co-payment)	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
<i>Net cost PBS/RPBS March 2019 submission</i>	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
4.5 Estimated financial implications for the health budget						
Number of IFX infusions	4	4	1	1	1	1
Number of VDZ infusions	4	4	1	1	1	1
Net cost MBS	\$ 6	\$ 6	\$ 6	\$ 6	\$ 6	\$ 6
Net cost to health budget (less co-payment)	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
<i>Net cost to health budget March 2019 submission</i>	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6

Source: Compiled during the evaluation from Section 4 workbook "Utilisation and cost-model"; Table 4.2.1, 6.07.COM.42.

*Estimates presented in the March 2019 Commentary were corrected for errors in the submission model

Abbreviations: ADA=adalimumab, bDMARDs=biological disease modifying antirheumatic drug, GOL=golimumab, IFX=infliximab, TOF=tofacitinib, VDZ=vedolizumab.

The redacted values correspond to the following ranges:

¹5,000 to <10,000

²10,000 to <20,000

³20,000 to <30,000

⁴500 to <5,000

⁵<500

⁶\$0 to <\$10 million

⁷\$10 million to <\$20 million

⁸\$20 million to <\$30 million

6.31 The evaluation considered the predicted use and financial impacts of the proposed listing are uncertain for the following reasons:

- The financial estimates model led to cost-savings to the health budget by Year 6 of \$0 to <\$10 million compared to a saving of \$0 to <\$10 million presented in the March 2019 submission. Compared to the March 2019 submission, the resubmission estimated a higher number of bDMARD scripts substituted by TOF (10,000 to <20,000 vs. 500 to <5,000 by Year 6) and more TOF scripts (20,000 to <30,000 vs. 500 to <5,000 by Year 6). These are large increases, mainly driven by the assumed growth rates and TOF substitution rates for each bDMARD. Both were inadequately justified by the resubmission; for example, a fixed rate of substitution across all listed comparators appears unlikely and justification for this assumption was not provided in the resubmission.
- Any additional growth due to TOF listing beyond current market trends is uncertain. Furthermore, the resubmission added the additional growth rate due to TOF to estimate the number of competitor biologic therapy scripts in future years, thereby increasing the cost-offsets. This was inappropriate; any increased utilisation of injectable biologic therapies **as a result of TOF listing** should instead be counted as additional cost to government rather than deductions, given they would not be there if TOF is not listed on the PBS. The ESC agreed with the evaluation and considered that any additional use of other bDMARDs should be counted as a cost to government. On balance, the ESC considered that with a more appropriate simplified cost minimisation approach, listing of TOF was unlikely to result in a net save to the PBS.
- Compliance was reduced from 100% in the March 2019 submission to 89% in the current resubmission. As an oral agent, TOF would potentially lead to higher compliance than ADA (93%) or GOL (91%). The ESC considered this was poorly justified in the resubmission.

Financial Management

6.32 A Special Pricing Arrangement was requested.

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

7 PBAC Outcome

7.1 The PBAC reaffirmed its recommendation for tofacitinib (TOF) in moderate-to-severe ulcerative colitis (MSUC) and decided to amend the clinical and economic basis of its recommendation. The PBAC's revised recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of TOF would be acceptable if it were cost minimised against the least costly biologic therapy of infliximab (IFX), golimumab (GOL) or vedolizumab (VED). The PBAC accepted that TOF is likely of non-inferior safety and efficacy to these agents in MSUC, and that there is sufficient basis to conclude that TOF, for some patients, provides a significant improvement in efficacy in the induction phase compared to ADA, based on the ITT analyses (para 6.21).

