5.03 BARICITINIB, Tablet 2 mg, Tablet 4 mg, Olumiant®, Eli Lily Australia Pty Ltd

1 Purpose of application

1.1 Authority Required, Restricted Benefit listing for baricitinib for treatment of severe rheumatoid arthritis (RA).

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

Component	Description
Population	Patients with severe active RA in whom an adequate response has not been achieved with at least 6 months of intensive treatment with DMARDs, as per current criteria for PBS-listed bDMARD therapies
Intervention	Baricitinib, administered orally, 4 mg once daily (or 2 mg once daily in case of renal impairment or drug interaction).
Comparator	Primary: adalimumab, 40 mg in 0.8mL biweekly; secondary: tofacitinib, 5 mg twice daily
Outcomes	Clinical response as defined by ACR20, ACR50 and ACR70, structural joint damage assessed radiographically and expressed as change from baseline in mTSS, improvement in physical function measured by HAQ-DI, and patient reported outcomes of duration and severity of morning joint stiffness in the first 12 weeks of treatment.
Clinical claim	In patients with severe active RA for whom an adequate response has not been achieved with conventional therapies, baricitinib is superior to adalimumab for reducing signs and symptoms of RA, improving physical function, patient reported outcomes and low disease activity rates. Baricitinib is equivalent to adalimumab with respect to adverse events.

Source: Table 1.1.1, p 31 of the submission.
ACR = American College of Rheumatology criteria; DMARDs = disease modifying anti-rheumatic drugs; bDMARDs = biological disease modifying anti-rheumatic drugs; HAQ-DI = Health Assessment Questionnaire-Disability Index; mTSS modified Total Sharp Score; PBS = Pharmaceutical Benefits Scheme; RA = rheumatoid arthritis;

2 Requested listing

2.1 The submission requested the same restriction wording and number of repeats for baricitinib as for the currently listed bDMARDS for rheumatoid arthritis, therefore these restrictions have not been duplicated here. The proposed grandfather restriction is included below.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BARICITINIB				
2 mg film-coated tablet, 28	1	3	$[redacted]	Olumiant® Eli Lilly Australia Pty Ltd
4 mg film-coated tablet, 28	1	3	$[redacted]	

Category / Program	*GENERAL – General Schedule (Code GE)*
Prescriber type:	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *Midwives*
Severity:	*Severe active*
Condition:	*Rheumatoid arthritis*
PBS Indication:	*Severe active rheumatoid arthritis*
Treatment phase:	*Initial treatment - Initial 3 (Grandfather patients)*
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 rheumatoid arthritis.*
Clinical criteria:	*Patient must have a documented history of severe active rheumatoid arthritis,* *AND* *Patient must have been receiving 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 not receive more than 16 weeks of treatment under this restriction.*
Population criteria:	*Patient must be aged 18 years or older.*
Prescriber Instructions	*The authority application must be made in writing or online and must include the following (or electronic equivalent):* • *a completed authority prescription form; and* • *a completed Rheumatoid Arthritis PBS Authority Application - Supporting Information Form; and* • *a signed patient acknowledgement.* *All applications for treatment with this drug for this condition under this restriction must include baseline joint count and ESR and/or CRP as determined at the completion of a 6 month intensive DMARD trial but prior to ceasing DMARD therapy.* *If the requirement to demonstrate an elevated ESR or CRP cannot be met, the application must state the reasons why this criterion cannot be satisfied.* *A patient may qualify for PBS-subsidised treatment under this restriction once only.*

Administrative Advice ***(not included in LI)***	*Note:* *Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au.* *Applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Prior Written Approval of Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

2.2 The recommended dose of baricitinib is 4 mg daily, administered as a single tablet once daily. The recommended dose of baricitinib in patients taking organic anion transporter 3 (OAT3) inhibitors with a strong inhibition potential, such as probenecid, is 2 mg once daily.

2.3 The submission requested a special pricing arrangement that would maintain the list price at the same level as that of the published DPMQ for tofacitinib ($[redacted]). The submission did not request a specific effective price, noting that the comparators' effective prices were not available to the sponsor. The submission recognised that the effective price for baricitinib would be revealed post-PBAC, pending recommendation, and would reflect the price considered cost-effective with reference to the comparator's effective price, which is currently unknown.

2.4 The submission stated that the sponsor intended to request the PBAC-approved RA indication specific price for bDMARDs prior to application of the F1 5% reduction on 1 April 2017. The DPMQs of adalimumab and tofacitinib were updated after November 2016 ($1,401.30 and $1,266.87, respectively at May 2017). The published prices no longer appear to reflect this 5% difference, thus it was unclear whether requested price for baricitinib would stay consistent with November 2016 prices or updated prices. The PSCR (p3) stated that the effective price for baricitinib would be the price considered cost-effective with reference to the comparator's effective price.

2.5 In its pre-PBAC Response - noting the ESC advice that all bDMARDs have the same effective ex-manufacturer price for RA – the sponsor re-iterated its intention to request price-parity to tofacitinib. The pre-PBAC response further stated that this removed the need for a cost utility analysis; as a cost-minimisation to tofacitinib, performed on a per pack basis, would be sufficient.

