6.11 TOFACITINIB, Tablet 5 mg, Xeljanz®, Pfizer Australia Pty Ltd

1 Purpose of Application

1.1 The submission requested an Authority Required listing for tofacitinib for the treatment of severe psoriatic arthritis (PsA) in patients meeting specified criteria. This was the first submission for tofacitinib for PsA to be considered by the PBAC. Tofacitinib is listed on the PBS for the treatment of rheumatoid arthritis (RA).

1.2 The basis for the requested listing was a cost-minimisation analysis to adalimumab, which was stated to be the most commonly prescribed therapy for the treatment of PsA in the requested patient population. While the nomination of adalimumab as the main comparator was considered reasonable, any of the currently PBS-listed bDMARDs for the treatment of PsA represent relevant comparators.

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

Component	Description
Population	Patients with severe psoriatic arthritis who have had an inadequate response to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs).
Intervention	Tofacitinib, 5mg, taken orally twice daily (bd) in combination with csDMARDs.
Comparator	Adalimumab, 40mg, administered subcutaneously, once a fortnight (main comparator) with or without concomitant csDMARDs. The nominated comparator was considered appropriate, however all other PBS-listed bDMARDs are also relevant comparators.
Outcomes	Main outcomes: ACR20 and ACR50 at Month 3 for the direct comparison using the OPAL BROADEN trial (comparison of tofacitinib, adalimumab and placebo); Supplementary outcome: PASI75 The PBAC previously considered that the outcome of most relevance is ACR50 given that it reflects to a greater degree the criteria for the current PBS eligibility for continuing treatment with a bDMARD. The assessment of outcomes at Month 3 was consistent with the timing of assessment on the PBS for adalimumab and the proposed timing of assessment for tofacitinib.
Clinical claim	Tofacitinib is non-inferior to adalimumab in terms of efficacy and safety for the treatment of psoriatic arthritis. Based on the data presented in the submission, the possibility that tofacitinib is inferior to adalimumab could not be excluded.

Abbreviations: ACR, American College of Rheumatology; ACR20, ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of 5 remaining ACR core set measures; ACR50, ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of 5 remaining ACR core set measures; PASI, Psoriasis Area and Severity Index; PASI75, ≥75% improvement from baseline PASI.
Source: Table 1.1, p12 of the submission

2 Requested listing

2.1 An abbreviated form of the requested listing is detailed below. In addition to the Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more) and continuing treatment summarised in the table above, the submission also sought PBS listing for Initial 2 (patients changing or recommencing treatment), Initial 3 (grandfathering of patients on non-PBS tofacitinib) and balance of supply, consistent with existing bDMARD listings for PsA.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Initial TOFACITINIB, tablet, 5 mg	1	56	3	$1,764.24*	Xeljanz®, Pfizer Australia Pty Ltd
Continuing TOFACITINIB, tablet, 5mg	1	56	5	$1,764.24*	Xeljanz®, Pfizer Australia Pty Ltd

Category/Program:	General Schedule
PBS indication:	Severe active psoriatic arthritis
Treatment phase:	Initial treatment – initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)
Restriction:	Authority required
Clinical criteria:	Patient must have severe active psoriatic arthritis, AND Patient must have received no prior PBS-subsidised treatment with a biological agent for this condition; OR Patient must have received no PBS-subsidised treatment with a biological agent for at least 5 years if they have previously received PBS-subsidised treatment with a biological agent for this condition, AND Patient must have failed to achieve an adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months, AND Patient must have failed to achieve an adequate response to sulfasalazine at a dose of at least 2 g per day for a minimum period of 3 months; OR Patient must have failed to achieve an adequate response to leflunomide at a dose of up to 20 mg daily for a minimum period of 3 months, AND Patient must not receive more than 16 weeks of treatment under this restriction.
Treatment criteria:	Continuing treatment
Clinical criteria:	Patient must have a documented history of severe active psoriatic arthritis, AND Patient must have received this drug as their most recent course of PBS-subsidised treatment with a biological agent for this condition in the current Treatment Cycle, AND Patient must demonstrate, at the time of application, an adequate response to treatment with this drug, AND Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction

Source: Table 1.9, p28 and Section 1.4.2 and 1.4.3, pp28-38 of the submission

* The submission requested the indication specific price for PsA for etanercept that was in place prior to the application of relevant F1 and F2 statutory price cuts. The current published price for tofacitinib 5mg tablets with a maximum quantity of 56 is $1,267.64.
Note: For the purposes of this restriction 'biological agent' means adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, tofacitinib, or ustekinumab.

2.2 The requested listing for tofacitinib would provide a sufficient quantity for initial (16 weeks) and continuing (24 weeks) treatment for patients who meet the specified clinical criteria, consistent with the current listing of adalimumab and the other bDMARDs.

2.3 The clinical evidence for tofacitinib for this PBAC application came solely from the OPAL BROADEN trial, where patients were TNF inhibitor naïve. While the TGA Round One Clinical Evaluation Report indicated that there was sufficient evidence of efficacy for tofacitinib in patients who had previously used TNF inhibitors, given the lack of comparative evidence against adalimumab, the evaluator considered whether it would be appropriate to limit treatment with tofacitinib to the TNF inhibitor naïve patient population. The Pre-Sub-Committee Response (PSCR) disagreed with the evaluation and argued the OPAL BROADEN trial was included as it provided a common reference to allow an indirect comparison with adalimumab and the included adalimumab trials. The PSCR noted a similar approach was used for the application for tofacitinib for rheumatoid arthritis, which was accepted by the TGA and PBAC. The ESC and PBAC agreed with the PSCR and considered the approach taken by the submission was appropriate. The ESC and PBAC further considered there may be an argument for a role for tofacitinib in patients who have previously failed treatment with a TNF-inhibitor.

2.4 No special pricing arrangement (SPA) was proposed in the submission. However, the pre-PBAC response requested the consideration of a SPA if the PBAC recommended tofacitinib at a price lower than that requested in the submission.

2.5 The price requested was based on a cost-minimisation analysis versus adalimumab, with the submission requesting the indication specific price for PsA for etanercept that was in place prior to the application of relevant F1 and F2 statutory price cuts and other price changes.

