

6.19 OMALIZUMAB

**75 mg/0.5 mL injection, 1 x 0.5 mL syringe; 150 mg/mL injection, 1 x 1 mL syringe 1 pack;
Xolair®, Novartis Pharmaceuticals Australia Pty Ltd**

1 Purpose of Application

To request an amendment to the current PBS eligibility criteria of omalizumab for the treatment of severe allergic asthma with respect to baseline human immunoglobulin (IgE).

2 Requested listing

- 2.1 The submission proposed that patients with baseline IgE of 30 to 75 IU/mL have a high disease burden and clinical need similar to patients with IgE \geq 76 IU/mL but are not able to trial PBS-subsidised omalizumab. So the submission requested to amend the current PBS restriction with respect to baseline IgE.

Current eligibility criteria	Requested amendment
total serum human immunoglobulin E (IgE) greater than or equal to <u>76 IU/ml</u> and assessed in the previous 12 months	total serum human immunoglobulin E (IgE) greater than or equal to <u>30 IU/ml</u> and assessed in the previous 12 months

- 2.2 Although patients with total serum IgE of 30-75 IU/mL are included in the TGA approved dosing table, the TGA-approved approved Product Information states that *'Patients with severe asthma and a baseline IgE lower than 76 IU/mL were less likely to experience benefit'*. Accordingly at its November 2014 meeting, the PBAC recommended that the sponsor submit a major resubmission to justify reducing the baseline IgE threshold as well as other requested changes to the wording of the restriction.

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

3 Background

- 3.1 Omalizumab was first TGA registered in June 2002 for the management of adults and adolescent patients with moderate allergic asthma. Registration was extended in December 2005 to include management of adult and adolescent patients with moderate to severe allergic asthma, who are already being treated with inhaled steroids, and who have serum immunoglobulin E levels corresponding to the recommended dose range.
- 3.2 The PBAC rejected omalizumab for listing for the treatment of patients with uncontrolled severe allergic asthma in November 2009. Following this outcome, a post-PBAC meeting was held in December 2009 and a PBAC-convened stakeholder meeting was held in April 2010. A resubmission was considered and approved by the PBAC for listing in November 2010. The resubmission included the restrictions that were agreed to at the April 2010 stakeholder meeting.

- 3.3 In February 2013, DUSC considered the utilisation of omalizumab over the first 12 months of listing, which was approximately █% of predicted. In April 2013, the PBAC considered that access to appropriately qualified prescribers, establishing eligibility to access PBS-subsidised omalizumab; and the requirement to maintain patients on long-term corticosteroids contributed to the low uptake of omalizumab.
- 3.4 In June 2014, DUSC considered the utilisation of omalizumab over the first 24 months of listing, which was approximately █% of predicted in the second year. In July 2014, the PBAC recalled that a stakeholder meeting in 2010 had been required to finalise the restriction, and requested that such a group be reconvened to discuss potential changes. The PBAC particularly noted the elements of the current restriction referring to oral corticosteroid use were developed in consultation with the stakeholder group and reflected the best practice guidelines at the time. The PBAC recalled that oral corticosteroid use had been an important element in cost effectiveness analysis underpinning the original recommendation. The PBAC considered therefore that a change to the restriction could influence the cost effectiveness of omalizumab.
- 3.5 The sponsor noted that while the restriction for omalizumab would be considered through the review of Authority Required listings, the scope may not allow for a detailed analysis of the eligibility criteria and this would not occur until the third round of reviews.
- 3.6 In November 2014, the Sponsor proposed approximately 10 changes to the restriction (see the Table in November 2014 PBAC minutes). The PBAC recommended amending the restriction wording of omalizumab to align the definition of optimal asthma therapy with current clinical guidelines (refers to row 1.8b in the Table in November 2014 PBAC Public Summary Document) and to extend the period for assessment of response from 2 weeks to 4 weeks (refers to row 3 Table in November 2014 PBAC Public Summary Document). The PBAC noted that the remaining requested changes to the restriction for omalizumab would require formal evaluation prior to consideration by PBAC. Accordingly, the PBAC recommended that the sponsor submit a major resubmission to justify reducing the baseline IgE threshold as well as other requested changes to the wording of the restriction.

4 Current situation

- 4.1 The minor submission proposed an amendment to one of the PBS restrictions to allow patients with IgE 30-75 IU/mL who meet all other existing PBS eligibility criteria to have the opportunity to trial use of omalizumab for their severe allergic asthma.
- 4.2 The submission proposed a rebate of █ of the cost of up to 28 weeks of therapy for the patients with IgE 30-75 IU/mL who do not respond to omalizumab.