3 Background

3.1 TGA status at time of PBAC consideration: The submission was made under TGA/PBAC Parallel Process. At the time of PBAC advice, the first round TGA clinical evaluator's report was available, but the TGA delegate's overview was not available. The PBAC noted that baricitinib has been approved by EMA and that the FDA Complete

Response Letter on April 14th 2017 indicated that additional clinical data are needed to determine the most appropriate doses and to further characterise safety concerns.

3.2 The pre-PBAC Response provided an update on the progress of the TGA application for registration. The sponsor noted that the evaluation timeline was extended to allow for additional requests for information from the TGA – which have been provided. It noted that the delegate's decision was anticipated to be received by mid-September 2017.

3.3 Baricitinib has not been previously considered by the PBAC.

3.4 Several bDMARDs are listed on the PBS for treatment of RA, including abatacept certolizumab pegol, golimumab, adalimumab, etanercept, infliximab, and rituximab. Tofacitinib, a JAK inhibitor, is the only PBS-listed pharmacological analogue to baricitinib. The PBAC noted that, with the exception of etanercept (the first bDMARD PBS-listed for the treatment of RA), all subsequent bDMARDs have been listed on a cost-minimisation basis.

3.5 The submission noted that baricitinib and tofacitinib are technically targeted synthetic DMARDs as opposed to bDMARDs. As no differences in PBS restrictions are based on this distinction, for concision, unless otherwise specified, tofacitinib and baricitinib are referred to as bDMARDs.

4 Population and disease

4.1 RA is an autoimmune disease that causes painful inflammation in the lining of joints and surrounding structures.

4.2 The submission indicated that baricitinib is intended to be used following inadequate response to a non-biologic DMARD, consistent with the current restrictions for biological DMARDs.

5 Comparator

5.1 The submission nominated adalimumab as the main comparator on the basis that adalimumab was the most commonly prescribed bDMARD in Australia and consequently the most likely to be replaced. The submission also nominated tofacitinib as a supplementary comparator given that it is the only PBS-listed pharmacological analogue to baricitinib, but did not make a clinical claim against it. Though these are both appropriate comparators, any bDMARD PBS-listed for the treatment of RA represented relevant comparators.

5.2 The ESC noted the Department's advice that all bDMARDs have had the same effective ex-manufacturer price for RA (taking into account dosage relativities and dosing regimens) since 1 April 2017 as the result of the application of reference pricing following the listing of tocilizumab subcutaneous injections with a lower price.

5.3 The ESC noted that the market leader is generally only used as a comparator if there is a good reason to exclude pharmacological analogue or the least expensive alternative therapy, and considered that the submission did not adequately justify excluding the pharmacological analogue, tofacitinib, as a comparator.

5.4 In its pre-PBAC response, the sponsor agreed that tofacitinib is a relevant comparator as both medicines belong to the same therapeutic class. Further, it stated that if, the PBAC agreed with ESC that tofacitinib is a more appropriate comparator than adalimumab, then it would agree that a cost-minimisation to tofacitinib is a reasonable approach based on the current body of evidence.

5.5 The PBAC considered that any of the currently PBS listed bDMARDs could be an appropriate alternative therapy.

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 the organisation, 'Creaky Joints Australia', a Health Professional and individuals (21) via the Consumer Comments facility on the PBS website. The comments noted support for availability of this drug and described a range of potential benefits of treatment, including: the availability of an alternate treatment option for those patients who have disease progression or significant adverse reactions to current medication and the availability of an oral treatment which was viewed as preferable to injections and avoids the complexities of cold chain management and storage of medications in a fridge. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.3 The submission is based on one head-to-head trial comparing baricitinib to placebo and to adalimumab (JADV: N = 1,307). Four other placebo-controlled trials were used as supplementary evidence to provide data regarding to use of baricitinib in (i) the bDMARD intolerant or refractory population (JADW); (ii) use of baricitinib with a broader range of concomitant DMARDs including no background cDMARD (JADX and JADZ) and (iii) long term efficacy and safety (JADY).

