

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

1 Purpose of Application

1.1 The submission requested Section 100 written authority required listing for omalizumab for the treatment of chronic idiopathic urticaria (CIU) in patients who meet certain criteria.

2 Requested listing

2.1 A short version of the requested restriction is provided below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
OMALIZUMAB syringe 150 mg/mL	2	23	\$ [REDACTED] (Public)* \$ [REDACTED] (Private)*	Xolair® Novartis Pharmaceuticals Australia Pty Ltd

Treatment phase: Initial treatment (new patient)	
Condition	Severe Chronic Idiopathic Urticaria
Restriction	Section 100: Public and private hospital authority required
Clinical criteria	The condition must be based on both physical examination and patient history (to exclude any factors that may be triggering the urticaria), AND Must be treated by a clinical immunologist, allergist, dermatologist or general physician with expertise in the management of chronic idiopathic urticaria (CIU), AND Patients must have had uncontrolled chronic idiopathic urticaria defined as the presence of itch and hives that persist on a daily basis for at least 6 weeks despite treatment with H ₁ antihistamines,
Treatment criteria	Patients must have failed to achieve an adequate response to standard therapy which must include H₁ antihistamines at maximally tolerated doses in accordance with clinical guidelines, and/or H₂ receptor antagonist (150 mg twice per day) and/or leukotriene receptor antagonist (LTRA) (10 mg per day) and/or doxepin (up to 25mg three times a day) for a minimum of 2 weeks (unless contraindicated or not tolerated). <i>Patients must have failed to achieve an adequate response to standard therapy which must include H₁ antihistamines at maximally tolerated doses and at least two of: H₂ antagonist (ranitidine or cimetidine), montelukast, or doxepin.</i> The following initiation criteria indicates <u>failure to achieve an adequate response</u> to standard therapy and must be demonstrated at the time of the initial application: A current Urticaria Assessment Score 7 (UAS7) score of ≥28 with an itch score of greater than 8, as assessed while still on standard therapy. The current UAS7 assessment must be no more than 1 month old at the time of the application.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
OMALIZUMAB syringe 150 mg/mL	1	5	\$ [REDACTED] (Public)* \$ [REDACTED] (Private)*	Xolair® Novartis Pharmaceuticals Australia Pty Ltd

Treatment phase: Continuing treatment	
Condition	Severe Chronic Idiopathic Urticaria
Restriction	Section 100: Public and private hospital authority required
Clinical criteria	<p>Patient must have a documented history of severe chronic idiopathic urticaria (CIU),</p> <p>AND</p> <p>Patient must demonstrate, at the time of application, an adequate response to their most recent course of treatment with omalizumab,</p> <p>AND</p> <p>Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.</p> <p>An adequate response to treatment is defined as a reduction in UAS7 to ≤6 when compared with the pre-omalizumab treatment baseline value</p> <p>Note: The first assessment should occur after patients have received 3 monthly doses of omalizumab and should, where possible, be completed by the same physician who initiated treatment with omalizumab. A proportion of patients respond to 150mg 4-weekly so where a substantial improvement has been obtained with a 300mg dose it is reasonable to back-titrate dose after initial treatment.</p> <p>At the time of the authority application, medical practitioners should request the appropriate maximum quantity to provide for a continuing course of omalizumab consisting of the number of doses required for either 300mg or 150mg to be administered every 4 weeks for a further 24 weeks.</p> <p>Cessation of therapy should be considered after the patient has demonstrated clinical benefit with omalizumab to re-evaluate the need for continued therapy. Any patient who ceases therapy and whose CIU relapses will need to re-initiate omalizumab as a new patient on the PBS.</p>

* The prices shown are the same published Section 100 prices as currently exist for the severe allergic asthma PBS listing.

- 2.2 Listing was requested on a cost-minimisation basis to cyclosporin and a cost-effectiveness basis to “standard of care” therapies.
- 2.3 The DPMQs reflected the requested published DPMQs. A confidential rebate of [REDACTED]% on net Commonwealth expenditure was proposed. The requested price for CIU was the same price as the current PBS-listing for uncontrolled severe allergic asthma, at both published and effective prices.
- 2.4 The ESC and PBAC considered that there were numerous potential issues with the proposed restriction. The key issues included:
- The timing to assess treatment continuation was not explicit in the proposed restriction.
 - In relation to the previous therapy under which a patient must have failed to achieve an adequate response, the ESC considered that the wording was unclear and proposed alternative wording (see restriction above).
 - The requested quantity and repeats for initiating therapy is sufficient for three doses of omalizumab. The PSCR agreed to this suggestion and provided revised estimates of the ICER and financial estimates to reflect this change.
 - The extent of the use of the Urticaria Assessment Score over 7 days (UAS7) in clinical practice is unknown. Additionally, there are different UAS7 scoring systems available compared to the UAS7 used in the omalizumab trials.
 - There are likely issues relating the use of a self-reported tool with subjective outcomes (severity of itch) to assess eligibility and response among patients who may be aware of the requirements for initiating and ongoing treatment. The

sponsor proposed an informed consent process to ensure that patients are aware of the criteria to qualify for ongoing therapy.

- It was unclear whether the nominated response threshold may exclude patients experiencing substantial clinical benefit from continuing therapy despite not reaching the appropriate UAS 7 score for continuation criteria.