2.6 As tofacitinib is currently PBS listed for RA, a weighted price based on the two indications (RA and PsA) would be necessary if listed for PsA without a SPA. The 5mg tablet with a maximum quantity of 56 (four weeks' supply) is currently listed on the PBS for RA with a published price (DPMQ) of $1,267.64.

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

3 Background

Registration status

3.1 TGA status at the time of PBAC consideration: The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the ACM advice was

available. The proposed TGA indication, is "[tofacitinib] in combination with non-biological DMARDs is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate to response to a prior DMARD therapy".

3.2 Tofacitinib is TGA registered for patients with moderate to severe active rheumatoid arthritis and listed on the PBS for the treatment of patients with severe active rheumatoid arthritis.

4 Population and disease

4.1 PsA is a chronic progressive inflammatory arthritis, characterised by pain, stiffness and swelling of joints that can affect the whole body. If left untreated, it may result in permanent joint damage and disability. It can present in several clinical manifestations, including a combination of; peripheral joint inflammation and damage leading to arthritis, psoriasis (in the skin and nails), enthesitis, dactylitis, and spondylitis. This can lead to progressive damage, disability and adverse effects on quality of life, which include fatigue and impaired physical function.

4.2 Tofacitinib is a potent, selective inhibitor of the Janus-associated kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. It has a different mechanism of action to the other therapies listed for the requested indication, and a different method of administration, being administered orally.

4.3 Tofacitinib would be the ninth therapy to join eight bDMARDs currently listed (or recommended for listing in the case of ixekizumab) on the PBS for the treatment of patients with severe active PsA who have failed to achieve an adequate response to non-biologic DMARDS. The addition of tofacitinib to the clinical management algorithm is not expected to alter clinical practice, but it would allow for an additional non-parenteral option.

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

5 Comparator

5.1 The submission nominated adalimumab as the main comparator, based on a 10% sample of PBS data that showed it was most commonly prescribed. The ESC agreed that adalimumab is an appropriate clinical comparator, but noted that other bDMARDs currently listed for PsA, including certolizumab pegol, etanercept, golimumab, infliximab, secukinumab and ustekinumab, may also be replaced by tofacitinib and are therefore also relevant comparators. The PSCR acknowledged that tofacitinib could replace any of the bDMARDs in PsA, but reiterated that adalimumab is the appropriate main comparator as it is the therapy that prescribers would most replace with tofacitinib (with a market share of 44%). The PSCR further stated that certolizumab pegol and ustekinumab are not relevant main comparators for tofacitinib on the basis that these bDMARDs are unlikely to be replaced with tofacitinib in any large extent (with a market share of 4% and 2% respectively).

5.2 Although nominating adalimumab as the main comparator, it was noted that for the requested population, a number of bDMARDs are less costly than adalimumab (see Table 2); and subsequently the requested price for tofacitinib was higher than the potentially lowest cost comparator (and as noted in Section 1.4 a higher price than the current adalimumab price is requested). Under Section 101(3B) of the National Health Act 1953, 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.

Table 2: Dispensed price for maximum quantities and bases of listings for the currently PBS-listed bDMARDs for PsA

bDMARD	Dispensed price maximum quantity (as of 31 Aug 2018)	Basis of listing
Etanercept	$1,049.54 (SPA applies)	CE versus placebo
Infliximab	$507.42 (public) or $535.01 (private)	CM versus etanercept
Adalimumab	$1,269.60	CM versus etanercept
Golimumab	$1,318.17	CM versus etanercept and adalimumab
Certolizumab pegol (continuing)	$1,014.61 (SPA applies)	Compared to adalimumab, at a lower price
Ustekinumab (continuing)	$4,348.38 (SPA applies)	CM versus certolizumab pegol
Secukinumab (continuing)	$1,586.52	CM versus certolizumab pegol and ustekinumab
Ixekizumab	Not applicable	CM to least costly bDMARD

CE = cost-effectiveness analysis; CM = cost-minimisation analysis; SPA = special pricing arrangement

5.3 It was also noted that certolizumab pegol, ustekinumab and secukinumab are considered to represent the 'lower tier' of alternatives for the treatment of PsA on the PBS (paragraph 5.1, abatacept March 2018 PSD).

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician clarified the likely use of tofacitinib in PsA, including for patients with a preference for oral agents or who may be intolerant/contraindicated to a TNF-inhibitor.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on one direct head-to-head trial comparing tofacitinib 5mg orally twice daily and adalimumab 40mg subcutaneously every second week to placebo (the OPAL-BROADEN trial). The trial also included a tofacitinib 10mg twice daily treatment group, however as this dose is not proposed for registration in Australia, results for the treatment group were reasonably not presented in the submission.

6.4 The OPAL BROADEN trial, while including an adalimumab treatment arm, was not designed or powered to establish non-inferiority of tofacitinib to adalimumab. Thus, the submission also presented two supplementary analyses: an indirect comparison of tofacitinib to adalimumab via the common reference of placebo (unadjusted placebo arm), and a network meta-analysis (NMA; which adjusted for placebo response rates).

6.5 Details of the trials presented in the submission for the direct and indirect comparisons are provided in Table 3.

Table 3: Trials and associated reports presented in the direct comparison provided in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Tofacitinib versus adalimumab, Tofacitinib versus placebo; Adalimumab versus placebo – used in the direct and indirect comparisons and the network meta-analysis		
OPAL BROADEN	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of Tofacitinib (CP-690,550) or Adalimumab in Subjects With Active	Clinical Study Report: 31 August 2017
	Mease, PJ et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis.	New England Journal of Medicine 2017a; 377(16):1537-1550
Adalimumab versus placebo – used in the indirect comparison and the network meta-analysis		
SPIRIT-P1	Mease, P.J., et al. "Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1	Annals of the Rheumatic Diseases. 2017b; 76(1): 79-87
ADEPT	Mease, PJ et al. Adalimumab for the treatment of patients with moderately to severely active Psoriatic Arthritis.	Arthritis & Rheumatism 2005; 52(10):3279-3289
	Gladman, DD et al. Adalimumab for long-term treatment of Psoriatic Arthritis.	Arthritis & Rheumatism 2007; 56(2): 476-488
	Mease, PJ et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT).	Annuals of the Rheumatic Diseases 2009; 68: 702-709
Genovese 2007	Genovese, MC et al. Safety and Efficacy of Adalimumab in Treatment of Patients with Psoriatic Arthritis Who Had Failed Disease Modifying Antirheumatic Drug Therapy.	Journal of Rheumatology 2007; 34(5): 1040-1050