6.4 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trials		
JADV (RA-BEAM)	A Randomised, Double-Blind, Placebo- and Active-Controlled, Phase 3 Study Evaluating the Efficacy and Safety of Baricitinib in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Methotrexate Therapy. (JADV CSR)	18 Dec 2015
	Taylor PC, Keystone EC, van der Heijde D, Tanaka Y, Ishii T, Emoto K, Yang L, Arora V, Gaich CL, Rooney T, Schlichting DE, Macias W, de Bono S, Weinblatt ME. Baricitinib versus placebo or adalimumab in patients with active rheumatoid arthritis (RA) and an inadequate response to background methotrexate therapy: results of a phase 3 study	[abstract]. Arthritis Rheumatol. 2015;67(suppl 10)2L.
	Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, del Carmen Morales L, Reyes Gonzaga J, Yakushin S, Ishii T, Emoto K, Beattie S, Arora V, Gaich C, Rooney T, Schlichting D, Macias ML, de Bono S, and Tanaka Y.. "Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis."	N Engl J Med. 2017:376:652-662.
Supplementary trials		
JADW (RA-BEACON)	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Evaluating the Efficacy and Safety of Baricitinib (LY3009104) in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Tumor Necrosis Factor Inhibitors	19 Aug 2016
	Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Beattie SD, Koch AE, Cardillo TE, Rooney TP, Macias WL, de Bono S, Schlichting DE, and Smolen JS. "Baricitinib in Patients with Refractory Rheumatoid Arthritis."	N Engl J Med. 2016: 374:1243-1252.
JADX (RA-BUILD)	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib (LY3009104) in Patients with Inadequate Response to Conventional Disease-Modifying Antirheumatic Drugs with Moderately to Severely Active Rheumatoid Arthritis	05 Nov 2015
	Dougados M, vand der Hijde, D, Chen YC, Greenwald M, Drescher E, Liu J, Beattie S, Witt S, inmaculada de la Torre CG, Rooney Schlichting D, de Bono S, and Emery P. "Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs."	Ann Rheum Dis. 2016 0: 1-8
JADZ (RA-BEGIN)	Study I4V-MC-JADZ was a Phase 3, randomized, double-blind, active-controlled study of baricitinib for the treatment of moderately to severely active rheumatoid arthritis during a 52-week treatment period in patients with early rheumatoid arthritis who have had limited treatment with disease-modifying ant rheumatic drugs.	18 Nov 2015
	Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, Zerbini CAF, Gurbuz S, Dickson C, de Bono S, Schlichting D, Beattie S, Kuo WL, Rooney T, Macias WL, and Takeuchi T. "Baricitinib, Methotrexate, or Combination in Patients with Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment."	Arthritis & Rheumatism 2016: (accepted article):1-44.
JADY (RA-BEYOND)	A Phase 3, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Rheumatoid Arthritis	10 August 2015

Source: Table 2.2.3, p77 of the submission.

6.5 The primary trial used as the evidence base of the submission was JADV (baricitinib versus placebo and adalimumab), with the supplementary trials and a network meta-

analysis (NMA) conducted for the economic evaluation. The key features of JADV are summarised in Table 3.

Table 3: Key features of JADV (baricitinib versus adalimumab)

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
JADV	1,307	R, DB, MC/ 52 weeks	Low	Moderate to severe RA	ACR20/50/70, DAS28, mTSS, HAQ-DI	ACR20/50/70, baseline HAQ-DI

Source: compiled during the evaluation.
ACR = American College of Rheumatology; DAS = Disease Activity Score; DB=double blind; HAQ-DI = Health Assessment Questionnaire – disability index; MC=multi-centre; mTSS = modified Total Sharp Score; R=randomised; RA = rheumatoid arthritis

6.6 The JADV trial had the following differences with the Australian treatment population:

- The Australian treatment population is restricted to severe disease, whereas JADV included patients with moderate RA. The submission included subgroup analyses of patients with severe disease both defined by disease activity score 28 - erythrocyte sedimentation rate >5.1 (DAS28-ESR >5.1) and PBS criteria.
- The requested restriction allows for treatment with baricitinib after failure of bDMARDs, whereas the JADV trial population was restricted to patients who were bDMARD naive. The submission addressed this issue by presenting results of the JADW trial, examining the response to baricitinib in the treatment of patients with moderate to severe active RA who had inadequate response to a TNF inhibitor, or other bDMARD. The submission also included results of a post hoc analysis of patients switching from adalimumab to baricitinib in JADV (Taylor et al 2016).
- The Australian population is restricted to patients who have trialled at least 4 months' continuous treatment with each of at least two conventional DMARDs, whereas the JADV population was restricted to patients who had only received methotrexate (MTX) prior to trial entry. To address this issue, the submission presented data from two additional trials: JADX and JADZ. These trials examined the response of baricitinib treatment in patients with moderately to severely active RA who either had inadequate response to cDMARDs (JADX) or had not received prior cDMARDs (JADZ).

6.7 While the submission's analyses indicated generally consistent results using the various supplementary trials, supporting the applicability of the JADV trial to the Australian treatment population, only the subgroup analyses of the JADV trial actually provided specific estimates of treatment effect compared to adalimumab. Given the small incremental improvement in outcomes in the JADV trial, it remained difficult to assess whether this small improvement would be maintained in the Australian setting.

6.8 In its pre-PBAC Response, the sponsor expressed disappointment with the ESC's assessment that it remained difficult to assess whether this small improvement would be maintained in the Australian setting. However, the sponsor acknowledged that head-to-head data for baricitinib and adalimumab is limited to 52 weeks in duration; and noting that all bDMARDs have been PBS-listed on a cost-minimisation basis in RA,

(with the exception of the first bDMARD) the sponsor accepted that the PBAC may not be willing to definitively accept a conclusion of clinical superiority to adalimumab at this time.

Comparative effectiveness

6.9 The submission stated that the key secondary outcomes of interest to the submission were the analysis of baricitinib compared to adalimumab at week 12 measured by both ACR20 and DAS28-hsCRP.

6.10 The submission stated that the trial was powered for both a non-inferiority analysis and a secondary gated analysis that was planned to test for superiority under defined circumstances. Specifically, the pre-determined non-inferiority margin of -12% was selected. If the lower confidence interval in the difference of rates (or risk difference) was greater than -12%, baricitinib would be determined non-inferior to adalimumab. Secondly, if the lower confidence interval were found to be greater than 0%, baricitinib would be determined to be superior to adalimumab.

