

7.18 OMALIZUMAB
pre-filled syringe, 150 mg/mL
Xolair[®],
Novartis Pharmaceuticals Australia Pty Ltd.

1 Purpose of Application

- 1.1 The minor resubmission requested a reassessment of the PBAC recommended equi-effective dose of omalizumab compared with cyclosporin for the treatment of chronic spontaneous urticaria (CSU).

Issue	November 2015 submission	Nov 2015 PBAC Public Summary Document (PSD)	Current minor submission
Equi-effective dose	Omalizumab 197.22 mg cyclosporin 4 mg/kg.	omalizumab 300 mg cyclosporin 3 mg/kg	omalizumab 197.22 mg cyclosporin 3 mg/kg.

- 1.2 No new clinical trial data were presented in the minor submission.

2 Requested listing

- 2.1 The requested listing in the minor resubmission was unchanged from the November 2015 recommendation, except that 'spontaneous' replaces 'idiopathic' in the condition name.
- 2.2 If the resubmission is rejected by the PBAC, it would not meet the criteria for an Independent Review as it is a request to change an existing recommended indication.

3 Background

- 3.1 Omalizumab received a positive recommendation at the November 2015 PBAC meeting to extend listing to include patients with severe chronic spontaneous urticaria (at that time referred to as chronic idiopathic urticarial), on the basis of cost minimisation against cyclosporin.
- 3.2 The November 2015 submission presented an indirect comparison between 300 mg omalizumab (GLACIAL, ASTERIA I and II trials) and 4 mg/kg cyclosporin (Grattan et al. 2000). The key clinical data, including data for the 150 mg dose of omalizumab, are presented in Table 1. The November 2015 PBAC PSD stated:
"There were statistically significant reductions in the weekly itch severity score from baseline at Week 12 among patients treated with omalizumab 300 mg every four weeks versus those treated with placebo across all three pivotal trials (GLACIAL, ASTERIA I, ASTERIA II). Omalizumab 150 mg was also statistically significantly better than placebo in reducing the weekly itch severity score at

Week 12 (ASTERIA I, ASTERIA II); but the magnitude of the reduction was numerically smaller.”

Table 1. Change from baseline to Week 12 in UAS7 (range 0-42)

Trial	Omalizumab			Placebo			LS mean difference in change (95% CI)
	n	Mean baseline (SD)	Mean change (SD)	n	Mean baseline (SD)	Mean change (SD)	
Omalizumab 300 mg							
GLACIAL ^a	252	31.2 (6.6)	-19.01 (13.15)	83	30.2 (6.7)	-8.50 (11.71)	-10.02 (-13.17, -6.86)
ASTERIA I ^a	81	31.3 (5.8)	-20.75 (12.17)	80	31.1 (6.7)	-8.01 (11.47)	-12.80 (-16.44, -9.16)
ASTERIA II ^a	79	29.5 (6.9)	-21.74 (12.78)	79	31.0 (6.6)	-10.36 (11.61)	-12.40 (-16.13, -8.66)
X-ACT ^b (supportive)	44	26.5 (8.2)	-16.4 (14.3)	47	27.9 (8.7)	-4.4 (13.3)	-13.2 (-19.3, -7.1)
Omalizumab 150 mg							
ASTERIA I ^a	80	30.3 (7.3)	-14.44 (12.95)	80	31.1 (6.7)	-8.01 (11.47)	-6.54 (-10.33, -2.75)
ASTERIA II ^a	82	31.4 (7.0)	-17.89 (13.23)	79	31.0 (6.6)	-10.36 (11.61)	-7.69 (-11.49, -3.88)

Source: Table 3, page 5 of the minor resubmission

Abbreviations: BOCF = baseline observation carried forward; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; mITT = modified intention-to-treat; SD = standard deviation; UAS7 = Urticaria Activity Score over 7 days

Note: Treatment group difference (omalizumab minus placebo)

^a mITT population (BOCF)

^b Extracted from the Novartis Clinical Trial Results Database. The main outcome was measured at Week 28, but week 12 data were included in this table to increase comparability with the other trials. Analysis based on the FAS (LOCF).

- 3.3 The submission proposed equi-effective doses of omalizumab 197.22 mg and cyclosporin 9,296 mg (4 mg/kg). At the November 2015 meeting, the PBAC noted that in determining the equi-effective doses of omalizumab and cyclosporin, the submission allowed down-titration for omalizumab but applied the trial-based dose of cyclosporin without titration. The PBAC considered that the dose of cyclosporin proposed in the submission’s calculation of the equi-effective doses was higher than would likely be used in clinical practice. The PBAC advised that the appropriate equi-effective doses were omalizumab 300 mg and cyclosporin 3 mg/kg.

