4.02 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).

1.2 The resubmission was based on a cost-minimisation analysis against tofacitinib.

2 Requested listing

2.1 The requested listing in the minor submission was unchanged from that requested at the July 2017 PBAC meeting, with the exception of a lower requested DPMQ, and 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 The original submission was made under TGA/PBAC parallel process. The Sponsor had indicated that the TGA delegate's overview wasn't expected to be available until the week before the November 2017 PBAC meeting.

3.2 This was the second submission for baricitinib to the PBAC. At the July 2017 PBAC meeting, 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.

3.3 The TGA delegate's overview had not been received at the time of the November PBAC meeting.

4 Current situation

4.1 The minor resubmission did not address the PBAC's concerns about clinical need for an additional bDMARD for the treatment of severe RA.

4.2 The resubmission sought to address PBACs concerns around comparative efficacy, safety profile, and revised the economic analysis to reflect the revised clinical claim.

5 Comparator

5.1 The previous major submission considered by the PBAC in July 2017 nominated adalimumab as the main comparator. The PBAC considered that any of the currently PBS listed bDMARDs could be an appropriate comparator. The comparator was updated to tofacitinib in the minor resubmission.

5.2 The PBAC did not comment on the comparator, deciding to defer its discussion of this resubmission pending the receipt of the TGA delegate's overview.

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

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

Clinical trials

6.3 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.

6.4 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 PBAC did not consider the clinical evidence for the comparison against tofacitinib at the July 2017 meeting.

6.5 The minor resubmission was based on the indirect comparison against tofacitinib. No new trials were presented.

Comparative effectiveness

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

6.7 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]

[redacted]

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

6.8 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

6.9 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 in the baricitinib group.

6.10 The minor resubmission 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. However, based on a review of the individual trial adverse event results and the meta-analysed results, the submission considered that there was no clinically meaningful difference in the safety profiles of baricitinib and tofacitinib.

6.11 The pre-PBAC response 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 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.

Clinical claim

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

6.13 The PBAC decided to defer its discussion of this item pending the receipt of the TGA delegate's overview.

Economic analysis

6.14 In the previous 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 pre-PBAC response stated a willingness to accept listing on a cost-minimisation basis against tofacitinib. The PBAC accepted that a cost-minimisation against the least costly comparator might be a reasonable approach. At the time of the July 2017 PBAC meetings, all bDMARDs had the same effective ex-manufacturer price for rheumatoid arthritis.

6.15 The PBAC further considered that it may be appropriate to consider an economic evaluation that took into consideration the likely inferior safety profile of baricitinib against other bDMARDs. If the claim of equivalent safety of baricitinib to tofacitinib is accepted by PBAC, a cost-minimisation against any bDMARD would be appropriate.

6.16 In considering a cost-minimisation against the least costly bDMARD, the PBAC considered that more detail would be required to establish equi-effective doses, in particular about whether to incorporate the safety differences into the economic evaluation.

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

baricitinib 4 mg = tofacitinib 10 mg

6.18 [redacted]

6.19 The PBAC decided to defer its discussion of this item pending the receipt of the TGA delegate's overview

Estimated PBS usage & financial implications

6.20 The minor submission 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 net financial implication as baricitinib would substitute for other bDMARDs.

6.21 The PBAC decided to defer its discussion of this item pending the receipt of the TGA delegate's overview

7 PBAC Outcome

7.1 The PBAC decided to defer its discussion of this item pending the receipt of the TGA delegate's overview, in the context of concerns about the safety profile of baricitinib, particularly in relation to serious adverse events. The Committee considered the outcomes of the TGA's evaluation of safety were germane to the PBAC deliberations.

7.2 The PBAC noted that this submission is not eligible for an Independent Review as it has been deferred.

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.