6.11 The selection of the -12% non-inferiority threshold was based on that of the AMPLE study comparing the efficacy of abatacept SC and adalimumab in patients with RA. The 12% threshold in AMPLE was expected to preserve at least 50% of the treatment effect based on results from other studies. This allowed for a maximum difference of -4.7% (95% CI: -12%, 2.6%) in the ACR20 response, a difference that was considered to be clinically meaningful.

6.12 The PBAC has previously accepted the outcomes of ACR20, ACR50 and DAS28 scores for bDMARD therapies for the treatment of RA. The ACR50 outcome has also previously been considered to be outcome of most interest in the assessment of bDMARDs for the treatment of psoriatic arthritis as it is more stringent than ACR20 and reflects to a greater degree the current PBS criteria for eligibility for continuing treatment with a bDMARD (Certolizumab PSD, November 2014).

6.13 The selection of 0% as a threshold for superiority allowed any marginal statistically significant improvement over adalimumab to be judged as superiority, in the absence of demonstrating this was a clinically meaningful difference. Applying the additive inverse of the non-inferiority margin (+12%) to determine superiority may be useful.

6.14 Table 4 presents the key efficacy outcomes of JADV.

Table 4: Results of ACR20 and ACR50 outcomes in the direct randomised JADV trial

Dichotomous outcomes		Baricitinib n (%) (N=487)			Adalimumab n (%) (N=330)			Odds ratio (95% CI)	Risk difference (95% CI)
Week 12									
ACR20		339 (69.6)			202 (61.2)			**1.5 (1.08,1.95)**	**0.08 (0.02, 0.15)**
ACR50		219 (45.0)			115 (34.8)			**1.53 (1.15, 2.04)**	**0.10 (0.03, 0.17)**
Week 24									
ACR20		360 (73.9)			219 (66.4)			1.30 (0.96, 1.75)	0.06 (-0.01, 0.12)
ACR50		246 (50.5)			150 (45.5)			1.23 (0.93, 1.62)	0.05 (-0.02, 0.12)
Week 52									
ACR20		347 (71.3)			203 (61.5)			**1.55 (1.15, 2.09)**	**0.10 (0.03, 0.16)**
ACR50		272 (55.9)			155 (47.0)			**1.43 (1.08, 1.89)**	**0.09 (0.02, 0.16)**
Continuous outcomes		**Baricitinib**			**Adalimumab**				**Difference in means**
		Baseline (SD)	**End point (SD)**	**Change (SD)**	**Baseline (SD)**	**End point (SD)**	**Change (SD)**		**LSM difference (95% CI)**
DAS28-hsCRP (Week 12)		5.76 (0.92)	3.49 (1.27)	-2.27 (1.22)	5.76 (0.94)	3.76 (1.38)	-1.98 (1.28)		**-0.28 (-0.44, -0.12)**
HAQ-DI (Week 12)		1.57 (0.68)	0.91 (0.69)	-0.65 (0.59)	1.59 (0.70)	1.03 (0.69)	-0.56 (0.54)		**-0.10 (-0.17, -0.03)**
mTSS	Week 16	42.46 (50.11)	42.83 (50.42)	0.33 (1.33)	44.35 (51.02)	44.51 (51.12)	0.26 (1.13)		0.07 (-0.15, 0.29)
	Week 24		42.88 (50.21)	0.35 (1.59)		44.64 (51.12)	0.29 (1.47)		0.07 (-0.19, 0.34)
	Week 52		43.06 (50.13)	0.60 (2.54)		44.87 (51.27)	0.51 (2.78)		0.10 (-0.40, 0.61)

Source: 2.5.11, p106 of the submission and Tables JADV.11.10-12, p p270-279 of the JADV CSR, 2.5.3 p,97 of the submission and Table JADV 11.13, p281-282 of CSR, 2.5.5 of the submission and Table JADV 14.24, p 1367 & 1376 of the CSR

ACR = American College of Rheumatology; CI = confidence interval; DAS28 = disease activity scale; HAQ health assessment questionnaire; disability index; hsCRP = high sensitivity C-reactive protein; n = number of participants with event; mTSS = modified Total Sharp Score; N = total participants in group; SD = standard deviation

Note: the submission and CSR presented difference in rates; these values were presented as risk differences (e.g. 0.084 instead of 8.4) for consistency with previous PBAC considerations.

Note: No statistical comparisons between baricitinib and adalimumab were included in the submission for weeks 24 and 52. Consequently, risk differences and odds ratios were calculated during the evaluation.

Bold typography indicates statistically significant differences.

6.15 The results indicated a statistically significant improvement in ACR outcomes at week 12. There was also a statistically significant improvement in DAS28-hsCRP at week 12 compared to adalimumab. There were no statistically significant changes in radiographic progression defined by mTSS.

6.16 However, the ESC considered that the difference was marginal and was unlikely to be clinically meaningful as no point estimate was above the non-inferiority margin of 12%. The Pre-Sub-Committee Response (PSCR p1-2) claimed that the consistency in direction of effect across primary and secondary outcomes supported the clinical significance of the results. However, the ESC noted there was considerable overlap in the factors used to calculate the ACR20 and the secondary outcome measures, and

therefore this does not provide any additional certainty of effect. Further, the ESC noted that the rates of ACR20 response at 16 weeks (the last time point before 'rescue') did not differ significantly between baricitinib and adalimumab.