4 Consideration of evidence

Sponsor hearing

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

Consumer comments

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

Basis for claims in the resubmission

- 4.3 The minor resubmission noted that an updated search of the literature did not locate any new RCTs for omalizumab or cyclosporin in CSU. The resubmission presented an indirect comparison of omalizumab 150 mg to cyclosporin, based on the same data presented in the November 2015 submission.

- 4.4 The resubmission stated that the equi-effective dose recommended by the PBAC from the RCT evidence based on a downward titration of cyclosporin (from 4 mg/kg to 3 mg/kg) without allowing for downward titration of omalizumab was inconsistent. The resubmission’s justification for allowing down-titration of omalizumab from 300 mg to 150 mg in some patients, as well as down-titration of cyclosporin, for the estimation of equi-effective doses was based on the justifications as outlined in Table 2.

Table 2. Justification for down-titration

Justification	Source/Comment
Recommendation to down-titrate in the Australian CSU guidelines	CSU guidelines provided as Attachment 2 to the resubmission
Randomised clinical trial evidence for the 150 mg dose	The resubmission presents an indirect comparison of omalizumab 150 mg versus cyclosporin is presented (based on clinical data presented in previous submission).
Published observational studies in CSU which show down-titration of omalizumab in clinical practice	A review of 22 non-randomised studies presented in Section C.3 of the Nov 2015 CSU submission

- 4.5 As it is a minor submission, the current resubmission was not evaluated. However the clinical data were evaluated in the previous submission (albeit in the context of an indirect comparison of omalizumab 300 mg, rather than 150 mg).

Indirect comparison of effectiveness

- 4.6 The minor resubmission noted that, consistent with the November 2015 submission, “there are two key outcomes common and indirectly comparable via placebo across one cyclosporin RCT (Grattan et al. 2000) and a meta-analysis of the omalizumab arm from the omalizumab RCTs; the mean reduction in UAS7 from baseline and proportion of patients achieving a clinically meaningful UAS7 after treatment”. Table 3 presents the indirect comparison for omalizumab and cyclosporin from the minor resubmission (via placebo).

Table 3. Indirect comparison for omalizumab and cyclosporin (via placebo) on the key efficacy outcomes in CSU

Outcome	Time point (weeks)	Analysis	Omalizumab vs PBO (95% CI)	cyclosporin vs PBO (95% CI)	Omalizumab vs cyclosporin (95% CI)	P-value	SS
Continuous outcomes			WMD <0 favours omalizumab				
UAS7 - change from baseline (150mg) Data from ASTERIA I for OM150mg	4-12	WMD	-6.54 (-10.33, -2.75)	-10.4 (-16.92, -3.88)	3.86 (-3.682, 11.402)	0.3158	NO
UAS7 - change from baseline (150mg) Data from ASTERIA II for OM150mg	4-12	WMD	-7.69 (-11.49, -3.88)	-10.4 (-16.92, -3.88)	2.71 (-4.839, 10.259)	0.5661	NO
Source: Attachment 6 Indirect comparison. Data for omalizumab 150mg from Section B.6.1 of the July 2015 CSU submission represented in PBAC MINS 11-2015 section 6.9 and 6.21							
UAS7 - change from baseline (300mg) Presented in July 2015 PBAC submission	4-12	WMD	-11.43 (-13.42, -9.45)	-10.4 (-16.92, -3.88)	-1.03 (-7.845, 5.785)	0.7671	NO
Source: Section B1 Indirect comparison with cyclosporin from July 2015 CSU submission (attachment 1)							
Dichotomous outcomes							
UAS response - change to <25 from baseline or UAS7 ≤6 Data from ASTERIA I for OM150mg	4-12	OR	5.15 (2.60, 11.75)	12.67 (0.64, 249.69)	0.406 (0.019, 8.801)	0.5661	NO
UAS response - change to <25 from baseline or UAS7 ≤6 Data from ASTERIA II for OM150mg	4-12	OR	3.18 (1.56, 6.48)	12.67 (0.64, 249.69)	0.251 (0.012, 5.38)	0.3767	NO
Source: Attachment 6 Indirect comparison. Data for omalizumab 150mg from Section B.6.1 of the July 2015 CSU submission represented in PBAC MINS 11-2015 section 6.9 and 6.21							
UAS response - change to <25 from baseline or UAS7 ≤6 (300mg) Presented in July 2015 PBAC submission	4-12	OR	8.22 (12.66, 5.34)	12.67 (0.64, 249.69)	0.649 (0.032, 13.192)	0.7783	NO
Source: Section B1 Indirect comparison with cyclosporin from July 2015 CSU submission (attachment 1)							

Source: Table 1, page 9 of the minor resubmission.

