4.08 BARICITINIB
Tablet 2 mg,
Tablet 4 mg,
Olumiant®, Eli Lilly Australia Pty Ltd

1 Purpose of Application

1.1 The minor resubmission requested Authority Required general schedule listing for baricitinib for treatment of severe rheumatoid arthritis (RA).

2 Requested listing

2.1 The requested listing was unchanged from the minor resubmission at the November 2017 PBAC meeting. This did not differ from the requested listing in the original submission in July 2017, with the exception of a lower requested DPMQ, which the sponsor claimed is the same as currently listed bDMARDs for RA. The submission proposed an initial treatment course of 16 weeks duration, and a continuing treatment course of 24 weeks duration.

3 Background

3.1 This was the second resubmission for baricitinib to the PBAC. The original submission was discussed at the July 2017 PBAC meeting, where the PBAC was of a mind to reject baricitinib 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 pending the provision of the relevant TGA delegate's overview.

3.2 A minor resubmission to the November 2017 PBAC meeting, which sought to address the PBAC's concerns around comparative efficacy, was deferred without discussion pending provision of the TGA delegate's overview, as the Committee considered the outcomes of the TGA's evaluation of safety were germane to the PBAC deliberations.

3.3 The March 2018 minor resubmission remained unchanged from the November 2017 resubmission.

Registration status

3.4 The TGA delegate's overview was received on 15 January 2018. [redacted] the delegate [redacted] sought the ACM's advice on the issues of concern.

3.5 The ACM considered baricitinib to have an overall positive benefit-risk profile for its proposed indication. The ACM advised:

- 4 mg to be the usual dose, and that 2 mg is the recommended dose in patients with moderate renal impairment. This was based on [redacted] and that the 4 mg/day dose provided a more rapid onset and a numerically higher clinical response rate than the 2 mg/day dose. [redacted]
- [redacted] The ACM suggested amendment of the product information to advise on the risk of VTE and how to manage it, [redacted]
- The recommended dose was not substantially affected by body weight.
- Pregnancy Category D was reasonable [redacted]
- The benefit-risk balance was favourable. Efficacy had been demonstrated in patients who are methotrexate (MTX) naïve, inadequate responders to MTX, and inadequate responders to TNF inhibitors. [redacted]

3.6 [redacted] The risk of VTE has been noted in the baricitinib Product Information (pg.4-5) and the provision of a patient alert card to prescribers has been agreed to by the pre-PBAC response.

3.7 Following the positive advice from the ACM, the TGA delegate decided to approve baricitinib. It was included on the ARTG on 23 January 2018 for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately, or who are intolerant, to one or more DMARDs.

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

4.1 The original major submission considered by the PBAC in July 2017 nominated adalimumab as the main comparator, with tofacitinib listed as a supplementary comparator. At that time, the PBAC considered that any of the currently PBS listed bDMARDs could be an appropriate comparator. The comparator was updated to tofacitinib in the November 2017 and March 2018 minor resubmissions, as it was

considered by the sponsor to be an appropriate comparator given that it is a pharmacological analogue of baricitinib.

4.2 The pre-PBAC response reiterated that the choice of comparator for pricing of baricitinib should not be any other bDMARD for the treatment of RA. It argued that baricitinib would most likely replace adalimumab in clinical practice, and that tofacitinib would remain the appropriate comparator as it is a pharmacological analogue of baricitinib. The pre-PBAC response reasserted that the price of baricitinib should be equivalent to that of tofacitinib.

4.3 The PBAC noted it could only recommend listing baricitinib at a higher price than the alternative therapy or therapies if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The alternative therapies in this case include all other bDMARDs for the treatment of RA. Since there are no data to establish superiority over other bDMARDs for RA, there is no justification for the price of baricitinib to be higher than any other bDMARD for RA.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

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

Clinical trials

5.3 The July 2017 major submission was based on one head-to-head trial comparing baricitinib to placebo and to adalimumab, with four other placebo-controlled trials used as supplementary evidence.