Comparative harms

6.17 Table 5 presents a summary of key adverse events in the JADV trial.

Table 5: Summary of key adverse events in the JADV trial

Trial ID	Placebo, n (%) (N=488)	Baricitinib, n (%) (N=487)	Adalimumab, n (%) (N=330)	RD (Bari vs Ada) (95% CI)
Weeks 0-12				
Patients with ≥1 AE	430 (88.1)	432 (88.7)	292 (88.5)	0.00 (-0.04, 0.05)
Serious adverse event by ICH	14 (2.9)	12 (2.5)	4 (1.2)	0.01 (-0.01, 0.03)
Discontinuation due to AE or death	13 (2.7)	12 (2.5)	6 (1.8)	0.01 (-0.01, 0.03)
Interruption from study drug due to AE	32 (6.6)	33 (6.8)	19 (5.8)	0.01 (-0.02, 0.04)
TEAE	232 (47.5)	259 (53.2)	169 (51.2)	0.02 (-0.05, 0.09)
TEAE rated as severe	14 (2.9)	10 (2.1)	4 (1.2)	0.01 (-0.01, 0.03)
Adverse event related to study drug	78 (16.0)	105 (21.6)	66 (20.0)	0.02 (-0.04, 0.07)
Weeks 0 -24				
Patients with ≥1 AE	441 (90.4)	448 (92.0)	300 (90.9)	0.01 (-0.03, 0.05)
Serious adverse event by ICH	22 (4.5)	23 (4.7)	6 (1.8)	**0.03 (0.01, 0.05)**
Discontinuation due to AE or death	17 (3.5)	24 (4.9)	7 (2.1)	0.03 (0.00, 0.05)
Interruption from study drug due to AE	45 (9.2)	48 (9.9)	29 (8.8)	0.01 (-0.03, 0.05)
TEAE	295 (60.5)	347 (71.3)	224 (67.9)	0.03 (-0.03, 0.10)
TEAE rated as severe	19 (3.9)	21 (4.3)	6 (1.8)	0.03 (0.00, 0.05)
Adverse event related to study drug	102 (20.9)	156 (32.0)	92 (27.9)	0.01 (-0.03, 0.05)
Weeks 0 – 52				
Serious adverse event	NA	38 (8)	13 (4)	0.04 (0.01, 0.07)
Any adverse event after start of therapy		384 (79)	253(77)	0.02 (-0.04, 0.08)
Withdrawal because of adverse event		36 (7)	13 (4)	0.04 (0.00, 0.07)
Infection		233 (48)	145 (44)	0.04 (-0.03, 0.11)
Serious infection		10 (2)	5 (2)	0.01 (-0.01, 0.02)
Cancer		3 (<1)	0	0.00 (-0.00, 0.01)

Source: Tables 2.5.13, 2.5.15, and 2.5.18 p 113,114-115 and p119 of the submission.
Abbreviations: AE = adverse event; CI = confidence interval; ICH = international conference on harmonization; RD = risk difference; TEAE = treatment emergent adverse event
Bold typography indicates statistically significant differences

6.18 Overall, there were no differences in adverse events between adalimumab and baricitinib in the JADV trial, with the exception of serious adverse events occurring more frequently among those treated with baricitinib. In the baricitinib group compared with the adalimumab group, there were also slightly higher rates, verging on statistical significance, in a few key adverse events, specifically, discontinuation

from study drug due to adverse events or death. The risk difference tended to increase as the study progressed given the increased duration of exposure to the study drugs.

6.19 The PSCR (p2) claimed that the difference in adverse events between baricitinib and adalimumab was a chance finding, and inconsistent with the data from adalimumab trials. The ESC noted that the sponsor believed AEs data unreliable, and considered whether a similar reliability issue existed with the effectiveness data.

Benefits and harms

6.20 On the basis of the comparison presented in the submission, the PBAC concluded that baricitinib was non-inferior to other bDMARDs in terms of effectiveness, but less safe. Accordingly, only comparative harms for baricitinib versus adalimumab are presented in Table 6.

Table 6: Summary of comparative harms for baricitinib versus adalimumab

Harms						
JADV	**Baricitinib n (%) (N=487)**	**Adalimumab n (%) (N=330)**	**RR (95% CI)**	**Events/100 patients***		**RD (95% CI)**
				Baricitinib	**Adalimumab**	
Serious adverse events (weeks 0-52)	38 (8)	13 (4)	1.98 (1.07, 3.66)	8/100	4/100	**0.04 (0.01, 0.07)**

Abbreviations: PBO = placebo; RD = risk difference; RR = risk ratio
Source: Compiled during the evaluation
* Trial duration of 52 weeks, with endpoint assessments at Weeks 12, 24 and 52
Bold typography indicates statistically significant differences

6.21 On the basis of JADV trial, for every 100 patients treated with baricitinib in comparison to adalimumab:

- approximately 4 additional patients would have serious adverse events in the first 52 weeks of treatment.