Source: Table 2.4 and 2.5, pp44-45 of the submission

6.6 Although the submission also provided the results of a network meta-analysis (NMA) including 13 placebo-controlled trials of tofacitinib (OPAL BROADEN), adalimumab

(OPAL BROADEN, Genovese 2007, ADEPT, SPIRIT-P1), certolizumab pegol (RAPID-PsA), etanercept (Mease 2000, 2004), golimumab (GO-REVEAL), infliximab (IMPACT, IMPACT-2), secukinumab (FUTURE 2) and ustekinumab (PSUMMIT-1, -2), the submission did not provide the citation or trial details. However, the PBAC has previously considered all 13 of these trials in prior bDMARD submissions for PsA.

6.7 The key features of the trials included in the direct and indirect comparisons are summarised in Table 4. Treatment arms in the trials that were not relevant to the analysis were excluded from the evaluation.

Table 4: Key features of the included trials for the direct and indirect comparisons

Trial	N[a]	Design / duration	Relevant comparison	Risk of bias	Patient population	Key outcomes
OPAL BROADEN	213	Phase 3, MC, R, DB; 52 weeks with placebo patients crossing over after 3 months.	Tofacitinib 5mg bd; Adalimumab 40mg injection Q2W; vs PBO	Low	Active PsA, TNF-i naïve	Primary ACR20 and ΔHAQ-DI month 3; Secondary ACR50 and PASI75
Genovese 2007	100	Phase 3, MC, R, DB for 12 wks. OL from 12-24wks.	ADA 40 mg Q2W; vs PBO	Low	Active PsA, TNF-i naïve	Primary: ACR20 Wk 12, Secondary: ACR 50
ADEPT	313	Phase 3, MC, R, DB for 24 wks. OL from 12-120wks.	ADA 40 mg Q2W; vs PBO	Low	Active PsA, TNF-i naïve	Primary: ACR20 Wk 12 & ΔmTSS Wk 24, Secondary: ACR50
SPIRIT-P1	207[b]	Phase 3, MC, R, DB for 24wks.	ADA 40mg Q2W; vs PBO	Low	Active PsA, TNF-i naïve	Primary: ACR20 Wk24; Secondary: ACR50

Source: compiled during the evaluation
MC = multi-centre; R= randomised, DB = double-blind; PBO=placebo; OL = open-label; ACR20/50 = ≥20% /50% improvement on the American College of Rheumatology Criteria; bd = twice daily; Q2W = every second week
[a] Number of patients analysed
[b] Excluding patients from treatment arms not relevant for the analysis

Comparative effectiveness

6.8 Response to bDMARDs on the PBS has previously been assessed using a combination of the American College of Rheumatology 20% and 50% improvement criteria (ACR20 and ACR50, respectively). The PBAC had previously considered that ACR50 was more relevant than ACR20 because it better reflected the current PBS criteria for response to initial therapy (see Ustekinumab PSD, November 2014). However, ACR20 has also been used to support non-inferiority (see Secukinumab PSD, March 2016).

6.9 Non-inferiority margins for ACR20 and ACR50 were nominated based on the PBAC's previous considerations (see Golimumab PSD, March 2010 and Secukinumab PSD, March 2016). For non-inferiority to be demonstrated, the submission stated that the lower bound of the 95% confidence interval (CI) around the relative risk (RR) must exceed 0.29 for ACR50 and 0.46 for ACR20.

6.10 The results for each of the three analyses are presented below: Firstly from the directly comparative trial, OPAL BROADEN, followed by the indirect comparison (unadjusted) and the network meta-analysis.

Direct analysis from OPAL BROADEN

6.11 The results for ACR20, ACR50 and PASI75 from OPAL BROADEN are detailed in Table 5.

Table 5: Results of ACR20, ACR50 and PASI75 from OPAL BROADEN at Month 3 - TNF inhibitor naïve population

Outcome	Tofacitinib	Comparator	Relative risk (95% CI)	Risk difference (95% CI)
ACR20	54/107 (50.5)	Adalimumab: 55/106 (51.9) Placebo: 35/105 (33.3)	0.97 (0.75, 1.26); p=0.84 **1.51 (1.09, 2.10); p=0.01**	-0.01 (-0.15, 0.12); p=0.84 **0.17 (0.04, 0.30); p=0.01**
ACR50	30/107 (28.0)	Adalimumab: 35/106 (33.0) Placebo: 10/105 (9.5)	0.85 (0.57, 1.28); p=0.43 **2.94 (1.52, 5.71); p=0.001**	-0.05 (-0.17, 0.07); p=0.43 **0.19 (0.08, 0.29); p=0.0004**
PASI75	35/82 (42.7)	Adalimumab: 30/77 (39.0) Placebo: 12/82 (14.6)	1.10 (0.75, 1.59); p=0.63 **2.92 (1.63, 5.21); p=0.0003**	0.04 (-0.12, 0.19); p=0.63 **0.28 (0.15, 0.41); p<0.0001**

Source: Tables 2.14 – 2.22, pp81-85 of the submission
Bold values statistically significant differences between treatments
Underlined values represent the values compared against the non-inferiority margin of 0.46 for ACR20 or 0.29 for ACR50
CI = confidence interval; n = number of participants with event; N = total participants in group; ACR = American College of Rheumatology; PASI = Psoriasis Area Severity Index

6.12 The results at Month 3 demonstrated that tofacitinib was more effective than placebo at producing a response. While the results also showed a trend towards suggesting that adalimumab treated patients would be more likely to be ACR20 and ACR50 responders compared to tofacitinib at Month 3, the differences were not statistically significant. The results indicate that the specified non-inferiority margins were met (lower bounds of the 95% CI surrounding relative risk being higher than the minimum values accepted by the PBAC previously of 0.46 and 0.29 for ACR20 and ACR50, respectively). However, given that the trial was not designed to establish non-inferiority, the possibility that tofacitinib is inferior to adalimumab could not be ruled out.