2.5 The PBAC considered that the proposed continuation rule would be difficult to implement in clinical practice.

2.6 The commentary assumed that an alternative definition of standard therapy, H₁ antihistamines at maximally tolerated doses in accordance with clinical guidelines in addition to H₂ receptor antagonist and/or leukotriene receptor antagonist and/or doxepin represented the intended requested restriction. The commentary also assumed that assessment of response was to occur at approximately Week 12.

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

3 Background

3.1 Omalizumab is TGA-approved for:

- the 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; and
- adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H₁ antihistamine treatment.

3.2 Omalizumab is currently PBS-listed as a Section 100 (Highly Specialised Drugs Program) written authority required item for the treatment of adolescents and adults with uncontrolled severe allergic asthma who have failed to achieve adequate control despite optimised asthma therapy, have a total serum immunoglobulin E of ≥ 76 IU/mL, and who fulfil certain criteria.

3.3 The PBAC has not previously considered omalizumab for CIU.

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

4 Clinical place for the proposed therapy

4.1 The submission proposed omalizumab as an alternative to immunomodulating agent (cyclosporin); and as a substitute, or an addition to, standard of care after use of (1) H₁ antihistamine, (2) increasing H₁ antihistamine dose up to four times the approved dose, and (3) adding H₂ antagonist and/or leukotriene receptor antagonist and/or doxepin.

5 Comparator

- 5.1 Cyclosporin as the main clinical comparator, and “standard of care” or placebo as another clinical comparator, where healthcare professionals are unwilling to accept the risk-benefit profile of cyclosporin or the use of cyclosporin is contraindicated. The “standard of care” therapies were not clearly defined.
- 5.2 Limited Australian utilisation data on current real-world usage of treatments for CIU were available. The sponsor acknowledged that dapsons and hydroxychloroquine may also be considered clinical comparators; but argued that their usage was expected to be low due to the low quality of evidence, the unfavourable safety profile of dapsons, and the slow onset of action of hydroxychloroquine. There were few comparable outcomes and a number of exchangeability issues between the available trials. The submission considered these agents as part of the “standard of care” comparator. However, the expert consensus statement for the omalizumab TGA submission (2013) stated that hydroxychloroquine is commonly used for CIU.
- 5.3 If the proposed restriction was assumed to be among those who are refractory to H₁ antihistamines in addition to H₂ antagonists and/or leukotriene receptor antagonists and/or doxepin, it appeared unlikely that patients would have exhausted all combinations or single use of these agents prior to trialling omalizumab. Therefore, omalizumab may substitute for some use of these medications.

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

6 PBAC consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item.
- 6.2 The clinician addressed the clinical positioning of omalizumab in the treatment algorithm as an immunosuppressive agent to lower the symptoms of chronic idiopathic urticaria. The clinician’s view was that the UAS7 was a validated measuring instrument recommended by FDA guidelines and widely used in the clinical management of the condition. The clinician emphasised that anaphylaxis, which is a known risk with omalizumab, is rare and manageable occurring in 0.1 – 0.2% of patients and that patients are fully informed for the management of this risk. The clinician, also commented that the cyclosporin dosing used in clinical practice was 2.5mg-3mg/kg/day. In terms of the dosing of omalizumab in clinical practice, the clinician noted that patients tend to be treated with 300mg dose with the time between injections increased if appropriate.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (7) and health care professionals (7) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of using omalizumab for the treatment of chronic idiopathic urticaria (CIU), including efficacy in patients who have failed multiple other treatments and lower toxicity than other treatments and therefore less

need for close monitoring. Several comments also noted that treatment benefit is usually seen quite early, and that sustained remission has been achieved in some cases, although other patients require maintenance therapy. The comments noted the relief that this treatment can provide for a condition that is often unpredictable in nature and highly disruptive to quality sleep and life in general.

Clinical trials

6.4 The submission was based on:

- For a comparison versus “standard of care” (placebo): Three pivotal head-to-head randomised trials (GLACIAL, ASTERIA I, ASTERIA II) and one supportive head-to-head randomised trial (X-ACT; limited information available as it was only available as a poster) comparing omalizumab versus placebo (as a proxy for standard of care).
- For a comparison versus cyclosporin: No head-to-head studies of omalizumab versus cyclosporin were available. Two placebo-controlled cyclosporin trials were identified (Grattan 2000 and Vena 2006). Indirect comparisons of omalizumab versus cyclosporin using placebo as the common reference were presented. Three placebo-controlled omalizumab trials (GLACIAL, ASTERIA I and ASTERIA II) and one placebo-controlled cyclosporin trial (Grattan 2000) informed the formal indirect comparisons.