SS = statistically significant

- 4.7 Based on the indirect comparison presented in the table above, the minor resubmission concluded that a monthly dose of omalizumab 150 mg was non-inferior in efficacy to cyclosporin 4 mg/kg administered daily based on the following two outcomes:
- Change from baseline UAS7 at 4 and 12 weeks for cyclosporin and omalizumab respectively based on omalizumab outcome from ASTERIA I (mean difference 3.86; 95%CI: [3.682, 11.402]; p=0.3158) and ASTERIA II (mean difference 2.71; 95%CI: [4.839, 10.259]; p=0.5661).
 - A reduction to <25% of baseline weekly UAS for cyclosporin and the proportion of patients achieving UAS7≤6 ('well controlled' CSU) at week 12 for omalizumab based on the omalizumab outcome from ASTERIA I (0.406; 95%CI: [0.019, 8.801]; p=0.5661) and ASTERIA II (0.251; 95%CI: [0.012, 5.38]; p=0.3767).

Indirect comparison of safety

- 4.8 The minor resubmission (p10) stated that “the equi-effective dose determined by the PBAC and resulting price difference underestimates the value of omalizumab given the better risk benefit profile offered with omalizumab. Cyclosporin is known to carry risks of minor side-effects and major complications”.
- 4.9 The November 2015 submission referred to two published systematic reviews conducted on adverse events associated with cyclosporin as well as a systematic review of select adverse events associated with cyclosporin in dermatologic use. The PBAC noted that “the comparative safety of omalizumab over cyclosporin was difficult to quantify due to differences in safety profiles”.
- 4.10 The minor resubmission acknowledged that it is not possible to quantify the differences in safety profile between omalizumab based on the systematic review of adverse events presented in the November 2015 submission. In order to support the claim of improved safety of omalizumab over cyclosporin, the minor resubmission presented an indirect comparison of “the percentage of patients experiencing an adverse event throughout the studies” as shown in Table 4.

Table 4. Results of the indirect comparison of proportion of patients experiencing adverse events

Outcome	Analysis	Omalizumab vs Placebo (95% CI)	Cyclosporin vs Placebo (95% CI)	Omalizumab vs Cyclosporin (95% CI)	P value
Dichotomous outcomes					
Any AE experienced by patients (pooled data from ASTERIA I and II for omalizumab 150 mg)	OR	1.646 (1.07,2.54)	4.667 (1.97, 11.04)	0.353 ^a (0.135,0.925)	0.0341
Any AE experienced by patients (pooled data from ASTERIA I, II and GLACIAL for omalizumab 300 mg)	OR	1.35 (0.98, 1.86)	4.667 (1.97, 11.04)	0.289 ^a (0.115, 0.725)	0.0081

Source: Table 2, page 15 of the minor resubmission

a: The indirect ORs (1/0.353=2.83 and 1/0.289=3.46) show that patients on cyclosporin are approximately 3 times more likely to experience an adverse event

- 4.11 The minor resubmission stated that the indirect comparison shows that omalizumab 150 mg and 300 mg are superior to cyclosporin with respect to proportion of patients experiencing an adverse event.

Down titration of omalizumab

- 4.12 The minor resubmission stated that the expected proportion of patients who will down-titrate was estimated from double blind RCTs by comparing the rate of response with the 150 mg and 300 mg doses at 12 weeks within the pooled ASTERIA I/II data (GLACIAL only used a 300 mg dose). According to the resubmission, 68.5% of patients responding with the 300 mg dose would have achieved the same response with a 150 mg dose, whereas the remaining 31.5% required the full 300 mg dose in order to achieve that response, as outlined in Table 5.

Table 5. Long term dose intensity

row	parameter	value	reference
A	Response (UAS7 ≤ 6) at 12 weeks – 150 mg	0.4301	Pooled ASTERIA I/II observed data
B	Response (UAS7 ≤ 6) at 12 weeks – 300 mg	0.6277	
C	Proportion of 300 mg response achieved with 150 mg dose	0.6852	A/B
D	Proportion of cohort requiring 300 mg dose	0.3148	1-C

Source: page 16 of the minor resubmission

- 4.13 The minor resubmission noted that in addition to the 22 non-randomised studies of omalizumab in clinical practice presented in the November 2015 submission, a further nine non-randomised studies were identified. Based on the 31 non-randomised studies, the minor submission claimed:
- Approximately 40% of patients across the trials were administered 300 mg omalizumab per month while the remainder of patients maintained response with 150 mg omalizumab per month or at longer intervals.
 - Approximately 70% of patients across the trials were administered omalizumab monthly with a proportion maintaining response on treatment every 6 weeks while the remaining were dosed according to a patient-driven approach.