Clinical claim

6.22 The ESC considered that the claim that baricitinib was superior in terms of effectiveness compared with adalimumab was not adequately supported. Specifically, the point estimates for the major secondary endpoint of ACR20 at week 12 failed to demonstrate an improvement of greater than 12%, when the pre-specified non-inferiority margin was -12%. Further, there was no clear evidence that the 12 week improvements would be maintained long term or in the Australian treatment setting.

6.23 The ESC considered that the overall claim of equivalent safety appeared to be supported, with the important exception of more serious adverse events in the baricitinib group compared to the adalimumab group. These differences could be meaningful in a larger population and over a longer time frame.

6.24 The ESC considered that claim of non-inferiority against adalimumab in terms of efficacy and safety may have been more appropriate.

6.25 The PBAC considered that the claim superior comparative effectiveness to adalimumab was not adequately supported by the data.

6.26 The PBAC considered that the claim of equivalent safety was not adequately supported by the data. In particular the PBAC expressed concerns about the higher number of serious adverse events in the baricitinb group.

6.27 The PBAC noted the sponsor's acknowledgement in its pre-PBAC response that a cost-minimisation to tofacitinib would also be appropriate, but did not consider the clinical evidence for this approach at this time.

Economic analysis

6.28 The submission presented a cost-utility analysis based on the results of the JADV trial as well as the results of a Bayesian network meta-analysis (NMA). The submission compared two sequences of RA medicines over a 5-year period, one sequence beginning with baricitinib and one beginning with adalimumab. The submission's primary basis for a superiority claim over adalimumab was marginal gains in ACR response that may not have been clinically meaningful. The submission also applied differential point estimates for the effectiveness of all subsequent therapies which was not supported given the results of the NMA indicate that all 95% confidence intervals overlapped to some degree and the history of listing of bDMARDs on the PBS has been based on non-inferiority conclusions and associated cost-minimisation approach. The base case of the economic model was based on small increments of both costs and effectiveness that made the results unlikely to be reliable over a 5-year period.

6.29 Table 7 presents the specific sequences in the base case, the submission's sensitivity analysis, and two alternative analyses tested during the evaluation. The base case presented in the submission was consistent with tofacitinib being the nominated comparator, as use of adalimumab was displaced and tofacitinib was replaced. The sensitivity analysis presented in the submission was consistent with adalimumab being the nominated comparator, and given the remaining sequence of treatments were identical between the two arms, negated the need for modelling costs and effects of subsequent therapies. However, the ESC noted that this assumes that patients in the two arms commence third line treatment at the same time.

Table 7: Treatment sequences in the base case and in sensitivity analyses

	1st line	2nd line	3rd line	4th line	5th line	Rescue
Base case						
Intervention*	Baricitinib	Adalimumab	Etanercept	Infliximab	Tocilizumab	Palliative**
Comparator*	Adalimumab	Tofacitinib				
Submission sensitivity analysis						
Intervention*	Baricitinib	Tofacitinib	Etanercept	Infliximab	Tocilizumab	Palliative**
Comparator*	Adalimumab					
Alternative analysis 1						
Intervention*	Baricitinib	Adalimumab	Etanercept	Infliximab	Tocilizumab	Palliative**
Comparator*	Tofacitinib					
Alternative analysis 2						
Intervention*	Adalimumab	Baricitinib	Etanercept	Infliximab	Tocilizumab	Palliative**
Comparator*		Tofacitinib				

Source: Table 3.3.2, p 174 and 3 and Table .9.1, p191

* All treatments were administered with concomitant methotrexate

** Palliative treatment was comprised of leflunomide, gold and cyclosporin

6.30 Table 8 presents a summary of the model structure and rationale.

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case versus 52 weeks in JADV trial (and 12 week JADV data included in the model).
Outcomes	HAQ, QALYs.
Methods used to generate results	Discrete event simulation (DES).
Health states	Each treatment in a sequence was associated with an ACR score that determined the probability of staying on treatment, or failing response and moving to the next treatment in the sequence. Each ACR state was associated with an HAQ score mapped to EQ-5D.
Utilities	Calculated through a 3-class mixture model mapping HAQ-DI to EQ-5D developed by Hernandez Alava (2012).
Cycle length	NA
Transition probabilities	Based on ACR response in JADV and Bayesian network meta-analysis (NMA).

Source: Table 3.1.1, p166 of the submission.

ACR = American college of rheumatologists; DES = discrete event simulation; EQ-5D = EuroQol 5 Dimensions; HAQ = Health Assessment Questionnaire – disability index; NA = not applicable; NMA = network meta-analysis; QALY = quality adjusted life-year

6.31 The submission considered that a discrete event simulation (DES) was more appropriate than a Markov model for RA, based on review of the literature. Specifically, the submission considered a DES could more efficiently incorporate the level of detail required in the model. The ESC agreed that this was an appropriate structure.