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

5 Clinical place for the proposed therapy

- 5.1 Omalizumab, administered as a subcutaneous injection, is an add-on treatment for the management of severe allergic asthma for patients who are treated with maximal recommended asthma maintenance medication, yet remain symptomatic (Public Summary Document, November 2009).

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 The PBAC noted and welcomed the input from health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments were supportive of the requested changes to the restriction criteria for the treatment of severe allergic asthma with respect to baseline human immunoglobulin. The PBAC noted the advice that PBS restrictions are not generally well understood by patients with severe allergic asthma and can present a barrier to accessing effective treatment options.
- 6.3 The PBAC noted and welcomed the input.

Clinical trials

- 6.4 The same trials presented in the November 2010 submission were re-presented in this submission.

Table 1: Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Primary outcomes	Secondary outcomes
2306	Direct randomised double blind trial with post-hoc adjustment for primary outcome	<ul style="list-style-type: none"> Clinically significant asthma exacerbation rate (see below). 	<ul style="list-style-type: none"> Use of asthma rescue medication (number of puffs/day) AQLQ Total daily clinical (nocturnal, morning and daytime) symptom score Patient and investigator GETE Pulmonary function tests Morning and Evening PEF (L/min) Number of days with >20% decrease in morning PEF compared to personal best
2425	Direct randomised open label trial	<ul style="list-style-type: none"> Persistency rate (%) of response; based on the investigator's and patient's Global Evaluation of Treatment Effectiveness (GETE). Investigator's and patient's GETE, dichotomised to responders (excellent or good) and non-responders (moderate, poor or worsening). 	<ul style="list-style-type: none"> Persistency rate (%) of non-response to omalizumab. Persistency rate (%) of response to optimised asthma therapy alone Lung function (FEV₁, ml). Rate of clinically significant and severe asthma exacerbations Individual and combined rates of hospitalisations, emergency room visits or unscheduled clinic interventions due to asthma worsening Reduction in use of maintenance oral corticosteroid in subgroup of patients requiring oral corticosteroids as asthma maintenance therapy ACQ, AQLQ, EQ5D and VAS scores Night time awakenings

Source: adapted from PSD, November 2009 PBAC

- 6.5 The submission presented the baseline characteristics of patients in trials 2306 and 2425 (pooled trials and treatment arms) to show that the current and proposed PBS criteria are selecting patients that have severe asthma and a high medical need for add-on treatment with omalizumab.

Table 2: Demographics of patients in trials 2306 and 2425 – data are presented for the total cohort (pooled trials and treatment arms) and those meeting certain PBS eligibility criteria

Characteristic	Trial ITT population	Subgroup meeting current PBS criteria - includes restriction for IgE≥76	Subgroup meeting proposed PBS criteria -includes restriction for IgE≥30	Small subgroup meeting PBS criteria and who have IgE 30-75
N in trial or PBS subgroup	819	118	146	28
IgE (mean)	213	242	206	53.5
Female (%)	66%	68%	68%	68%
Clinical symptom score (mean)	3.5	4.1	4.1	4.5
ACQ7 score (mean)	2.7	3.2	3.3	3.6
ACQ5 score (mean)	2.6	3.2	3.2	3.6
AQLQ score (mean)	3.9	3.5	3.5	3.3
Exacerbations in last 12mths (n)	2.3	2.5	2.5	2.4
Hospitalised in last 12mths (%)	31%	42%	45%	54%
OCS dose/day (mg)	3.6	16.2	16.8	19.3
EQ-5D (mean)	0.7	0.6	0.6	0.6
AQL5D (mean)	0.7	0.7	0.6	0.6

Source: Spreadsheet Att 5_Trial IPD demo resp data_Aug15, work sheet “Summary” and p iii of the submission

6.6 The minor submission claimed that the “...comparison of baseline characteristics across the existing PBS restriction (IgE≥76, n=118) and the proposed broader PBS restriction (IgE≥30, n=146) showed that the additional patients gaining access to omalizumab (i.e. IgE 30-75, n=28) have the same (if not higher) clinical need for treatment as the existing PBS population with respect to their disease severity”. This claim could not be evaluated in the context of a minor submission.