5.4 No head-to-head trials comparing baricinitib and tofacitinib were available. As such, an indirect comparison against tofacitinib, using placebo and adalimumab as common references, was included in an attachment to the major submission, and was presented in Attachment 2 of the commentary. The initial submission had not made a clinical claim against tofacitinib, and the PBAC did not consider the clinical evidence for the comparison against tofacitinib at the July 2017 meeting.

5.5 The November 2017 and March 2018 minor resubmissions were based on the indirect comparison against tofacitinib. No new trials were presented.

Comparative effectiveness

5.6 In July 2017, the PBAC did not accept the submission's claim that baricitinib was superior in terms of effectiveness compared to adalimumab.

5.7 In considering the indirect comparison against tofacitinib, the July 2017 evaluation noted that no statistically significant differences were observed for baricitinib compared to tofacitinib.

Table 1: ACR20 at 12 weeks in cDMARD-IR and bDMARD-IR populations

Trial		Treatment n/N (%)	Control n/N (%)	RD (95% CI)	OR (95% CI)	RR (95% CI)
cDMARD-IR population, via Ada						
Bari	JADV	339/487 (70)	202/330 (61)	**0.08 (0.02, 0.15)**	**1.45 (1.08, 1.95)**	[redacted]
Tofa	1064	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bari vs Tofa (via Ada)				[redacted]	[redacted]	[redacted]
cDMARD-IR population, via PBO						
Bari	JADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	JADN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	JADV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	JADX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Meta-analysis, Bari vs PBO				[redacted]	[redacted]	[redacted]
Tofa	1025	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1044	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1046	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1064	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Meta-analysis, Tofa vs PBO				[redacted]	[redacted]	[redacted]
Bari vs Tofa (via PBO)				[redacted]	[redacted]	[redacted]
bDMARD-IR population, via placebo						
Bari	JADW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofa	1032	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bari vs Tofa (via PBO)				[redacted]	[redacted]	[redacted]

Source: Table Att2.6.3 of the July 2017 Commentary

Ada = adalimumab; Bari = baricitinib; bDMARD = biological disease modifying anti-rheumatic drug; cDMARD = conventional disease modifying anti-rheumatic drug; CI = confidence interval; IR = inadequate response; OR = odds ratio; PBO = placebo; RD = risk difference; RR = risk ratio; Tofa = tofacitinib

Bold typography indicates statistically significant differences

5.8 In the March 2015 consideration of tofacitinib for rheumatoid arthritis, the PBAC accepted that tofacitinib was non-inferior in terms of comparative efficacy to adalimumab using ACR outcome measures (tofacitinib Public Summary Document, March 2015).

Comparative harms

5.9 In July 2017, the PBAC considered that the sponsor's claim of equivalent safety to adalimumab was not adequately supported by the data. In particular, the PBAC expressed concerns about the higher number of serious adverse events (SAEs) in the baricitinib group.

5.10 The November 2017 and March 2018 minor resubmissions presented safety results for baricitinib and tofacitinib. Safety results were not compared by indirect comparisons due to potential differences in adverse event reporting and analysis between trials. The submission considered that there was no clinically meaningful difference in the safety profiles of baricitinib and tofacitinib.

5.11 The pre-PBAC response from the November 2017 PBAC meeting made reference to the comparison between tofacitinib and adalimumab (Tofacitinib PSD; March 2015 PBAC meeting), in which tofacitinib showed a statistically significant difference in greater number of patients with serious adverse events. The November 2017 pre-PBAC response claimed the results were in line with the comparison of serious adverse events rates between baricitinib and adalimumab, and asserted that the PBAC had previously accepted a similar comparative safety profile for tofacitinib, which resulted in a positive recommendation for tofacitinib based on non-inferiority to adalimumab.