6.5 Details of the trials presented in the submission are provided in Table 1.

Table 1: Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Omalizumab versus placebo		
[4883] GLACIAL	Final Clinical Study Report – Q4883g - A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Safety Study of Xolair (Omalizumab) in Patients with Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Treatment With H1 Antihistamines, H2 Blockers, and/or Leukotriene Receptor Antagonists – 1054065	June 2013
	Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, Veith J, Kamath N, Staubach P, Jakob T, Stirling RG, Kuna P, Berger W, Maurer M, Rosen K. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy.	<i>J Allergy Clin Immunol</i> 2013; 132(1):101-109
	Antonova J, Raimundo K, Trzaskoma B, Solari P, Omachi T, Zazzali J. Improvement of sleep in patients with chronic idiopathic/ spontaneous urticaria (CIU/CIU) treated with omalizumab: Results of a randomized, double-blind, placebo-controlled clinical trial (GLACIAL).	<i>Ann Allergy Asthma Immunol</i> 2014; 113 (5): A114-A115
[4881] ASTERIA I	Final Clinical Study Report – Protocol Q4881g – A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study To Evaluate The Efficacy and Safety of Xolair (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Antihistamine Treatment (H ₁) – Report 1054397	June 2013
	Saini SS, Bindeslev-Jensen C, Maurer M, Grob JJ, Bulbul Baskan E, Bradley MS, Canvin J, Rahmaoui A, Georgiou P, Alpan O, Spector S, Rosen K. Efficacy and Safety of Omalizumab in Patients with Chronic Idiopathic/Spontaneous Urticaria Who Remain Symptomatic on H ₁ Antihistamines: A Randomized, Placebo-Controlled Study.	<i>J Invest Dermatol</i> 2015; 135(1): 67-75 Erratum in <i>J Invest Dermatol</i> 2015; 135(3): 925

Trial	Protocol title/ Publication title	Publication citation
[4882] ASTERIA II	Final Clinical Study Report – Protocol Q4882g – A Phase III, Multicenter, Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Study To Evaluate The Efficacy, Response Duration And Safety of Xolair® (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Antihistamine Treatment (H ₁) – Report 1053093	June 2013
	Maurer M, Rosén K, Hsieh H, Saini S, Grattan C, Giménez-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T. Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria.	<i>N Engl J Med</i> 2013; 368(10): 924-935 Erratum in <i>N Engl J Med</i> 2013; 368(24): 2340-2341
X-ACT NCT01723072	Metz M, Staubach N, Chapman-Rothe N, Sieder C, Braeutigam M, Canvin J, Maurer M. Omalizumab 300mg reduces effectively angioedema episodes in CSU.	Poster presented at the 23 rd World Congress of Dermatology 2015
Cyclosporin versus placebo		
Grattan (2000)	Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria.	<i>Br J Dermatol</i> 2000; 143(2): 365-372
Vena (2006)	Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P; and the NEO-I-30 Study Group. Cyclosporin in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial.	<i>J Am Acad Dermatol</i> 2006; 55(4): 705-709

Source: Adapted from Tables 13, p67-70; 16, p74 and 17, pp74-77 of the submission

6.6 The key features of the randomised trials are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Comparison	Main outcome(s)	Use in modelled evaluation
Omalizumab versus placebo							
GLACIAL	336	DB, MC, R 24 wk (+16 wk f/u)	Low	Moderate to severe CIU (UAS7 ≥16), symptomatic despite H ₁ antihistamine (up to 4× std dose) plus H ₂ antagonist and/or LTRA	Omalizumab 300 mg vs placebo every 4 weeks <u>Background:</u> H ₁ antihistamine (up to 4× std dose) PLUS H ₂ antagonist and/or LTRA	Primary: Safety Key secondary: Change from baseline in mean weekly itch severity score at Week 12	% of responders (UAS ≥ 6), UAS7 distribution, % who discontinue, EQ-5D-3L
ASTERIA I	319	DB, MC, R 24 wk (+16 wk f/u)	Low	Moderate to severe CIU (UAS7 ≥16), symptomatic despite H ₁ antihistamine (std dose)	Omalizumab 75 mg vs omalizumab 150 mg vs omalizumab 300 mg vs placebo every 4 weeks <u>Background:</u> H ₁ antihistamine	Change from baseline in mean weekly itch severity score at Week 12	Long-term dose intensity calculation, EQ-5D-3L
ASTERIA II	323	DB, MC, R 12 wk (+16 wk f/u)	Low	Moderate to severe CIU (UAS7 ≥16), symptomatic despite H ₁ antihistamine (std dose)	Omalizumab 75 mg vs omalizumab 150 mg vs omalizumab 300 mg vs placebo every 4 weeks <u>Background:</u> H ₁ antihistamine	Change from baseline in mean weekly itch severity score at Week 12	Long-term dose intensity calculation, EQ-5D-3L
X-ACT (supportive)	91	DB, MC, R 28 wk	Unclear	CIU with frequent angioedema not responding to H ₁	Omalizumab 300 mg vs placebo every 4 weeks <u>Background:</u>	Change from baseline in total CU-Q2oL score	Not used

Trial	N	Design/ duration	Risk of bias	Patient population	Comparison	Main outcome(s)	Use in modelled evaluation
		(+8 wk f/u)		antihistamine (2× to 4× std dose)	Likely H ₁ antihistamine (up to 4× std dose)	at Week 28	
Cyclosporin versus placebo							
Grattan (2000)	30	DB, R, 2 centres 4 wk (6 mth f/u)	High	Severe CIU, positive ASST, poor response to antihistamine	Cyclosporin 4 mg/kg/day vs placebo (non-responders at Week 4 offered OL cyclosporin) <u>Background:</u> Cetirizine 20 mg daily	% responders at Week 4 (UAS7 <25% of baseline) Change from baseline to Week 4 in UAS7	Not applicable
Vena (2006)	99	DB, MC, R 16 wk (+8 wk f/u)	High	Severe relapsing CIU, persisting symptoms despite cetirizine	Cyclosporin ^a for 16 wk vs cyclosporin ^a for 8 wk then placebo for 8 wk vs placebo for 16 wk <u>Background:</u> Cetirizine 10 mg daily	Change in severity score after 8 weeks	Not applicable

Source: Adapted from Tables 19, pp81-88 and 20, pp89-97 of the submission. Additional data extracted from the respective references.