Indirect comparison and results of the NMA

6.13 The indirect comparison (with no placebo adjustment) used the standard frequentist method, as described by Bucher et al, 1997 to compare tofacitinib to adalimumab using the OPAL BROADEN, ADEPT, Genovese 2007 and SPIRIT-P1 trials. The time point for both the ACR20 and the ACR50 analyses was stated to be Week 13 for tofacitinib and Week 12 for adalimumab. It appeared, however, that the adalimumab response in OPAL BROADEN was assessed at Month 3 (Week 13) rather than Week 12. It was unclear what effect this may have had on the overall analysis, however as ACR20 and ACR50 response rates have been shown to increase over this time period there may have been some bias associated with an analysis comparing response rates for tofacitinib at Month 3 to adalimumab at Weeks 12 to Month 3, with this bias being in favour of tofacitinib.

6.14 While the NMA was conducted to support the submission's clinical claim, the submission inappropriately did not:

- perform a risk of bias assessment of all included trials;
- provide the baseline characteristics of the patients enrolled in the trials (other than specifying all patients were bDMARD-naïve) to assess comparability between patients in the trials, or any potential biases; or
- report the primary and secondary outcomes of all of the trials (to get a sense of the power of the trials to make assessments regarding the results).

The submission additionally reported only selected results from the NMA – results only from the fixed effects (and not random effects) model and only for the comparison of tofacitinib and adalimumab (and not for any of the other bDMARDs included in the analysis).

6.15 The results of the standard indirect comparison ("Trial [Bucher]", with no placebo adjustment) and network meta-analyses (with placebo adjustment, reported using a fixed [NMA FE] and random [NMA RE] effects model) for ACR20 and ACR50 are provided in Table 6 and Table 7, respectively.

Table 6: ACR20 response for the unadjusted (Trial [Bucher]) and adjusted (NMA FE and NMA RE) indirect comparisons of tofacitinib to adalimumab - TNF inhibitor naïve population

Trial ID	bDMARD	Placebo	OR (95% CI) or (95% CrI)			RR (95% CI) or (95% CrI)		
			Trial [Bucher]	NMA FE	NMA RE	Trial	NMA FE	NMA RE
Tofacitinib 5mg bd versus placebo (month 3)								
OPAL BROADEN	54/107 (50)	35/105 (33)	**2.04 (1.17, 3.55)**	**2.72 (1.65, 4.55)**	2.63 (0.67, 10.08)	**1.51 (1.09, 2.10)**	**2.02 (1.40, 3.07)**	1.95 (0.72, 4.25)
Adalimumab 40mg Q2W versus placebo (week 12)								
OPAL BROADEN	55/106 (52)	35/105 (33)	**2.16 (1.17, 3.56)**	**3.67 (2.72, 4.98)**	**3.52 (1.64, 7.50)**	**1.56 (1.12, 2.16)**	**2.44 (1.70, 3.42)**	**2.33 (1.41, 3.96)**
SPIRIT-P1	52/101 (52)	33/106 (31)	**2.35 (1.33, 4.14)**			**1.65 (1.18, 2.32)**		
Genovese 2007	20/51 (39)	8/49 (16)	**3.31 (1.29, 8.49)**			**2.40 (1.17, 4.94)**		
ADEPT	87/151 (58)	23/162 (14)	**8.22 (4.76, 14.19)**			**4.06 (2.71, 6.07)**		
Meta-analysis	214/409 (52)	99/422 (24)	**3.44 (1.74, 6.81)**	-	-	**2.20 (1.36, 3.56)**	-	-
Indirect comparison (tofacitinib versus adalimumab)			0.59 (0.25, 1.43)	0.74 (0.45, 1.22)	0.74 (0.19, 2.88)	0.69 (<u>0.38</u>, 1.23)	0.85 (<u>0.59</u>, 1.11)	0.85 (<u>0.31</u>, 1.70)

ACR – American College of Rheumatology; bd – twice daily; CI - Confidence Interval; CrI – Credible interval; FE - Fixed Effect; n - number of participants with event; N - total number of participants in group; NMA - Network meta-analysis; OR - Odds Ratio; Q2W – once every 2 week; RE – Random Effect; RR - Relative Risk.

Bold typography indicates statistically significant differences between treatments

Underlined values represent the values compared against the non-inferiority margin of 0.46 for ACR20

Source: Table 2.44, p114 of the submission & Attachment 3 Appendix D (Network Meta-analysis Results) Excel Spreadsheet

Table 7: ACR50 response for the unadjusted (Trial [Bucher]) and adjusted (NMA FE and NMA RE) indirect comparisons of tofacitinib to adalimumab - TNF inhibitor naïve population

Trial ID	bDMARD	Placebo	OR (95% CI) or (95% CrI)			RR (95% CI) or (95% CrI)		
			Trial [Bucher]	NMA FE	NMA RE	Trial	NMA FE	NMA RE
Tofacitinib 5mg bd versus placebo (month 3)								
OPAL BROADEN	30/107 (28)	10/105 (10)	**3.70 (1.70, 8.04)**	**6.08 (3.14, 12.10)**	**5.79 (1.39, 12.12)**	**2.94 (1.52, 5.71)**	**4.64 (2.61, 8.54)**	**4.44 (1.36, 11.78)**
Adalimumab 40mg Q2W versus placebo (week 12)								
OPAL BROADEN	35/106 (33)	10/105 (10)	**4.68 (1.72, 7.97)**	**8.95 (5.65, 14.81)**	**9.21 (4.24, 23.65)**	**3.47 (1.81, 6.63)**	**6.21 (3.50, 10.30)**	**6.24 (3.09, 12.77)**
SPIRIT-P1	30/101 (30)	5/106 (4.7)	**8.54 (3.16, 23.07)**			**6.30 (2.54, 15.59)**		
Genovese 2007	13/51 (25)	1/49 (2)	**16.42 (1.29, 8.49)**			**12.49 (1.70, 91.91)**		
ADEPT	87/151 (58)	23/162 (14)	**14.47 (6.00, 34.92)**			**9.66 (4.28, 21.79)**		
Meta-analysis	214/409 (52)	99/422 (24)	**8.47 (4.67, 15.39)**	-	-	**6.01 (3.38, 10.70)**	-	-
Indirect comparison (tofacitinib versus adalimumab)			0.44 (0.16, 1.16)	0.68 (0.39, 1.19)	0.63 (0.14, 2.21)	0.49 (0.20, 1.18)	0.77 (0.47, 1.12)	0.74 (0.22, 1.60)

ACR – American College of Rheumatology; bd – twice daily; CI - Confidence Interval; CrI – Credible interval ; FE - Fixed Effect; n - number of participants with event; N - total number of participants in group; NMA - Network meta-analysis; OR - Odds Ratio; Q2W – once every 2 week; RE – Random Effects; RR - Relative risk.