- 7.2 The PBAC reaffirmed its view in March 2019 that TOF should be a General Schedule, Authority Required (Written) listing and agreed the line-agnostic restriction recommended at that time remained appropriate.
- 7.3 The PBAC recommended equi-effective doses are as follows:
- Induction: TOF 10 mg BD orally
- ≡ IFX 5 mg/kg IV Weeks 0, 2 and 6
 - ≡ VDZ 300 mg IV Weeks 0, 2 and 6
 - ≡ GOL 200 mg SC Week 0, 100 mg Week 2.
- Maintenance TOF 5mg or 10mg BD orally
- ≡ IFX 5 mg/kg IV every 8 weeks from week 14
 - ≡ VDZ 300 mg IV every 8 weeks from week 14
 - ≡ GOL 100 mg SC every 4 weeks from week 6.
- 7.4 The PBAC noted the comments from patients, clinicians and organisations highlighted the need for additional treatments for MSUC. The PBAC reaffirmed its view expressed at its March 2019 meeting that there was a clinical place for TOF for MSUC and that an oral therapy would provide a new treatment option for some patients, particularly those in rural or remote areas.
- 7.5 The PBAC agreed the nominated alternative therapies (comparators) of IFX, GOL, VED and ADA were reasonable, however did not accept the weighted comparator approach used in the submission. The PBAC noted the approach taken by the submission to separate the MSUC population into TNFi naïve and TNFi experienced patients was inconsistent with both the requested listing and the manner in which other biologic therapies for MSUC are PBS listed. Further, the submission did not identify any specific population(s) that could not use one or more of the potential alternative treatments; therefore, the PBAC considered the submission's weighted comparator approach was not adequately justified.
- 7.6 The PBAC noted the addition of two new VED trials (Motoya 2019 and Sandborn 2020) and further noted the exclusion of three trials included in the original submission (GOL: PURSUIT-J; ADA: Suzuki 2014; IFX: Kobayashi 2016) and considered their exclusion was inadequately justified.
- 7.7 The PBAC noted the main differences between the March 2019 submission and the resubmission was the inclusion of new subgroup analyses based on TNFi naïve/experienced status, alongside the previous ITT analyses; and changes to the statistical approach to use a random effects model rather than a fixed effects model in the indirect comparisons. The PBAC considered this change in statistical approach likely accounted for the observed differences in the ITT analyses between the March 2019 submission and the resubmission. The PBAC noted comparisons in the maintenance phase were unable to be undertaken between TOF and IFX or ADA due

to substantial differences in the trial designs.

- 7.8 The PBAC considered the ITT analyses were the most appropriate basis to consider the comparative effectiveness of TOF, given both the requested listing for TOF and the current biologic therapy listings for MSUC are line-agnostic and allow for any sequence of therapies within a treatment cycle. . The PBAC also reaffirmed its view expressed at its March 2019 meeting that relative risk (RR) may be a more appropriate measure than risk difference (RD) because placebo responses differed across the trials. The PBAC considered that the results of the analyses which achieved a statistically significant result for RD but not for RR should be interpreted with caution.
- 7.9 The PBAC considered the TNFi naïve/experienced subpopulation analyses were problematic for a number of reasons, including:
- The comparisons may not be a fair representation of comparative efficacy in patients who are TNF naïve or experienced as *a priori* patients who have failed a TNFi would be more likely to respond to TOF, and conversely, patients who have failed TOF (or another JAK inhibitor) would be more likely to respond to a TNFi; and
 - The subpopulation analyses would have reduced statistical power as there were potential differences between study populations that may be diluted by reduced sample size and would likely have a higher risk of bias due to increased risks of confounding effects.
- 7.10 Furthermore, the PBAC noted that each of the analyses represented a snapshot of a single outcome at a single point in time, and given the additional uncertainties introduced there was a greater chance that individual analyses could produce spurious results and the totality of available evidence should be considered.
- 7.11 The PBAC considered the results of the ITT analyses support the conclusion that TOF is likely to be of non-inferior comparative efficacy to IFX, GOL and VED for induction and GOL and VED (and by inference IFX) for maintenance therapy.
- 7.12 The PBAC noted no new safety information was provided and reaffirmed its March 2019 view that the claim of non-inferior comparative safety to IFX may be reasonable.
- 7.13 The PBAC considered the submission’s argument that the listing of TOF for MSUC would lead to a net save to the PBS was poorly justified. Specifically, the PBAC did not accept the assumptions in the submission that increased market growth rates due to the listing of TOF should not be counted as additional PBS costs and also did not consider the assumption of reduced compliance in the resubmission (89%, down from 100% in the March 2019 submission) was reasonable. The PBAC considered, however, that under the parameters of its recommended listing on a cost minimisation with the least costly of IFX, GOL and VED that the listing of TOF would likely be cost neutral to the PBS or result in a modest net save as it will predominantly replace therapies that are either of equivalent cost or more expensive.