6.32 Table 9 provides a summary of the key drivers of the model.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Drug prices	The submission used published prices from November 2016. The prices for many RA medicines including both adalimumab and tofacitinib have changed since then.	High, may favour baricitinib if baricitinib requested price remains consistent with Nov 2016 prices.
Adverse events	Not included in the base case	High, favours baricitinib
Hospitalisation costs	Derived from UK hospitalisation costs by HAQ score	Small, may favour baricitinib
Utilities	Three-class mixture model Hernandez Alava (2012). HAQ and HRQoL assumed to be flat until patient moves to palliative care.	Moderate, favours baricitinib
Effect estimates	Trial based JADV ACR response rates	Moderate, favours baricitinib
	Network Meta-Analysis ACR response rates	*High, favours baricitinib*
Association of ACR and HAQ	*HAC parameters assumed based on the ACR score.*	*Uncertain*
Treatment persistence	Persistence following ACR50 or ACR70 appears to be based on aggregate persistence and so underestimates duration of therapy whilst retaining the benefits.	Moderate/High, favours baricitinib

Source: compiled during the evaluation

6.33 Table 10 presents the results of the economic evaluation.

Table 10: Results of the base case of the economic evaluation (discounted)

Component		Baricitinib sequence	Adalimumab sequence	Increment
Base case				
Costs		$[redacted]	$[redacted]	$[redacted]
Effectiveness	Life years	4.29	4.29	0
	QALYs	2.11	2.10	0.01
Incremental cost/extra QALY gained				$[redacted]

Source: Table 3.8.3, p190 of the submission.
QALY = quality-adjusted life year

6.34 The ESC noted that the base case of the modelled economic evaluation presented by the submission with an estimated ICER of $15,000/QALY - $45,000/QALY was consistent with tofacitinib as the therapy that would be replaced. Comparable ICERs were estimated from 'Alternative analyses 1 and 2'. Altering the base case to be more consistent with adalimumab being the nominated comparator (the submission's sensitivity analysis for treatment sequence) led to baricitinib being dominated. Further, the submission's sensitivity analysis (which assumed substitution of adalimumab with baricitinib) resulted in an ICER of $45,000/QALY - $75,000/QALY.

6.35 The model was only marginally sensitive to changing the assumption that baricitinib was more effective than adalimumab in the base case treatment sequence. However, when no differences in effectiveness were assumed for baricitinib and adalimumab, baricitinib was dominated.

6.36 The submission stated that the intention of the analysis was to demonstrate that baricitinib is acceptably cost-effective compared to adalimumab at the PBS price applying in November 2016, prior to changes relating to the addition of new and unrelated indications. PBS published dispensed prices reviewed on 14 April 2017 were significantly different to those presented in the submission. The ESC noted that updating the base case of the model to reflect current published dispensed prices for the comparators, but maintaining the price assumed for baricitinib ($[redacted]), resulted in an ICER of more than $200,000/QALY (assuming that the published prices for the comparators reflect the actual prices paid for those drugs for RA).

6.37 The ESC also noted the following issues with the model:

- The model was dependent on the assumption that baricitinib was more effective than tofacitinib, which was not adequately supported by the data presented. This favoured baricitinib.
- The allocation of different estimates of effectiveness for subsequent bDMARD therapies was not appropriate, given that these have all been listed on the basis of non-inferiority. The ESC considered that the PSCR's argument (p3) that this was more realistic was inadequate and not supported by evidence.
- HRQoL was based on ACR scores mapped to the HAQ, which cannot be verified. However, the reference cited to support this (Carlson et al, 2015) presents the parameter values and cites a clinical trial (Gabay et al, 2013), which provides no reference to HAQ effects by ACR. Further, no sensitivity analyses were performed.
- The duration of time on therapy following ACR50 or ACR70 is extrapolated from a curve that reports aggregate treatment persistence (i.e. including <ACR50). If this was not calibrated to account for the persistence in patients with <ACR50 (which is unclear), it is likely that this would favour baricitinib because patients maintain the estimated HRQoL effects, whilst switching to a cheaper therapy earlier. No sensitivity analyses were presented on this parameter.
- The base case did not include adverse event costs for serious adverse events. The model was significantly sensitive to inclusion of these. The ESC noted that this may be relevant in light of the different rates of AEs between baricitinib and adalimumab observed in the trial data.

Drug cost/patient/year: $[redacted]

6.38 The total published cost per year of baricitinib was $[redacted] based on a dosage of one 4 mg tablet per day, a DPMQ of $[redacted] and a pack size of 28 tablets. The total annual cost of adalimumab was $21,907 based on a dosage of 40 mg weekly administered subcutaneously every week, a November 2016 DPMQ Of $1,679.35, and a pack size of 2 injections. Updating the DPMQ of adalimumab to the current published price ($1,401.30) resulted in an annual cost per patient of $18,279.

Estimated PBS usage & financial implications

6.39 This submission was not considered by DUSC. The submission's financial estimates were based on a market share approach using a 10% PBS sample of currently listed RA medicines to estimate total market growth as well as market share and market growth for individual RA medicines.

6.40 Table 11 presents the estimated use and financial implications.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of bDMARD patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of bDMARD scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib market share	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number of baricitinib scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of baricitinib						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost offsets of medicines replaced by baricitinib						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS other	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to Government budgets	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Excel workbook {baricitinib_section_4.xlsx}
bDMARD = biologic disease modifying anti rheumatic drug; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

6.41 The redacted table above shows that at year 6, the estimated number of baricitinib scripts was 50,000 – 100,000 and the net cost to the PBS would be $20 - $30 million.