Bold typography indicates statistically significant differences between treatments

Underlined values represent the values compared against the non-inferiority margin of 0.29 for ACR50

Source: Table 2.45, p115 of the submission & Attachment 3 Appendix D (Network Meta-analysis Results) Excel Spreadsheet

6.16 The results of the unadjusted (Trial [Bucher]) and adjusted (NMA FE and RE) indirect comparisons showed that there was no statistically significant difference between tofacitinib and adalimumab based on ACR20 and ACR50 outcomes. However, differences were noted between the comparisons with respect to whether the nominated non-inferiority margins of 0.46 for ACR20 and 0.29 for ACR50 were met.

Table 8: Summary of non-inferiority outcomes by analysis method

Comparison	NI met		Comment
	ACR20	ACR50	
Head-to-head	Yes	Yes	Trial not designed to demonstrate non-inferiority
Indirect (Bucher)	No	No	The high level of statistical heterogeneity in the meta-analyses of the adalimumab trials and variation in placebo response rates across the trials compromised the validity of the indirect comparison.
NMA (fixed effects)	Yes	Yes	Cannot be considered a reliable source of evidence to inform the clinical claim of the submission due to issues regarding the validity and reliability of the methods and results.
NMA (random effects)	No	No	

Source: Compiled during the evaluation.

6.17 Notably, ranking of the bDMARDs was also an output of the NMA, with tofacitinib fairly consistently being ranked as one of the least effective therapies (alongside certolizumab pegol and ustekinumab), with infliximab and golimumab being consistently ranked among the better treatments.

6.18 The PSCR argued there was sufficient evidence to support the non-inferiority of tofacitinib to adalimumab, noting that the minimally clinically important difference (MCID) was met for ACR50 in the head-to-head comparison. The PSCR acknowledged that the OPAL BROADEN trial was not powered to demonstrate non-inferiority, but considered it informs the relative efficacy of tofacitinib and adalimumab under the same controlled conditions. The PSCR also argued that, as noted by the evaluation, the results of the indirect comparison using the Bucher method were not reliable, and in the case of the network meta-analyses, stated that while there was insufficient data to inform the random effects model there was no meaningful difference in model fit between the random effects model and the fixed effects model (which met the MCID), therefore the claim of non-inferiority is reasonable. The pre-PBAC response maintained there is sufficient evidence to support the non-inferiority of tofacitinib to adalimumab.

6.19 The ESC noted the results of the four analyses presented in the evaluation and the arguments in the PSCR. Overall, ESC considered there was uncertainty regarding whether tofacitinib had satisfactorily established non-inferiority to adalimumab with regards to comparative effectiveness due to the variable outcomes of the methods used. The ESC considered there was a trend towards tofacitinib being inferior to adalimumab.

6.20 As noted above, certolizumab pegol, ustekinumab and secukinumab are considered to represent a 'lower tier' of alternatives for the treatment of PsA on the PBS. During the evaluation, indirect comparisons of tofacitinib versus certolizumab pegol and ustekinumab for ACR20 and ACR50 response indicated that the specified non-inferiority margin of 0.46 and 0.29, respectively, on the lower confidence interval of the relative risk statistic, was met when including all available evidence for the comparators (i.e. the meta-analyses). While slight differences in the placebo response rates were observed between the trials, the magnitude of the differences was far less than that observed in the indirect comparison versus adalimumab. The outcomes of the indirect comparisons with certolizumab pegol and ustekinumab undertaken during the evaluation are presented in the tables below for ACR20 and ACR50 outcomes, respectively.

Table 9: ACR20 response for the indirect comparison of tofacitinib to certolizumab pegol and ustekinumab - TNF inhibitor naïve population

Trial	bDMARD n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
Tofacitinib v placebo (13 weeks)					
OPAL-BROADEN	54/107 (50.5)	35/105 (33.3)	**2.04 (1.17, 3.55)**	**1.51 (1.09, 2.10)**	**0.17 (0.04, 0.30)**
Certolizumab pegol v placebo (12 weeks)[a b]					
RAPID-PsA 200mg	66/107 (61.7)	29/110 (26.4)	**4.50 (2.53, 8.00)**	**2.34 (1.66, 3.31)**	**0.35 (0.23, 0.48)**
RAPID-PsA 400mg	55/112 (49.1)		**2.70 (2.56, 7.90)**	**1.86 (1.29, 2.68)**	**0.23 (0.10, 0.35)**
Meta-analysis results			**3.46 (2.32, 5.17)**	**2.10 (1.63, 2.70)**	**0.29 (0.20, 0.38)**
Indirect (TOF v CZP 200mg)			0.45 (0.20, 1.01)	0.65 (0.40, 1.04)	-0.18 (-0.36, 0.00)
Indirect (TOF v CZP 400mg)			0.76 (0.34, 1.67)	0.81 (0.50, 1.33)	-0.06 (-0.24, 0.12)
Indirect (TOF vs CZP-meta-analysis)			0.59 (0.30, 1.17)	0.72 (0.48, 1.09)	-0.12 (-0.28, 0.04)
Ustekinumab v placebo (24 weeks)[c d]					
PSUMMIT 1 45mg	87/205 (42.4)	47/206 (22.8)	**2.49 (1.63, 3.82)**	**1.86 (1.38, 2.50)**	**0.20 (0.11, 0.28)**
PSUMMIT 2 45mg	23/43 (53.5)	12/42 (28.6)	**2.88 (1.17, 7.06)**	**1.87 (1.08, 3.26)**	**0.25 (0.05, 0.45)**
Meta-analysis results			**2.56 (1.74, 3.77)**	**1.86 (1.43, 2.42)**	**0.21 (0.12, 0.29)**
Indirect (TOF v UST 45mg PSUMMIT 1)			0.82 (0.41, 1.65)	0.81 (0.52, 1.26)	-0.03 (-0.19, 0.13)
Indirect (TOF v UST 45mg PSUMMIT 2)			0.71 (0.25, 2.04)	0.81 (0.43, 1.54)	-0.08 (-0.32, 0.16)
Indirect (TOF vs UST-meta-analysis)			0.80 (0.41, 1.57)	0.81 (0.53, 1.24)	-0.05 (-0.20, 0.12)