- 7.14 The PBAC noted the flow-on restriction changes to the listings of other biologics for MSUC to include TOF in the list of eligible biologic therapies as part of a treatment cycle.
- 7.15 The PBAC reaffirmed its view expressed at its March 2019 meeting that TOF, as the only oral therapy option for MSUC, has unique characteristics compared to the other available therapies for the purposes of the criterion 2 of the Special Pricing Arrangement (SPA) criteria.
- 7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because TOF is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over IFX, GOL or VED, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.17 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 indication (intent is unchanged from the March 2019 recommended listing, but is updated for administrative aspects – ‘Services Australia’ in place of ‘Department of Human Services’; inclusion of electronic upload of documents option in addition to postal service):

MEDICINAL PRODUCT medicinal product pack	Max. Qty (packs)	Max. Qty (units)	No. of repeats	PBS item code	Available brands
TOFACITINIB tofacitinib 5 mg, tablet, 56	1	56	3	NEW	Xeljanz
tofacitinib 10 mg, tablet, 56	1	56	3	NEW	Xeljanz

Restriction Summary NEW / ToC: NEW:

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type / Method: <input checked="" type="checkbox"/> Authority Required - delayed/non-immediate assessment by Services Australia (lodgement via postal service or electronic upload)
	Administrative Advice: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.

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	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Severity: Moderate to severe
	Condition: Ulcerative colitis
	Indication: Moderate to severe ulcerative colitis
	Treatment phase: : Initial treatment - Initial 1 (new patient)
	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)]; or
	AND
	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
	Clinical criteria:
	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
	Clinical criteria:
	Patient must have a Mayo clinic score greater than or equal to 6; OR

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	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).
	AND
	Population criteria:
	Patient must be aged 18 years or older.
	Prescribing 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].
	Prescribing Instructions: All tests and assessments should be performed preferably whilst still on treatment, but no longer than 4 weeks following cessation of the most recent prior conventional treatment.
	Prescribing Instructions: The most recent Mayo clinic or partial Mayo clinic score must be no more than 4 weeks old at the time of application.
	Prescribing Instructions: <i>A partial Mayo clinic assessment of the patient's response to this initial course of treatment must be conducted 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 tofacitinib, golimumab, infliximab and vedolizumab so that there is adequate time for a response to be demonstrated.</i>
	Prescribing Instructions: To demonstrate a response to treatment the application must be accompanied with the assessment of response, conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from cessation of the most recent course of biological medicine. It is recommended that an application for the continuing treatment be submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This is to ensure treatment continuity for those who meet the continuing restriction.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: 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.
	Prescribing Instructions: 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.

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	<p>Prescribing Instructions: A maximum of 16 weeks of treatment with this drug will be approved under this criterion.</p>
	<p>Administrative Advice: Details of accepted toxicities including severity can be found on the Services Australia website at www.servicesaustralia.gov.au.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia 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 Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

Restriction Summary NEW / ToC: NEW: Authority Required

	<p>Category / Program: GENERAL – General Schedule (Code GE)</p>
	<p>Prescriber type: <input type="checkbox"/>Dental <input checked="" type="checkbox"/>Medical Practitioners <input type="checkbox"/>Nurse practitioners <input type="checkbox"/>Optometrists <input type="checkbox"/>Midwives</p>
	<p>Restriction type / Method: <input checked="" type="checkbox"/>Authority Required - delayed/non-immediate assessment by Services Australia (lodgement via postal service or electronic upload)</p>
	<p>Administrative Advice: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS</p>
	<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply.</p>
	<p>Severity: Moderate to severe</p>
	<p>Condition: Ulcerative colitis</p>
	<p>Indication: Moderate to severe ulcerative colitis</p>
	<p>Treatment phase: Initial treatment - Initial 2 (change or re-commencement of treatment after a break in biological medicine of less than 5 years)</p>
	<p>Treatment criteria:</p>
	<p>Must be treated by a gastroenterologist (code 87); or</p>
	<p>Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or</p>
	<p>Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)]; or</p>