6.7 The minor submission presented the results of the study end points, which included response rates using PBS criteria. The submission proposed that the response rates in omalizumab-treated patients were very similar for the cohort with IgE ≥30 (n=94; response rate █████%) compared with the cohort with IgE ≥76 (n=80; response rate █████%). In the small subgroup of patients with IgE of 30-75 IU/mL (n=14) the response rate was approximately 10% lower, at █████%.

Table 3: Response rates in trials2306 and 2425 using the PBS response criteria – in omalizumab-treated patients who met the PBS eligibility criteria

Characteristic	Subgroup meeting current PBS criteria - includes restriction for IgE≥76	Subgroup meeting proposed PBS criteria - includes restriction for IgE≥30	Small subgroup meeting PBS criteria and who have IgE 30-75
N in PBS eligible subgroup	████	████	████
N responding via PBS criteria	████	████	████
Response rates	██████	██████	██████

Source: Spreadsheet Att 5_Trial IPD demo resp data_Aug15, work sheet “Summary” and p iv of the submission

- 6.8 The submission stated that using circulating total polyclonal IgE as a biomarker to predict response to omalizumab, excluded patients with asthma-inducing local tissue IgE from the TGA approved treatment.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

Economic analysis

- 6.9 The minor submission presented no new economic analyses.

Estimated PBS usage & financial implications

- 6.10 The submission presented financial estimates based on the expected increase in uptake and response/continuation rates of omalizumab due to the lower baseline IgE level being extended from 76 to 30 IU/mL. The submission further offered to rebate [redacted] of the cost of up to 28 weeks of therapy for the patients with IgE 30-75 IU/mL who do not respond to omalizumab.
- 6.11 The submission proposed that given there are a pool of patients with IgE 30-75 IU/mL waiting to be treated (based on advice from physicians and frequent requests for subsidy) the expected uptake rate has been set higher than the current uptake rate of [redacted]% in the IgE ≥76 patients. The rate for Year 1 is set at [redacted]%, Year 2 at [redacted]%, and then [redacted]% for subsequent years.
- 6.12 The submission estimated a net cost to the PBS of \$[redacted] in Year 5 of listing, with a total net cost to the PBS of less than \$10 million over the first 5 years of listing. This is summarised in the table below.

Table 4: Financial estimates for the change in PBS restrictions for patients with IgE 30-75

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients (New+Cont.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost at published \$	\$[redacted]	\$[redacted]	\$[redacted]	\$[redacted]	\$[redacted]
[redacted]					
Cost at effective \$	\$[redacted]	\$[redacted]	\$[redacted]	\$[redacted]	\$[redacted]
[redacted]					
Cost at effective \$	\$[redacted]	\$[redacted]	\$[redacted]	\$[redacted]	\$[redacted]

Source: Table 12 p 23 of the submission.

The redacted table above shows that the number of patients treated with omalizumab is estimated to be less than 10,000 per year at a net cost to the PBS of less than \$10 million per year.

- 6.13 The submission noted that these estimates represent the expected Commonwealth Expenditure (CE) at the published price and at the effective price [redacted]

- 6.14 The November 2014 minor submission had estimated a total net cost to the PBS of \$ [REDACTED] at the effective price, with an additional [REDACTED] patients treated in year 5.

Table 5: Estimated use and financial implications from November 2014 submission

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number currently treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number treated under proposed restriction changes	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS					
Net cost to PBS – published DPMQ	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS – effective price	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 14 p 44 of the submission and the Financial Workbook.