Source: Analyses conducted during evaluation based on data provided in NMA Excel Model (Attachment 3 Appendix D)
Bold typography indicates statistically significant differences between treatments
Underlined values represent the values compared against the non-inferiority margin of 0.46 for ACR20

[a] Results from the TNF-naïve sub-population
[b] Assessment for initial response on the PBS for certolizumab pegol occurs at 14-16 weeks (must not receive more than 18-20 weeks of treatment under Initial 1 criteria)
[c] Results from the TNF-naïve sub-population of PSUMMIT 2; results from the total trial population of PSUMMIT 1 as all PSUMMIT 1 patients were TNF-naïve
[d] Assessment for initial response on the PBS for ustekinumab occurs at 24 weeks (must not receive more than 28 weeks of treatment under Initial 1 criteria)

Abbreviations: bDMARD – biological disease-modifying anti-rheumatic drug; CI = confidence interval; n = number; OR = odds ratio; RD = risk difference; RR = relative risk

6.21 The indirect comparisons of tofacitinib versus certolizumab pegol and ustekinumab for ACR20 response indicated that the specified non-inferiority margin of 0.46 on the lower confidence interval of the relative risk statistic was met in both instances.

Table 10: ACR50 response for the indirect comparison of tofacitinib to certolizumab pegol and ustekinumab

Trial	bDMARD n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
Tofacitinib v placebo (13 weeks)					
OPAL-BROADEN	30/107 (28.0)	10/105 (9.5)	**3.70 (1.70, 8.04)**	**2.94 (1.52, 5.71)**	**0.19 (0.08, 0.29)**
Certolizumab pegol v placebo (12-14 weeks)[a] [b]					
RAPID-PsA 200mg + 400mg	74/219 (33.8)	14/110 (12.7)	**3.50 (1.82, 7.08)**	**2.65 (1.57, 4.48)**	**0.21 (0.12, 0.29)**
Indirect (TOF v CZP 200mg + 400mg)			1.06 (0.38, 2.97)	1.11 (0.48, 2.58)	-0.02 (-0.16, 0.12)
Ustekinumab v placebo (24 weeks)[c] [d]					
PSUMMIT 1 45mg	51/205 (24.9)	18/206 (8.7)	**3.46 (1.94, 6.17)**	**2.85 (1.72, 4.70)**	**0.16 (0.09, 0.23)**
Indirect (TOF v UST 45mg)			1.07 (0.41, 2.82)	1.03 (0.45, 2.37)	0.03 (-0.10, 0.16)

Source: Analyses conducted during evaluation based on data provided in NMA Excel Model (Attachment 3 Appendix D)
Bold typography indicates statistically significant differences between treatment groups
Underlined values represent the values compared against the non-inferiority margin of 0.29 for ACR50
[a] Results from the TNF-naïve sub-population, Certolizumab pegol PSD November 2014; Secukinumab PSD March 2016
[b] Assessment for initial response on the PBS for certolizumab pegol occurs at 14-16 weeks (must not receive more than 18-20 weeks of treatment under Initial 1 criteria)
[c] Results from the total trial population as all patients in PSUMMIT 1 were TNF-naive
[d] Assessment for initial response on the PBS for ustekinumab occurs at 24 weeks (must not receive more than 28 weeks of treatment under Initial 1 criteria)
Abbreviations: bDMARD – biological disease-modifying anti-rheumatic drug; CI = confidence interval; n = number; OR = odds ratio; RD = risk difference; RR = relative risk

6.22 The indirect comparisons of tofacitinib versus certolizumab pegol and ustekinumab for ACR50 response indicated that the specified non-inferiority margin of 0.29 on the lower confidence interval of the relative risk statistic was met in both instances.

6.23 As stated above, the PSCR and pre-PBAC response argued that certolizumab pegol and ustekinumab were not relevant main comparators on the basis those bDMARDs are unlikely to be replaced with tofacitinib to any large extent.

6.24 The ESC did not accept the PSCR arguments that certolizumab pegol and ustekinumab (and by extension, secukinumab) were not relevant comparators, as they are PBS-listed and used in PsA. The ESC considered that, on the basis of the indirect comparisons undertaken during the evaluation, it was likely that tofacitinib was non-inferior to certolizumab pegol and ustekinumab with regards to comparative effectiveness.

Comparative harms

6.25 Across all adverse events of interest in the OPAL BROADEN trial, adverse events were similar between the tofacitinib and adalimumab treatment groups. There were no statistically significant differences at Week 13, with the exception of injection site reactions. Eleven patients in the adalimumab treatment group (10.1%) experienced injection site reactions at Week 13 compared to no patients in the tofacitinib treatment group. At Week 52, there were more patients treated with adalimumab

who experienced a treatment emergent adverse event compared to tofacitinib (47.2% versus 31.8%, p<0.05).

Benefits/harms

6.26 On the basis of direct evidence (OPAL BROADEN), there were no statistically significant differences between tofacitinib and adalimumab in terms of improving tender and swollen joints (ACR20 and ACR50 response), which is a predominant feature of PsA.

6.27 On the basis of the direct evidence from the OPAL BROADEN trial, the frequency of adverse events between tofacitinib and adalimumab appeared to be comparable, although there were more injection site reactions with adalimumab: per 100 patients treated, 10 more patients with adalimumab will have injection site reactions over a 13 week period.

Clinical claim

6.28 The submission described tofacitinib as non-inferior in terms of comparative effectiveness and safety compared to adalimumab in patients with PsA who have inadequately responded to csDMARDs.