Abbreviations: ASST = autologous serum skin test; CIU = chronic idiopathic urticaria; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DB = double blind; f/u = follow-up; LTRA = leukotriene receptor antagonist; MC = multi-centre; mth = month; OL = open-label; R = randomised; std = standard; UAS7 = Urticaria Activity Score over 7 days; wk = week

^a Day 0-13: 5 mg/kg/day; Day 14-27: 4 mg/kg/day; from Day 28 onwards: 3 mg/kg/day

- 6.7 The risk of bias of the indirect comparison was potentially high due to the lack of exchangeability across the included trials.
- 6.8 The submission considered the GLACIAL trial as the most relevant evidence for the requested PBS-listing. The inclusion criterion of the GLACIAL trial in terms of failed medications was the most consistent with the requested PBS listing (with the exception of doxepin). The submission presented post hoc subgroup analyses of patients with baseline UAS7 ≥ 28 , consistent with the requested PBS population to inform the economic model (the trial recruited patients with a baseline of UAS7 ≥ 16).

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

Comparative effectiveness

- 6.9 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), see Table 3. 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 3: 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: Adapted from Tables 25, pp111-113 and 31, p139 of the submission.

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).

- 6.10 Similarly, treatment with omalizumab 300 mg every four weeks resulted in statistically significantly larger reductions in UAS7 from baseline at Week 12 compared to placebo across the pivotal and supportive trials. There were statistically significantly larger UAS7 reductions associated with omalizumab 150 mg treatment versus placebo in the ASTERIA I and II trials, but the magnitude of the UAS7 reductions were numerically smaller than those observed with the 300 mg dose. Given the nominated minimally important difference of ≥ 11 , the ESC noted that the reduction in UAS7 associated with omalizumab 150 mg may not be clinically relevant.
- 6.11 The proposed PBS-listing defined a responder as patients who achieved an UAS7 ≤ 6 (see Table 4). A statistically significantly higher proportion of patients achieved an UAS7 ≤ 6 at Week 12 with omalizumab 300 mg treatment (52% to 66% across the trials) and 150 mg treatment (40% and 43% for the ASTERIA I and II trials respectively) compared to placebo (between 11% and 19%). The submission applied the results from the GLACIAL trial in step 1 of the stepped economic model; but the observed dataset for a subgroup of GLACIAL patients with UAS7 ≥ 28 at baseline was applied in base case of the modelled economic evaluation.
- 6.12 The GLACIAL and the ASTERIA I trials included exploratory outcomes at Week 24. The results suggested that efficacy measured using the UAS7 was maintained to Week 24 for omalizumab 300 mg. However, there were no statistically significant differences between omalizumab 150 mg versus placebo at Week 24 (ASTERIA I).
- 6.13 There were statistically significant improvements in the total Dermatology Life Quality Index (DLQI) scores and total Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) scores at Week 12 among patients treated with omalizumab 300 mg versus those treated with placebo across the pivotal trials (GLACIAL, ASTERIA I, ASTERIA II). There were statistically significant improvements in the total DLQI scores and total CU-Q2oL scores for the omalizumab 150 mg arm versus placebo for the ASTERIA II trial, but not the ASTERIA I trial.

- 6.14 The mean change from baseline in EQ-5D-3L index score at Week 12 (exploratory outcome) was only statistically significantly larger for the omalizumab 300 mg versus placebo comparison of the ASTERIA I trial. The economic evaluation used post hoc analyses of utility data from all the pivotal trials to inform the utility values of the UAS7 severity categories in the economic model. The ESC noted the utility weights were derived by linking UAS7 severity scores and EQ-5D-3L responses. The EQ-5D-3L health states are valued using UK population values, which have a larger range than other valuation sets, including Australia. This will give a higher estimate of the QALY gain, and hence under-estimate the ICER.
- 6.15 The submission stated that the indirect comparison between omalizumab 300 mg and cyclosporin via placebo demonstrated that the mean change in UAS7 from baseline (-1.03; 95% CI: -7.85, 5.79) and the proportion of patients achieving a “clinically meaningful response” (OR 0.65; 95% CI: 0.03, 13.19) were not statistically significantly different. The submission therefore claimed that omalizumab 300 mg was non-inferior to cyclosporin. Formal non-inferiority testing was not conducted. The indirect comparisons may be invalid given the extent of the exchangeability issues (e.g. quality of the trials, data asymmetry, inclusion criteria, baseline characteristics, outcomes, duration of the trials and placebo response). Even if the trials were sufficiently exchangeable, it was difficult to concur with the submission’s claim of non-inferiority given the wide 95% CI around the odds ratio and the lack of nominated non-inferiority margins. The submission did not present indirect comparisons of omalizumab 150 mg versus cyclosporin. The ESC considered the wide CIs are due to the very small sample comparing cyclosporin and placebo which makes the indirect comparison very difficult to interpret.