Economic analysis

- 4.14 The minor resubmission presented the same cost minimisation analysis from the November 2015 submission, with the incorporation of cyclosporin at 3 mg/kg (as recommended by PBAC in November 2015) and at the AEMP expected after the 1 October 2016 price disclosure.
- 4.15 Consistent with the November 2015 submission, the minor resubmission assumed an average dose for omalizumab of 197 mg, based on the assumption that 68.52% of patients would down-titrate to 150 mg.
- 4.16 The equi-effective doses proposed in the minor resubmission were:
Omalizumab 197.22 mg = cyclosporin 3 mg/kg
- 4.17 The minor resubmission noted that based on the proposed equi-effective doses and the requested effective DPMQ (\$█ for 150 mg omalizumab) there was an additional cost to the Commonwealth of \$█ per patient per month compared to

cyclosporin. The resubmission claimed that the additional cost per month “should be viewed in the context that it does not include the cost offsets from lower side effects experienced with omalizumab”.

Drug cost/patient/course: \$ [REDACTED].

4.18 The minor submission presented a drug cost per patient per course (4 weeks) of \$ [REDACTED] based on the average dose of omalizumab 197 mg. This was derived from the requested effective DPMQ of \$ [REDACTED] for omalizumab 150 mg (the effective DPMQ was \$ [REDACTED] in the November 2015 submission).

Estimated PBS usage & financial implications

4.19 According to the minor resubmission (p18), the same financial model was provided as in the November 2015 submission, with the following updates:

- Update from the DUSC analysis to reflect the correct number of scripts used by continuation patients (a full year, rather than the “balance of first year” number referenced in the DUSC analysis).
- Increase in the proportion of patients expected to continue treatment in recognition of the PBAC’s acknowledgement that some patients with severe CSU will achieve a meaningful improvement without necessarily reaching the criteria required in the trials to be classified as “well controlled”.
- Increases in pharmacy fees and mark ups from 1 July 2016 and price reduction for cyclosporin (due to Price Disclosure from 1 October 2016).

4.20 The resubmission’s estimated financial impact to Government of the proposed listing of omalizumab is presented in Table 6. The redacted table below shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to Government would be less than \$10 million.

Table 6. Cost to Government of omalizumab and reduction in cost of other drugs (based on effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients treated with omalizumab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total packs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total cost to Govt (net effective DPMQ)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Reduction in cost of SOC drugs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Reduction in cost of cyclosporin	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total reduction in other drugs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Reduction in monitoring costs (cyclosporin patients)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to Govt	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 4, page 20 of the minor resubmission

Financial Management – Risk Sharing Arrangements

- 4.21 At the November 2015 meeting, the PBAC considered that there was a risk of use outside the requested restriction (particularly in milder disease and earlier line treatment). The PBAC considered that a Risk Share Arrangement would be appropriate based on the revised DUSC estimates to address any potential leakage and manage financial implications for use beyond the restriction.
- 4.22 The minor submission stated that the sponsor will work with the Department to ensure that these recommendations are implemented in a timely and effective manner.

5 PBAC Outcome

- 5.1 The PBAC recommended that the equi-effective doses are omalizumab 300 mg and cyclosporin 4 mg/kg, based on the un-titrated trial doses for both drugs.
- 5.2 The PBAC recalled from the November 2015 PSD that they had accepted that omalizumab was non-inferior to cyclosporin in terms of clinical effectiveness, but had noted that the small patient numbers in the available studies made the indirect comparison difficult to interpret. The PBAC considered that the comparison provided a reasonable basis for decision making in the context of a rare condition with limited data available.
- 5.3 The PBAC noted that both products were likely to be down-titrated in clinical practice, and noted the information provided in the submission to support the proposed rate of down-titration, but considered that the actual proportion of patients who would down titrate remained uncertain.
- 5.4 In the absence of more certainty around the proportion of patients in whom treatment would be down-titrated in clinical practice, the PBAC considered that the most appropriate approach was to base the equi-effective doses on the un-titrated trial doses for both omalizumab and cyclosporin.
- 5.5 The PBAC noted that the submission is not eligible for an Independent Review as it was a request to change an existing recommended indication.

Outcome:

Recommended

6 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.

7 Sponsor's Comment

The sponsor had no comment.