6.29 The claim of non-inferior safety of tofacitinib to adalimumab appears to be adequately supported. However, the ESC considered the claim of non-inferior comparative effectiveness was not definitively substantiated by the evidence presented in the submission and agreed with the evaluation that the possibility that tofacitinib is inferior to adalimumab in terms of effectiveness could not be excluded.

6.30 Indirect comparisons of tofacitinib versus certolizumab pegol and ustekinumab supported a conclusion of non-inferiority in terms of effectiveness to these 'lower tier' PBS-listed bDMARDs for the treatment of PsA.

6.31 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data, and that tofacitinib trended towards being inferior to adalimumab.

6.32 The PBAC considered that the claim of non-inferior comparative safety was reasonably supported by the data.

Economic analysis

6.33 A cost-minimisation analysis was presented for tofacitinib versus adalimumab, based on a claimed equi-effective dose of tofacitinib 5mg bd = adalimumab 40mg subcutaneously every two weeks.

6.34 The submission did not incorporate the cost of concomitant csDMARD use in the derivation of the cost-minimised price for tofacitinib ($1,764.24). The ESC noted the PSCR disagreed with the assertion in the evaluation that the cost of concomitant DMARD use should be included in the cost-minimised price as DMARD use is common for many patients on bDMARD treatment. The ESC agreed with the PSCR it was appropriate not to include the cost of DMARDs in the cost-minimised price.

6.35 The requested DPMQ for tofacitinib of $1,764.24 (5mg x 56 tablets) was based on the AEMP for adalimumab of $1,630.01 (with current mark-ups and dispensing fees added), which was the price adalimumab was originally listed at in March 2006. The submission cited Clause 5.7 of the Strategic Agreement with Medicines Australia for this approach, such that the statutory price reductions that have since been applied to adalimumab since listing are not taken into consideration in the current cost-minimised requested price.

6.36 The ESC noted there are two pricing tiers of bDMARDs used for the treatment of PsA – a 'lower tier' including certolizumab pegol, ustekinumab and secukinumab, and a 'higher tier' including adalimumab, etanercept, infliximab and golimumab. The ESC was not satisfied that tofacitinib had established non-inferiority with adalimumab; however, it considered that tofacitinib appeared to be non-inferior to certolizumab pegol and ustekinumab (based on the indirect comparisons undertaken during the evaluation).

6.37 The ESC noted that given the submission had not demonstrated that tofacitinib "provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative bDMARDs", the cost-minimisation should be to the lowest cost bDMARD for the treatment of PsA currently listed on the PBS.

Drug cost/patient/year

6.38 Tofacitinib drug cost per patient per year would be $22,935.12 based on the requested DPMQ of $1,764.24 and 13 scripts per year (each script sufficient for 28 days of treatment); this cost per year does not include the cost for required concomitant conventional synthetic disease modifying anti-rheumatic drug (csDMARD) use. This compares with $16,504.80 for adalimumab based on the current DPMQ of $1,269.60 and 13 scripts per year (each script sufficient for 28 days of treatment); adalimumab can be used with or without concomitant csDMARDs.

Estimated PBS usage & financial implications

6.39 This submission was not considered by DUSC.

6.40 While the usage estimates presented in the submission were considered in the evaluation to be relevant and informative, but likely underestimated, the total cost of tofacitinib is likely to vary from that presented depending on the accepted comparator price. The net financial implications of listing tofacitinib as presented in the submission are provided in Table 11 for completeness.

Table 11: Submission estimations of the net financial implications of listing tofacitinib

Estimated parameter	2019	2020	2021	2022	2023	2024
Annual market growth rate	18%	17%	16%	15%	14%	14%
Tofacitinib market share uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Total PBS/RPBS tofacitinib services	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PBS/RPBS costs (less co-payments)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total bDMARD script volume displacement by tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total bDMARD PBS/RPBS cost-offsets (less co-payment)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications to the PBS/RPBS of listing tofacitinib	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications to the health budget of listing tofacitinib	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Tables 4.4, 4.8, 4.10, 4.11, 4.13 & 4.14 in Section 4 of the submission
Abbreviations: bDMARD = biological disease-modifying anti-rheumatic agent; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted table shows that at Year 6 the estimated number of scripts dispensed was less than 10,000 per year.

6.41 In brief, based on the requested price for tofacitinib (DPMQ of $1,764.24), the submission estimated a net cost to government of less than $10 million per year in Year 1, rising to less than $10 million per year in Year 6. This is a likely underestimate as cost-offsets associated with adalimumab substitution were overestimated as the adalimumab DPMQ was assumed to be $1,764.24 rather than its current DPMQ of $1,269.60. The ESC considered annual growth rates of the bDMARD market was a likely underestimate with assumptions of decreasing growth from 2019 to 2024 and that the tofacitinib market share was underestimated.

6.42 Should tofacitinib be cost-minimised to the least costly bDMARD the net impact on the PBS/RPBS budget should result in nil cost.

Quality Use of Medicines

6.43 To address the concern of patient difficulty in adhering to the tofacitinib treatment regimen, the submission stated a consumer medicine information document, a patient information pack and a patient support program will be developed.

Financial Management – Risk Sharing Arrangements

6.44 In its Pre-PBAC Response, the sponsor requested consideration of a Special Pricing Arrangement (SPA) if the PBAC recommended tofacitinib at a price lower than that requested in the submission.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required listing of tofacitinib on a cost minimisation basis with the least costly biological disease modifying anti-rheumatic drug (bDMARD) for psoriatic arthritis (PsA). In making this recommendation, the PBAC accepted any of the current PBS listed bDMARDs for severe PsA could be an alternative therapy to tofacitinib.

7.2 The PBAC considered the equi-effective doses of tofacitinib (at the recommended dose of 5mg twice daily) and alternative bDMARDs could be derived from the product information and with reference to the previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets.

7.3 The PBAC noted that seven alternative bDMARDs were listed on the PBS for the treatment of PsA at the time of consideration and that it had recommended ixekizumab for this condition at its July 2018 meeting. The PBAC considered that while the clinical need for an additional treatment is low, it may be advantageous for a treatment option with a new mechanism of action and oral manner of administration to be listed for PsA.