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

Comparative harms

- 6.16 Upper respiratory tract infection, headache, arthralgia, and injection site reactions were numerically more frequently reported in the omalizumab arm(s) across the individual trials. Urticaria was generally more frequently reported in the placebo and omalizumab 75 mg arms. Discontinuations of study treatment due to adverse events were generally numerically higher in the placebo arm, with the most frequently reported event resulting in discontinuation being urticaria. A review of adverse events of special interest did not identify new safety signals. There were limited long-term safety data available.
- 6.17 The submission argued that the risk of anaphylaxis may be expected to be less common in CIU than in severe allergic asthma. The submission noted that the potential cases of anaphylaxis identified during the CIU clinical trial program were either unanimously adjudicated as not representing anaphylaxis (3 cases) or ultimately adjudicated anaphylaxis unrelated to omalizumab (2 cases). However, omalizumab accounted for more reported cases of anaphylaxis than any other drug in a study reviewing serious hypersensitivity reactions reported the US Food Drug Administration (FDA) between March 2012 and March 2013, despite having a small patient population. Overall, the risk of anaphylaxis among CIU patients was unclear.

- 6.18 The US FDA updated the omalizumab product label with information about the finding of slightly elevated risk of cardiovascular and cerebrovascular serious adverse events in a recently completed observational study in allergic asthma.
- 6.19 The commonly reported adverse events associated with cyclosporin across the trials were gastrointestinal disturbance, paraesthesia, infection and headache.
- 6.20 The submission presented a commissioned review on specific adverse events associated with cyclosporin use in dermatologic indications, with a focus on malignancies, infections, renal toxicity, raised lipid concentrations and hypertension. The review found that hypertension and renal toxicity were the most frequently reported safety events in the identified studies, with an apparent dose-effect. The frequency of discontinuations due to nephrotoxicity was unclear, but was claimed as to be “often” in the submission. It was difficult to draw conclusions on the causal link between cyclosporin and malignancies due to potential confounding. Infections and hepatotoxicity appeared to be relatively minor. Hypercholesterolaemia and hypertriglyceridaemia were the main lipid abnormalities reported.

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

Benefits/harms

- 6.21 A summary of the comparative benefits and harms for omalizumab versus placebo is presented in Table 4.

Table 4: Summary of comparative benefits and harms for omalizumab and placebo

Trial	Omalizumab	Placebo	OR (95% CI)	Event rate/100 patients		RD (95% CI)
				Omalizumab	Placebo	
Benefits						
Patients with UAS7 ≤6 at Week 12						
Omalizumab 300 mg						
GLACIAL	132/252	10/83	8.03 (3.96, 16.26)	52.4	12.0	0.40 (0.31, 0.50)
ASTERIA I	42/81	9/80	8.50 (3.75, 19.27)	51.9	11.3	0.41 (0.28, 0.54)
ASTERIA II	52/79	15/79	8.20 (3.96, 17.04)	65.8	19.0	0.47 (0.33, 0.60)
Omalizumab 150 mg						
ASTERIA I	32/80	9/80	5.15 (2.60, 11.75)	40.0	11.3	0.28 (0.16, 0.41)
ASTERIA II	35/82	15/79	3.18 (1.56, 6.48)	42.7	19.0	0.24 (0.09, 0.37)
Patients with UAS7 = 0 at Week 12						
Omalizumab 300 mg						
GLACIAL	85/252	4/83	10.05 (3.56, 28.38)	33.7	4.8	0.29 (0.22, 0.36)
ASTERIA I	29/81	7/80	5.82 (2.37, 14.29)	35.8	8.8	0.27 (0.15, 0.39)
ASTERIA II	35/79	4/79	14.92 (4.97, 44.78)	44.3	5.1	0.39 (0.27, 0.51)
Omalizumab 150 mg						
ASTERIA I	12/80	7/80	1.84 (0.69, 4.95)	15.0	8.8	NS
ASTERIA II	18/82	4/79	5.27 (1.69, 16.38)	22.0	5.1	0.17 (0.07, 0.27)
Harms						
Any adverse event						
Omalizumab 300 mg						
GLACIAL (24 wk)	164/252	53/83	1.05 (0.63, 1.77)	65.1	63.9	NS
ASTERIA I (24 wk)	46/81	41/80	1.25 (0.67, 2.33)	56.8	51.3	NS
ASTERIA II (12 wk)	35/79	32/79	1.17 (0.62, 2.20)	44.3	40.5	NS
Omalizumab 150 mg						
ASTERIA I (24 wk)	60/87	41/80	2.12 (1.12, 3.97)	69.0	51.3	<i>0.18 (0.03, 0.32)</i>
ASTERIA II (12 wk)	42/88	32/79	1.34 (0.73, 2.48)	47.7	40.5	NS
Any treatment-related adverse event						
Omalizumab 300 mg						
GLACIAL (24 wk)	28/252	11/83	0.82 (0.39, 1.73)	11.1	13.3	NS
ASTERIA I (24 wk)	14/81	4/80	3.97 (1.25, 12.65)	17.3	5.0	<i>0.12 (0.03, 0.22)</i>
ASTERIA II (12 wk)	7/79	3/79	2.46 (0.61, 9.89)	8.9	3.8	NS
Omalizumab 150 mg						
ASTERIA I (24 wk)	9/87	4/80	2.19 (0.65, 7.42)	10.3	5.0	NS
ASTERIA II (12 wk)	8/88	3/79	2.53 (0.65, 9.91)	9.1	3.8	NS