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	AND
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle,
	AND
	Clinical criteria:
	Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition during the current treatment cycle.
	Population criteria:
	Patient must be aged 18 years or older.
	Prescribing Instructions: 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) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition if relevant; and (ii) the details of prior biological medicine treatment including the details of date and duration of treatment-.
	Prescribing Instructions: To demonstrate a response to treatment the application must be accompanied with the assessment of response, conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from cessation of the most recent course of biological medicine. It is recommended that an application for the continuing treatment be submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This is to ensure treatment continuity for those who meet the continuing restriction.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A patient who fails to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this treatment cycle. A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the initial 3 treatment restriction.
	Prescribing Instructions: A maximum of 16 weeks of treatment with this drug will be approved under this criterion.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

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	<p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
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Add initial 3 treatment:

Restriction Summary NEW / ToC: NEW: Authority Required

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction type / Method: <input checked="" type="checkbox"/> Authority Required - delayed/non-immediate assessment by Services Australia (lodgement via postal service or electronic upload)
	Administrative Advice: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Severity: Moderate to severe
	Condition: Ulcerative colitis
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial treatment - Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
	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)]; or
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with a biological medicine for this condition
	AND

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	Clinical criteria:
	Patient must have had a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition
	AND
	Clinical criteria:
	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).
	AND
	Population criteria:
	Patient must be aged 18 years or older.
	Prescribing Instructions: Application for authorisation must be made 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) the details of prior biological medicine treatment including the details of date and duration of treatment.
	Prescribing Instructions: All tests and assessments should be performed preferably whilst still on treatment, but no longer than 4 weeks following cessation of the most recent prior conventional treatment.
	Prescribing Instructions: The most recent Mayo clinic or partial Mayo clinic score must be no more than 4 weeks old at the time of application.
	Prescribing Instructions: <i>A partial Mayo clinic assessment of the patient's response to this initial course of treatment must be conducted 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 tofacitinib, golimumab, infliximab and vedolizumab so that there is adequate time for a response to be demonstrated.</i>
	Prescribing Instructions: To demonstrate a response to treatment the application must be accompanied with the assessment of response, conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from cessation of the most recent course of biological medicine. It is recommended that an application for the continuing treatment be submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This is to ensure treatment continuity for those who meet the continuing restriction.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions:

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	If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A maximum of 16 weeks of treatment with this drug will be approved under this criterion.
	Administrative Advice: <i>Details of accepted toxicities including severity can be found on the Services Australia website at www.servicesaustralia.gov.au.</i>
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia 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 Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

Add BOS restriction

Restriction Summary NEW / ToC: NEW: Authority Required

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/electronic
	Administrative Advice: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial 1 (new patient) or Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) - balance of supply
	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)]

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	AND
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient) restriction to complete 16 weeks treatment; or
	Patient must have received insufficient therapy with this drug for this condition under the Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction to complete 16 weeks treatment; or
	Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete 16 weeks treatment
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

MEDICINAL PRODUCT medicinal product pack	Max. Qty (packs)	Max. Qty (units)	No. of repeats	PBS item code	Available brands
TOFACITINIB tofacitinib 5 mg, tablet, 56	1	56	5	NEW	Xeljanz
TOFACITINIB tofacitinib 10 mg, tablet, 56	1	56	5	NEW	Xeljanz

Restriction Summary NEW / ToC: NEW: Authority Required

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction type / Method: <input checked="" type="checkbox"/> Authority Required –Telephone / electronic
	Administrative Advice: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.

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	Severity: Moderate to severe
	Condition: Ulcerative colitis
	Indication: Moderate to severe ulcerative colitis
	Treatment phase: Continuing treatment
	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)]; or
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	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
	AND
	Population criteria:
	Patient must be aged 18 years or older.
	Prescribing 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.
	Prescribing 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.
	Prescribing Instructions: At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from cessation of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions:

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	Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Restriction Summary NEW / ToC: NEW: Authority Required

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction type / Method: <input checked="" type="checkbox"/> Authority Required - delayed/non-immediate assessment by Services Australia (lodgement via postal service or electronic upload)
	Administrative Advice: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Severity: Moderate to severe
	Condition: Ulcerative colitis
	Indication: Moderate to severe ulcerative colitis
	Treatment phase: Initial treatment - Grandfather treatment
	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)]; or
	AND