6.42 The estimates were based on November 2016 PBS prices. As such, the results were not up to date or accurate. The ESC also noted that the estimates were highly sensitive to this.

6.43 The submission assumed the first full year of listing would be 2017, though listing was expected in December 2017. Consequently, it may have been more appropriate to use 2018 as the first full year of listing. Given the linear increase in the total market, this would have led to slightly higher estimates of total costs.

6.44 Uptake rates for baricitinib used to estimate market share each year of listing were not adequately explained. It was unclear how accurate these estimates were, and whether they would be over- or under-estimates.

6.45 The underlying approach to estimating cost offsets was by estimating a percentage of each currently listed therapy being 'displaced' by baricitinib, and calculating the total cost of these offsets. This calculation however, would be better named replacement rather than displacement, as each year the same percentage of each medication was simply removed from use and replaced by baricitinib, with no accounting for use further down the treatment sequence. This approach was unlikely to capture baricitinib's effect on use of other RA medicines and the submission's calculation of cost offsets was unlikely to be accurate.

6.46 The submission assumed there would be no changes to MBS or other government health budgets and that net costs to the PBS would equal net cost to Government. This underestimated savings from reduction administration costs for intravenous bDMARDs, but also underestimated costs associated with management of adverse events.

Quality Use of Medicines

6.47 The submission stated that the sponsor planned to implement a range of activities supporting the quality use of medicines in the treatment of rheumatoid arthritis, and the appropriate use of baricitinib in accordance with the TGA indication and proposed PBS listing. These included a patient support program and clinician education.

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

7 PBAC Outcome

7.1 The PBAC was of a mind to reject baricitinib for treatment of severe rheumatoid arthritis (RA) based on uncertain clinical need and efficacy and concerns about the safety profile, particularly in relation to serious adverse events. However, the PBAC deferred making a recommendation on the listing of baricitinib pending the provision of the relevant TGA delegate's overview.

7.2 The PBAC accepted that the clinical place for therapy of baricitinib would be as an alternative treatment option to the currently PBS listed bDMARDs. However, the PBAC noted the availability of a number of alternative bDMARDs listed on the PBS for the treatment of severe RA and concluded that it was uncertain how baricitinib addressed a clinical need that was not provided by another bDMARD.

7.3 The PBAC noted the ESC advice and the sponsor's agreement in its pre-PBAC response that tofacitinib would be an appropriate comparator. The PBAC considered that any of the currently PBS listed bDMARDs could be an appropriate comparator, noting that, with the exception of etanercept (the first bDMARD PBS-listed for the treatment of RA), all subsequent bDMARDs have been listed on a cost-minimisation basis.

7.4 The PBAC noted that in its pre-PBAC Response, the sponsor – citing ESC advice that all bDMARDs have the same effective ex-manufacturer price for RA – stated that it would be willing to accept listing on a cost-minimisation basis against tofacitanib, based on a per pack basis. Although the PBAC accepted that a cost-minimisation might be a reasonable approach, the committee decided to advise that, in the absence of any basis to conclude superior comparative effectiveness or safety over any alternate bDMARD, baricitinib would need to be cost-minimised against the least costly bDMARD. In making this decision, the PBAC recalled it had previously made a similar decision relating to the least costly bDMARD in its consideration of ixekizumab for psoriasis (ixekizumab PSD, July 2016, paragraphs 7.2 and 7.3).

7.5 The PBAC did not accept the submission's claim that baricitinib was superior in terms of effectiveness compared with adalimumab. Specifically, the PBAC noted that the major secondary endpoint of ACR20 at week 12 failed to demonstrate an improvement of greater than 12%, when the pre-specified non-inferiority margin was -12%. Further, noting that only short-term comparative outcomes were available, the PBAC considered there was no clear evidence that demonstrated that baricitinib provided a significant improvement in effectiveness over adalimumab.

7.6 The PBAC considered that the sponsor's claim of equivalent safety was not adequately supported by the data. In particular, the PBAC expressed concerns about the higher number of serious adverse events in the baricitinb group. The PBAC expressed concern that baricitinib appeared to have a worse safety profile than currently listed bDMARDS and noted that it was awaiting the outcome on the TGA evaluation for further information on the safety profile of baricitinb. Accordingly, the PBAC considered that it may be more appropriate to consider an economic evaluation that took into consideration the likely inferior safety profile of baricitinib against other bDMARDs.

7.7 The PBAC considered there were a number of issues with the model presented including that model was dependent on the assumption that baricitinib was more effective than tofacitinib - which was not adequately supported by the data presented; and the use of different estimates of effectiveness for subsequent bDMARD therapies - given that these have all been listed on the basis of non-inferiority. In addition, the base case did not include adverse event costs for serious adverse events and the model was significantly sensitive to their inclusion.

7.8 Although the PBAC considered an alternative cost-minimisation approach against the cheapest listed bDMARD might be appropriate, more detail would be required to establish the equi-effective doses. However, the PBAC did not finalise its view at this time, pending the provision of the TGA delegate's overview and any further input from the sponsor in response to the committee's views about incorporating the safety differences into the economic evaluation.

Outcome:

Deferred

8 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.

9 Sponsor's Comment

The sponsor had no comment.