Source: Compiled during the evaluation

Abbreviations: PBO = placebo; RD = risk difference; NS = not significant; OR = odds ratio; wk = week

- 6.22 On the basis of direct evidence presented in the submission, for every 100 patients treated with omalizumab 300 mg every 4 weeks in comparison to placebo:
- Approximately 40 to 47 additional patients would achieve an UAS7 ≤6 at Week 12.
 - Approximately 27 to 39 additional patients would achieve an UAS7 = 0 (complete response) at Week 12.
 - Approximately 12 additional patients would experience any treatment-related adverse events over a 24 week duration based on one of the trials. There were no statistically significant differences between arms for the other trials.
- 6.23 On the basis of direct evidence presented in the submission, for every 100 patients treated with omalizumab 150 mg every 4 weeks in comparison to placebo:
- Approximately 24 to 28 additional patients would achieve an UAS7 ≤6 at Week 12.

- Approximately 17 additional patients would achieve an UAS7 = 0 (complete response) at Week 12 based on one of the trials. The difference between arms in the other trial was not statistically significant.
- Approximately 18 additional patients would experience any adverse events over a 24 week duration based on one of the trials. The difference between arms in the other trial was not statistically significant.

6.24 A summary of the comparative benefits and harms for omalizumab versus cyclosporin was not presented given the lack of exchangeability across the trials included in the indirect comparisons.

Clinical claim

6.25 The submission described omalizumab as superior in terms of comparative efficacy and non-inferior in terms of comparative safety over placebo injection (as a proxy for standard of care). This claim was reasonable in terms of comparative efficacy, but not in terms of comparative safety. The ESC noted the discussion in the PSCR (p2) about the comparative safety, but remained concerned about the difference in anaphylaxis.

6.26 The submission described omalizumab as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over cyclosporin. This claim may be reasonable. However, the indirect comparisons of efficacy outcomes were not robust and may not be valid due to the lack of exchangeability across the included trials. Formal non-inferiority testing was not conducted. It was difficult to quantify the differences in safety profiles between omalizumab and cyclosporin.

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

Economic analysis

6.27 The submission presented a cost-minimisation analysis versus cyclosporin, as well as a cost-effectiveness analysis and a cost-utility analysis versus placebo as a proxy for standard of care.

6.28 The submission estimated equi-effective dose over a four week duration as:
Omalizumab 197.22 mg is equi-effective to cyclosporin 9,296 mg.

6.29 The equi-effective dose of omalizumab used in the cost-minimisation analysis was lower than the dose used in the formal indirect comparisons (300 mg every four weeks), as an adjusted omalizumab dose assuming that 68.52% of patients receive 150 mg every four weeks was applied. The submission applied the trial-based initial cyclosporin dose from Grattan (2000) without downward titration, and was 4mg/kg/day, which is at the higher end of dosing seen in the literature. The inconsistent approach was inadequately justified and biased the cost-minimisation analysis in favour of omalizumab.

Table 5: Cost-minimisation analysis (4 weeks duration)

	Omalizumab	Cyclosporin	Incremental cost
Base case presented in the submission (omalizumab 197.22 mg : cyclosporin 9,296 mg)			
Drug costs	\$ [REDACTED]	\$558.46	-\$ [REDACTED]
Administration costs	\$ [REDACTED]	-	\$ [REDACTED]
Monitoring costs	-	\$37.33	-\$37.33
Total	\$ [REDACTED]	\$595.79	-\$ [REDACTED]
Based on the doses used in the indirect comparisons (omalizumab 300 mg : cyclosporin 9,296 mg)			
Drug costs	\$ [REDACTED]	\$558.46	\$ [REDACTED]
Administration costs	\$ [REDACTED]	-	\$ [REDACTED]
Monitoring costs	-	\$37.33	-\$37.33
Total	\$ [REDACTED]	\$595.79	\$ [REDACTED]

Source: Tables 116, p 336 and 117, p 337 of the submission. *Additional data in italics calculated during the evaluation assuming that there were no cyclosporin dose adjustments.*

- 6.30 The submission stated that the omalizumab-treated patients were \$ [REDACTED] per 4 weekly cycle less costly than cyclosporin-treated patients. The incremental cost associated with omalizumab was \$ [REDACTED] per 4 weekly cycle if the doses used in the indirect comparisons were used to inform the cost-minimisation analysis. The cost-minimisation analysis was highly sensitive to the estimated equi-effective doses. The average dose of cyclosporin in clinical practice is likely to be lower than this.
- 6.31 The submission presented a stepped economic evaluation comparing omalizumab versus standard of care (placebo), based on the GLACIAL trial and implementing a modelled evaluation. The model was a Markov model, comparing omalizumab with placebo in patients with severe CIU. The model had a mix of treatment and health states: “on treatment”; “no treatment”; remission; and dead (absorbing health state). The “on treatment” and “no treatment” states incorporated distribution of CIU severity based on the UAS7: urticaria free (UAS7 of 0); well-controlled (UAS7 of 1 to 6); mild (UAS7 of 7 to 15); moderate (UAS7 of 16 to 27); and severe (UAS7 of 28 to 42). This approach increased the complexity of the model.
- 6.32 In the base case analysis, all patients enter the model with severe CIU (UAS7 ≥28), with those in the omalizumab arm starting in the “on treatment” state, and all patients in the comparator arm beginning in the “no treatment” state. At each cycle, all patients were at risk of death. Patients who survived and who were in either the “on treatment” or “no treatment” states could experience spontaneous remission of CIU. Patients who were in the remission state were assumed not to relapse.
- 6.33 All patients in the “on treatment” state received 3 cycles of omalizumab. Discontinuation due to adverse events was applied at Week 12 prior to the application of the continuation criteria. Patients who did not achieve an adequate response, defined as UAS7 ≤6, discontinued treatment after 3 cycles. The ESC questioned whether this assumption was correct and whether omalizumab will be discontinued in patients who demonstrate partial response. Omalizumab responders remained in the “on treatment” state for as long as response was maintained over the duration of the model. A proportion of the patients (68.52%) were assumed to receive a lower dose of omalizumab. The model did not allow for re-treatment after discontinuation. Net benefits in the omalizumab arm were achieved through having fewer patients in the “no treatment” state.