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	Clinical criteria:
	<i>Patient must have previously received non-PBS-subsidised therapy with this drug for this condition prior to <<listing date>>,</i>
	AND
	Clinical criteria:
	Patient must be receiving treatment with this drug for this condition at the time of application
	AND
	Clinical criteria:
	<i>Patient must have had a Mayo clinic score greater than or equal to 6 prior to commencing non-PBS subsidised treatment with this drug for this condition; or</i>
	<i>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 non-PBS subsidised treatment with this drug for this condition; or</i>
	<i>Patient must have a documented history of moderate to severe refractory ulcerative colitis prior to having commenced non-PBS subsidised treatment with this drug for this condition where a Mayo clinic, partial Mayo clinic baseline assessment is not available,</i>
	AND
	Clinical criteria:
	<i>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 of non-PBS-subsidised treatment with this drug for this condition.</i>
	AND
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment under this restriction
	Population criteria:
	Patient must be aged 18 years or older.
	<p>Prescribing Instructions: <i>Application for authorisation of initial treatment must be in writing and must include:</i> <i>(a) a completed authority prescription form; and</i> <i>(b) a completed Ulcerative Colitis PBS Authority Application - Supporting Information Form which includes the following:</i> <i>(i) the completed baseline Mayo clinic or partial Mayo clinic calculation sheet prior to initiating treatment (if available) and current Mayo clinic or partial Mayo clinic calculation sheet to demonstrate response, including the date of assessment;</i> <i>(ii) If the baseline Mayo or partial Mayo clinic calculation is not available, reason must be provided;</i> <i>(iii) the date of commencement of this drug</i></p>

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	<p>Prescribing Instructions: The current Mayo clinic or partial Mayo clinic assessment must be no more than 4 weeks old at the time of application.</p>
	<p>Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only.</p>
	<p>Prescribing Instructions: For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p>
	<p>Prescribing Instructions: The assessment of the patient's response to this PBS-subsidised course of therapy must be conducted no later than 4 weeks from the cessation of the treatment course.</p>
	<p>Prescribing Instructions: Where the response assessment is not submitted within this timeframe, the patient will be deemed to have failed to respond to treatment with this drug</p>
	<p>Prescribing 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.</p>
	<p>Prescribing 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.</p>
	<p>Prescribing Instructions: At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia 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 Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

Add continuing BOS restriction

Restriction Summary NEW / ToC: NEW: Authority Required

	<p>Category / Program: GENERAL – General Schedule (Code GE)</p>
	<p>Prescriber type: <input type="checkbox"/>Dental <input checked="" type="checkbox"/>Medical Practitioners <input type="checkbox"/>Nurse practitioners <input type="checkbox"/>Optometrists <input type="checkbox"/>Midwives</p>
	<p>Restriction Level / Method: <input checked="" type="checkbox"/>Authority Required – Telephone/electronic</p>
	<p>Administrative Advice: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS</p>

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	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Continuing treatment or Grandfathered patients - balance of supply
	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)]
	AND
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under the Continuing treatment restriction to complete 24 weeks treatment; or
	Patient must have received insufficient therapy with this drug for this condition under the Grandfathered treatment restriction to complete 24 weeks treatment
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Amend overarching note Admin advice [24855]:

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 [listing date], 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~~ biological medicine 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~~ a PBS-subsidised biological medicine while they continue to show a response to therapy.

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A patient who received PBS-subsidised ~~adalimumab, infliximab, vedolizumab~~ biological medicine treatment prior to ~~1 June 2018~~ *[listing date]* is considered to start their first cycle as of ~~1 June 2018~~ *[listing date]*. 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~~ biological medicine 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~~ biological medicine treatment in the most recent cycle to the date of the first application for initial treatment with ~~adalimumab, golimumab, infliximab, tofacitinib or vedolizumab~~ a PBS-subsidised biological medicine under the new treatment cycle.

Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment, including serious infusion or injection related reactions, Steven's Johnson Syndrome, development of a demyelinating lesion, progressive multifocal leukoencephalopathy and malignancy related to treatment with the biological medicine, is not considered as a treatment failure.

A patient who has failed fewer than 3 trials of ~~either adalimumab, golimumab, infliximab, tofacitinib or vedolizumab~~ a biological medicine in a treatment cycle and who has a break in therapy of more than 5 years, may commence a new treatment cycle *under the Initial 3 treatment restrictions*.