- 6.15 The minor submission’s estimates differ significantly from those in the November 2014 minor submission (Net PBS cost in year 5: \$ [REDACTED] vs. \$ [REDACTED]; total number of patients treated in year 5: [REDACTED] vs. [REDACTED]). The differences in these estimates could not be further elucidated, nor could the validity of projected uptake rates be assessed, in the context of a minor submission.
- 6.16 The sponsor argued that a trial of omalizumab to test for response is appropriate given the equivalent medical need and disease burden in the IgE 30-75 cohort compared with the higher IgE patients. In support of this the submission proposed to repay of [REDACTED]% of the cost of treatment (initial 28 weeks) for patients with IgE 30-75 IU/mL that fail to respond to omalizumab at the initial assessment and do not go on to continuation therapy.
- 6.17 The minor submission estimates a total of \$ [REDACTED] in rebates for the cost of the initial 28 weeks of treatment for patients that are shown then not to respond at a 22-26 week assessment. The submission estimated a 65% response rate at six months in patients with IgE 30-75, “...based on the [REDACTED]% in patients with IgE 30-75 in 2306/2425 trials and 80% in real world in higher IgE patients [those that went on to continuation therapy]...” The DUSC 24 month Predicted vs Actual (PvA) analysis in June 2014 determined a continuation rate of 80% in PBS utilisation (a population with total serum IgE greater than or equal to 76 IU/mL. Evaluation of the estimated 65% response rate in patients with IgE 30-75 IU/mL was not possible in the context of a minor submission, therefore the validity of this assumption is unknown.
- 6.18 The PBS restriction requires that patients on continuing treatment demonstrate a sustained response to continue to access PBS-subsidised omalizumab. The sponsor’s proposed rebate would not account for patients who are not able to sustain a response to omalizumab and discontinue treatment after assessment at 22-26 weeks (i.e. after commencing their first continuation prescription).
- 6.19 The sponsor’s assumption of a lower response rate in patients with IgE 30-75 IU/mL than demonstrated in patients with IgE greater than or equal to 76 IU/mL may suggest that omalizumab is less effective in patients with lower IgE. The submission refers also to the following statement in the approved Product Information (PI): “Patients with severe asthma and a baseline IgE lower than 76 IU/mL were less likely to experience benefit”.

- 6.20 The sponsor argues that because "...the clinical and economic data on low IgE patients has already been fully evaluated (and the price, and thus ICER is now 16% lower) and because there are no new IgE data to present, Novartis has elected to submit this proposal for a rebate for low IgE patients who don't respond to omalizumab at the initial assessment, as minor re-submission."
- 6.21 The base case ICER considered acceptable by the PBAC in November 2010 of \$15,000/QALY - \$45,000/QALY was in the context of a restriction to patients with IgE greater than or equal to 76 IU/mL.

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

7 PBAC Outcome

- 7.1 The PBAC recommended amendment to the PBS restriction of omalizumab 75mg and 150mg pre-filled syringe to allow patients with a baseline IgE 30-75 IU/mL who meet all other existing PBS eligibility criteria to have the opportunity to trial use of omalizumab for their severe allergic asthma on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program).
- 7.2 The recommendation was made on the basis of a risk share arrangement whereby the sponsor will rebate ■■■% of the cost of up to 28 weeks of therapy for the patients with IgE of 30-75 IU/mL who do not respond to omalizumab.
- 7.3 In making this recommendation, the PBAC recommended review of utilisation of omalizumab and existing cap arrangements.
- 7.4 The PBAC considered amending the existing clinical criteria for omalizumab 75mg and 150mg pre-filled syringe for the treatment of severe allergic asthma to include the restriction wording "*total serum human immunoglobulin E (IgE) greater than or equal to 30 IU/mL and assessed in the previous 12 months*".
- 7.5 The PBAC advised that the current continuation rule which applies to the patients with IgE of ≥ 76 should be applied for this patient group with IgE of 30-75 IU/mL.
- 7.6 The PBAC noted from the subgroup analyses of the clinical trials, that an estimated ■■■% will be added to the current treatment population who meet the PBS eligibility criteria and have the same clinical need for treatment as the existing PBS population. The PBAC noted that the response rates were similar between the subgroups.
- 7.7 The PBAC considered the financial estimates in the submission were reasonable given the majority of patients with baseline IgE 30-75 require 1 syringe/month which is less than the required quantity for patients with $\text{IgE} \geq 76$. The PBAC noted that the listing of omalizumab is likely to cost less than \$10 million over the next five years.
- 7.8 The PBAC advised that under subsection 101(3BA) of the *National Health Act 1953*, that omalizumab should not be treated as interchangeable on an individual patient basis with any other drug.
- 7.9 The PBAC advised that omalizumab is not suitable for prescribing by nurse

practitioners.

- 7.10 The PBAC recommended that the Safety Net 20 Day rule should not apply.
- 7.11 The submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Amend existing listing as follows:

Item numbers 10110D, 10118M, 10109C, 10122R

“Patient must have total serum human immunoglobulin E greater than or equal to 76 IU/ml”
to

“Patient must have total serum human immunoglobulin E (IgE) greater than or equal to 30 IU/ml”

9 Context for Decision

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

10 Sponsor’s Comment

Novartis is very pleased that patients with total serum IgE 30 to 75 IU/mL who meet other PBS criteria will now be eligible to trial omalizumab for management of their severe allergic asthma. Novartis wishes to thank the consumer and physician organisations that supported improved patient access to omalizumab, as well as the PBAC and government.