- 6.34 The submission claimed that the inclusion of the placebo effect for the “no treatment” state was conservative. However, this approach was not as conservative as claimed as clinicians were unlikely to persist with failed treatment(s) or do nothing in practice, given the available alternatives despite the lower level of evidence.

Table 6: Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case versus 12 weeks in the GLACIAL trial. Results up to 24 weeks were available, but were not used.
Outcomes	Responders (UAS7 ≤6), quality adjusted life years (QALYs)
Methods used to generate results	Markov cohort expected value analysis
Cycle length	4 weeks
Transition probabilities	Data from the GLACIAL trial used to inform the omalizumab treatment-related transition probabilities. Data from the van der Valk et al (2002) study used to inform the probability of spontaneous remission of CIU. Background mortality informed by the ABS life tables.
Half cycle correction	Applied to benefits and health state costs. The drug and administration costs of omalizumab were applied at the beginning of each cycle (except the final cycle); with no half-cycle correction.

Source: compiled during the evaluation

Abbreviations: ABS = Australian Bureau of Statistics; CIU = chronic idiopathic urticaria; UAS7 = Urticaria Activity Score over 7 days

Table 7: Key drivers of the model

Description	Method/Value	Impact
Continuation criteria	Only patients who meet the PBS continuation criteria (UAS7 ≤6) continued omalizumab therapy beyond 3 doses. This assumes no leakage to those who respond, but not to the level required for continuation.	High, favours omalizumab
Long term dose intensity	68.52% of responders down-titrate to omalizumab 150 mg every 4 weeks for the remainder of the model. The submission argued that 68.52% of patients receiving omalizumab 300 mg every four weeks would have otherwise responded if they had received a lower dose of 150 mg (ratio of the proportion of responders between the 150 mg and 300 mg doses of the ASTERIA I and II trials). This reduces the costs of omalizumab (while applying the treatment benefit from a fixed-dose 300 mg arm).	High, favours omalizumab
Maintenance of treatment effect among responders	The submission stated that the mean change in UAS7 beyond Week 12 was assumed to be zero, and that Week 12 distribution was applicable to the long term. The submission argued all treated patients were not assumed to remain in the “urticaria free” or “well-controlled” categories; rather the distribution reflected the status of patients who do maintain response. The structure of the model resulted in the implicit assumption that patients who incurred the costs of omalizumab maintained the same distribution of UAS7 as at Week 12 for the duration of the model (i.e. the same treatment effect). This assumption was uncertain. No sensitivity analyses attenuating the treatment effect (and treatment state costs) among responders were presented.	Likely to be high, favours omalizumab

Source: compiled during the evaluation

Abbreviations: ICER = incremental cost-effectiveness ratio; UAS7 = Urticaria Activity Score over 7 days

Table 8: Results of the stepped economic evaluation

Step and component	Omalizumab	Placebo	Increment
Step 1(a): Trial-based, mITT population (missing/discontinued=non-responder); drug costs only; 12 weeks			
Costs	\$ [redacted]	\$0	\$ [redacted]
Responders (UAS7 ≤6) at Week 12	0.524	0.120	0.403
Incremental cost/extra responder gained			\$ [redacted]
Step 1(b): Trial-based, observed dataset (missing data excluded); drug costs only; 12 weeks			
Costs	\$ [redacted]	\$0	\$ [redacted]