There is no limit to the number of treatment cycles a patient may undertake in their lifetime.

(4) How to prescribe PBS-subsidised *biological medicine* treatment with ~~adalimumab, golimumab, infliximab, tofacitinib and vedolizumab~~ after ~~1 June 2018~~ *[listing date]*.

(1) Initial treatment.

Applications for initial treatment should be made where:

(i) an adult patient has not received ~~no~~ prior PBS-subsidised biological medicine 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 *biological medicine therapy* (initial or continuing) ~~adalimumab, golimumab, infliximab, tofacitinib or vedolizumab~~ therapy and wishes to trial an alternate *agent medicine* (Initial 2 - Change or Re-commencement of treatment after a break in *biological medicine* 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~~ a *specific biological medicine* following a break in PBS-subsidised therapy of less than 5 years with the same agent (Initial 2 - Change or Re-commencement of treatment after a break in *biological medicine* therapy of less than 5 years); or

(iv) an adult patient wishes to recommence treatment with a *biological medicine* following a break in PBS-subsidised therapy of more than 5 years (Initial 3 - recommencement of treatment after a break in *biological medicine* of more than 5 years).

Treatment authorisations under Initial 1, ~~and~~ Initial 2 and Initial 3 will be limited to provide for a maximum of 16 weeks of therapy for ~~adalimumab and tofacitinib~~, 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, ~~tofacitinib~~ and vedolizumab. For second and subsequent courses of PBS-subsidised biological medicine treatment, it is recommended that a patient is reviewed in the ~~month~~ 4 weeks prior to completing their current course of treatment.

(2) Continuing treatment.

Following the completion of an initial treatment course with ~~adalimumab, golimumab, infliximab, tofacitinib or vedolizumab~~ a *specific biological medicine*, 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~~ 4 weeks prior to completing their current course of treatment *to ensure uninterrupted biological medicine supply*.

Infliximab only:

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For the first continuing treatment course of PBS-subsidised biological medicine treatment, it is recommended that a patient is reviewed for response following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment under the Initial 1, Initial 2 or Initial 3 treatment restrictions.

For the second and subsequent continuing courses of PBS-subsidised biological medicine treatment, it is recommended that an assessment of a patient's response is conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment.

(2) (3) Swapping therapy.

Once initial treatment with the first PBS-subsidised *biological medicine* treatment is approved, a patient may swap if eligible to the an alternate ~~adalimumab, golimumab, infliximab, tofacitinib or vedolizumab~~ *biological medicine* 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 *biological medicine* 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 *biological medicine* ~~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) (4) 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 cycle~~ following a break in PBS-subsidised ~~adalimumab, golimumab, infliximab, tofacitinib or vedolizumab therapy~~ *biological medicine therapy* of at least 5 years, must requalify for under initial ~~4~~ Initial 3 treatment restriction and meet the relevant criteria 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.

(5) Grandfather patients (tofacitinib only):

A patient who commenced treatment with tofacitinib for moderate to severe ulcerative colitis prior to [listing date] and who continues to receive treatment at the time of application, may qualify for treatment under the 'Grandfather' treatment restriction.

A patient may only qualify for PBS-subsidised treatment under this restriction 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.

Flow Admin advice [24855]: onto:

Adalimumab: 10955N, 10944B, 10945C, 10972L, 10960W, 10961X, 11127P, 11121H

Infliximab: 10196P, 10184B, 11461F, 11459D, 11796W, 11797X

Vedolizumab: 10384M, 10398G

Golimumab: 11382C, 11381B, 11502J

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Pfizer Australia welcomes the PBAC's revised recommendation to list tofacitinib (Xeljanz®) on the PBS for the treatment of moderate to severe ulcerative colitis, offering these patients an effective and convenient oral alternative with a different mechanism of action to the bDMARDs currently available. Pfizer is pleased that the PBAC has appropriately recognised that there is sufficient basis to conclude that tofacitinib, provides a significant improvement in efficacy in the induction phase compared to adalimumab based on the available clinical evidence. Pfizer notes that the Outcome does not include advice from the PBAC on interchangeability.