5.12 The March 2018 pre-PBAC response again requested the similar comparative safety profile for tofacitinib that resulted in a positive recommendation be considered in the PBAC deliberations for baricitinib.

5.13 The March 2018 pre-PBAC response also stated the finding of higher rates of SAEs in baricitinib compared to adalimumab may not be legitimate, as baricitinib showed equivalent rates of SAEs to placebo (4.7% vs 4.5% respectively) in the JADV trial, whilst adalimumab showed lower rates of SAEs (1.8%) compared to placebo. The pre-PBAC response questioned how an immunomodulatory agent could have a lower SAE rate than placebo, which was supported by the TGA clinical evaluation report for adalimumab which showed 10.7% of adalimumab-treated patients reported treatment-emergent SAEs (Humira AusPAR, Table 18, pg.55).

Clinical claim

5.14 The submission claimed non-inferior comparative effectiveness and equivalent safety of baricitinib compared with tofacitinib.

5.15 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

5.16 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

5.17 In the major submission considered by PBAC in July 2017, the submission presented a cost-utility analysis based on the clinical claim of superior comparative effectiveness to adalimumab. The July 2017 pre-PBAC response stated a willingness to accept listing on a cost-minimisation basis against tofacitinib. At that time, the PBAC accepted that a cost-minimisation against the least costly comparator might be a reasonable approach.

5.18 The resubmission estimated equi-effective doses for a cost-minimisation to be:

baricitinib 4 mg = tofacitinib 10 mg

Estimated PBS usage & financial implications

5.19 The minor resubmission did not update estimated PBS usage and financial implications. If recommended for listing on the PBS on a cost-minimisation basis, there should be no, or minimal net financial implications as baricitinib would substitute for other bDMARDs.

5.20 The minor resubmission noted that tofacitinib is listed on the PBS subject to Special Pricing Arrangements (SPA), and has requested an SPA for baricitinib that reflects a cost-minimisation approach to the effective price of tofacitinib.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended the listing of baricitinib on a cost-minimisation basis against the least costly biological disease modifying anti-rheumatic drug (bDMARD) for rheumatoid arthritis.

6.2 The PBAC noted that the sponsor is required to carry out pharmacovigilance in accordance with the Risk Management Plan agreed with the TGA.

6.3 In making this recommendation, the PBAC recalled that it had previously considered abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib should be treated as interchangeable on an individual patient basis for the treatment of rheumatoid arthritis.

6.4 The PBAC therefore considered that any of the currently PBS listed bDMARDs for RA could be an alternative therapy to baricitinib, that baracitinib could be considered equi-effective to any of the medicines listed at paragraph 6.3, and that, in the absence of demonstrated superior comparative effectiveness or safety over the alternative bDMARDs, baricitinb should be cost-minimised to the least costly bDMARD for rheumatoid arthritis. The PBAC agreed with the resubmission's proposed equi-effective doses between baricitinib and tofacitinib, and recommended that the appropriate equi-effective doses between baricitinib and the least costly bDMARD for rheumatoid arthritis be derived with reference to its

previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets.

6.5 The PBAC noted that the uptake of tofacitinib has been lower than expected and considered that upon PBS listing, baricitinib is likely to rapidly gain market share, as its once daily dosing may be perceived as more convenient, it may have a perceived superiority over tofacitinib, and the time to response is quicker than most of the injectable alternatives.

6.6 The PBAC advised that baricitinib is not suitable for prescribing by nurse practitioners.

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

6.8 The PBAC advised that the restriction is complex and will include a note update that will flow on to the other bDMARDs used in the treatment of rheumatoid arthritis.

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

6.10 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that baricitinib should be treated as interchangeable on an individual patient basis with abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib for the treatment of rheumatoid arthritis.

Outcome:

Recommended

7 Recommended listing

7.1 Add new item:

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.

7.2 The proposed grandfather restriction is included below.

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

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*

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.