7.4 The submission nominated adalimumab as the comparator. The PBAC considered any of the currently PBS listed bDMARDs for severe PsA could be considered an alternative therapy to tofacitinib for the treatment of severe PsA. As described in section 5.2 above, tofacitinib could only be recommended for listing with a higher price than alternative therapies if the PBAC is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction in toxicity.

7.5 No evidence was presented in the submission to support the claim that tofacitinib provided a significant improvement in efficacy or reduction of toxicity compared to the any of the currently PBS listed bDMARDs for severe PsA. The PBAC noted the results of the indirect comparisons with certolizumab pegol and ustekinumab undertaken during the evaluation supported a conclusion of non-inferior effectiveness between tofacitinib and these therapies.

7.6 The submission described tofacitinib to be non-inferior in terms of comparative effectiveness and safety in severe PsA versus adalimumab. The PBAC noted the randomised head-to-head trial (OPAL BROADEN) was not powered to demonstrate the non-inferiority of tofacitinib and adalimumab and that conclusions regarding the non-inferiority of these therapies were difficult based on this study alone. In considering the supplementary analyses, the PBAC noted that while tofacitinib met non-inferiority margins in two of the four analyses (direct comparison and network meta-analysis with fixed effects model), it did not demonstrate non-inferiority in the other two analyses (indirect comparison and network meta-analysis with random effects model). Based on the evidence presented in the submission, the PBAC considered there was some uncertainty around the claim of non-inferior comparative effectiveness. The PBAC considered the trial evidence supported a conclusion of non-

inferior comparative safety between tofacitinib and adalimumab, and was likely to be of similar overall safety to the other bDMARDs PBS listed for PsA. The PBAC considered the the price should be calculated with reference to the previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets against the least costly bDMARD listed for this indication.

7.7 The PBAC considered it would be appropriate to align the listing of tofacitinib with the other written authority bDMARD listings for PsA, including the requested grandfather restriction and that flow-on changes to notes in the other listings to include tofacitinib in the list of therapies would be required to facilitate the listing. The PBAC advised that grandfathered patients will be required to meet the PBS eligibility criteria and noted the grandfather restriction will be removed from the listing after 12 months, in line with standard procedure.

7.8 The PBAC considered there was some uncertainty as to the likely utilisation of tofacitinib, however considered the estimates in the submission were likely to be reasonable. The PBAC considered factors such as tofacitinib being an oral agent compared to other available biologics were likely to drive utilisation. However the PBAC also considered that tofacitinib is likely to be less effective than other agents in patients with more severe skin disease which was likely to be a clinical consideration that may limit the use of tofacitinib. The PBAC considered it would be appropriate if the listing of tofacitinib would be cost neutral or cost saving to the PBS if priced on a cost-minimisation basis versus the lowest cost bDMARD for PsA.

7.9 The PBAC noted the sponsor requested consideration of a special pricing arrangement (SPA) in its pre-PBAC response if the PBAC were minded to recommend tofacitinib at a price lower than that requested in the submission. The PBAC considered that, under criterion 2 of the Special Pricing Arrangement Criteria, tofacitinib has unique characteristics compared to other available therapies for the treatment of severe PsA as the only oral agent.

7.10 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that tofacitinib may be treated as interchangeable on an individual patient basis with ixekizumab, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab and ustekinumab for severe PsA.

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

7.12 The PBAC noted the flow-on restriction changes to the other bDMARDs PBS listed for PsA (noted in Section 8 below).

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Restrictions to be the same as for other bDMARDs for PsA.

Update administrative notes for adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab and ustekinumab to include tofacitinib in the list of drugs eligible as part of a treatment cycle for PsA as follows:

(1) The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological agents adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, tofacitinib and ustekinumab for adult patients with severe active psoriatic arthritis.
(2) Where the term 'biological agents' appears in notes and restrictions, it refers to adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, tofacitinib and ustekinumab only.
(3) All applications for initial treatment will be limited to provide for a maximum of 16 weeks of therapy for adalimumab, etanercept, golimumab, ~~and~~ secukinumab and tofacitinib, 18 to 20 weeks of therapy for certolizumab pegol (depending upon the dosing regimen), 22 weeks of therapy for infliximab, and 28 weeks of therapy for ustekinumab. It is recommended that patients be reviewed in the month prior to completing their course of initial treatment to ensure uninterrupted biological agent supply.
(4) For the purposes of this restriction 'biological agent' means adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, tofacitinib or ustekinumab.

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Severe active psoriatic arthritis
PBS Indication:	Severe active psoriatic arthritis
Treatment phase:	Initial treatment - Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more) Initial treatment - Initial 2 (change or recommencing treatment after a break of less than 5 years)
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
TOFACITINIB Tablet 5 mg, 56	1	2	Xeljanz®	Pfizer Australia Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Severe active psoriatic arthritis
PBS Indication:	Severe active psoriatic arthritis
Treatment phase:	Initial treatment - Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more) or Initial 2 (change or recommencing treatment after a break of less than 5 years) - balance of supply
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Severe active psoriatic arthritis
PBS Indication:	Severe active psoriatic arthritis
Treatment phase:	Initial 3 - grandfather treatment Continuing treatment Initial 3 (grandfather treatment) or Continuing treatment - balance of supply
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.

Clinical criteria:	Patient must have a documented history of severe active psoriatic arthritis, AND Patient must have received non-PBS treatment with this drug for this condition prior to <PBS listing date>, AND Patient must be receiving treatment with this drug for this condition at the time of application, AND Patient must have failed to achieve an adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months, AND Patient must have failed to achieve an adequate response to sulfasalazine at a dose of at least 2 g per day for a minimum period of 3 months; or Patient must have failed to achieve an adequate response to leflunomide at a dose of up to 20 mg daily for a minimum period of 3 months, AND Patient must have demonstrated an adequate response to treatment with this drug, AND Patient must not receive more than 24 weeks of treatment under this restriction.
Population criteria:	Patient must be aged 18 years or older.

9 Context for Decision

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

10 Sponsor's Comment

Pfizer Australia welcomes the PBAC recommendation to list Xeljanz on the PBS for the treatment of severe psoriatic arthritis (PsA).