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Step and component	Omalizumab	Placebo	Increment
Responders (UAS7 ≤6) at Week 12	0.634	0.149	0.485
Incremental cost/extra responder gained			\$ [REDACTED]
Step 2: Trial-based, limit to those with severe CIU at baseline (UAS7 ≥28); drug costs only; 12 weeks			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
Responders (UAS7 ≤6) at Week 12	0.588	0.132	0.456
Incremental cost/extra responder gained			\$ [REDACTED]
Step 3: Modelled evaluation (apply the parameters as per Step 1(b) and 2; drug costs only; 12 weeks)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
Responders (UAS7 ≤6) at Week 12	0.588	0.132	0.456
Incremental cost/extra responder gained			\$ [REDACTED]
Step 4: Modelled evaluation (allow discontinuations due to AE at Week 12; drug costs only; 12 weeks)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
Responders (UAS7 ≤6) at Week 12	0.560	0.132	0.428
Incremental cost/extra responder gained			\$ [REDACTED]
Step 5: Modelled evaluation (transform to QALYs; drug costs only; 12 weeks)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs	0.1845	0.1748	0.0097
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 6: Modelled evaluation (extrapolate to 5 years, allow mortality and discounting; drug costs only)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs	3.7209	3.4349	0.2860
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 7: Modelled evaluation (apply omalizumab administration costs)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs	3.7209	3.4349	0.2860
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 8: Modelled evaluation (apply health state costs)			
Costs	\$ [REDACTED]	\$2,708	\$ [REDACTED]
QALYs	3.7209	3.4349	0.2860
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 9: Modelled evaluation (apply long-term dose intensity – reduces omalizumab continuing dose)			
Costs	\$ [REDACTED]	\$2,708	\$ [REDACTED]
QALYs	3.7209	3.4349	0.2860
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 10: Modelled evaluation (allow spontaneous remission)			
Costs	\$ [REDACTED]	\$2,539	\$ [REDACTED]
QALYs	3.7395	3.4716	0.2679
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 11: Modelled evaluation (allow long-term discontinuation due to disease progression)			
Costs	\$ [REDACTED]	\$2,539	\$ [REDACTED]
QALYs	3.7086	3.4716	0.2370
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 12: Modelled evaluation (correcting “no treatment” UAS7 distribution during the evaluation)			
Costs	\$ [REDACTED]	\$2,479	\$ [REDACTED]
QALYs	3.7265	3.5069	0.2196
Incremental cost/extra QALY gained (amended during the evaluation)			\$ [REDACTED]

Source: Worksheet entitled 'SecEv' in 'Omalizumab_CIU_ModelInputsCMA.xlsx' and Table 112, p327 of the submission
Abbreviations: AE= adverse event; CIU = chronic idiopathic urticaria; mITT = modified intention-to-treat; QALY = quality adjusted life year; UAS7 = Urticaria Activity Score over 7 days

^a Minor discrepancy noted, as \$199,124 per QALY gained calculated during the evaluation.

^b Week 8 data, instead of Week 12 data, were extrapolated for the duration of the model for the “no treatment” state.

- 6.35 There were concerns that the base case incremental cost-effectiveness ratio (ICER) was an underestimate due to the various favourable assumptions within the model (the key assumptions were the reduction in omalizumab dose after initial therapy and the maintenance of the treatment effect for the duration of the model). The ICER is dependent on the effective application of the continuation criteria.
- 6.36 The PSCR (p1) noted that increasing the number of repeats from 2 to 3 for initiating patients increased the ICER from \$45,000/QALY – \$75,000/QALY.

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

Drug cost/patient:

- 6.37 The DPMQ of cyclosporin based on the PBS Online changed between August 2015 and September 2015. The PSCR (p5) accurately stated that the current DPMQ of cyclosporin 100 mg (8660T) is \$366.39 per 60 capsules.

Table 9: Drug and administration cost per patient

	Dose	Duration of course	Drug cost/patient/course	Administration cost/patient/course ^b
Omalizumab				
Initiating course	300 mg every 4 weeks	3 doses	\$ [redacted] ^a	\$ [redacted]
Initiating course (to ensure supply during authority application)	300 mg every 4 weeks	4 doses	\$ [redacted] ^a	\$ [redacted]
Maintenance	300 mg every 4 weeks	Annual ^c	\$ [redacted] ^a	\$ [redacted]
Maintenance	150 mg every 4 weeks	Annual ^c	\$ [redacted] ^a	\$ [redacted]
Average maintenance as per the submission’s assumed split	31.48% on 300 mg: 68.52% on 150 mg	Annual ^c	\$ [redacted] ^a	\$ [redacted]
Cyclosporin (83 kg patient)				
4 mg/kg/day	332 mg per day	Annual ^c	\$ [redacted] ^d	NA
1 mg/kg/day	83 mg per day	Annual ^c	\$ [redacted] ^d	NA

^a Effective price of \$ [redacted] per 150 syringe (economic evaluation). Assumes 23% of dispensing through private hospitals.

^b \$ [redacted] per administration as per the economic evaluation.

^c 13 doses per year assumed. The omalizumab cost of \$ [redacted] per annum in the executive summary could not be verified.

^d Values from the updated cost-minimisation analysis used (\$ [redacted] per 28 days for 4 mg/kg/day).

Estimated PBS usage & financial implications

- 6.38 This submission was considered by the Drug Utilisation Sub-Committee (DUSC). An epidemiological approach was undertaken. DUSC considered that the estimates presented in the submission and updated in the Pre-Sub-Committee Response were slightly overestimated.
- 6.39 DUSC considered that the estimates included with the PSCR were slightly overestimated because point prevalence should not have been used as a proxy for incidence. The estimates have been corrected to remove the added continuing patients as per a prevalence approach. This change results in a slightly lower estimated net cost to the PBS than the estimates provided with the PSCR.
- 6.40 In relation to the updated set of estimates, DUSC considered that a number of issues remained:

- The proportion of people diagnosed and treated might be underestimated, as the definition of CIU required overlapping supply of antihistamine and a second medicine for CIU.
- The source for proportion of severe CIU patients refractory to treatment was clinical opinion on being refractory to antihistamines only, and neglects other therapies, thus may be overestimated. Additionally, the 30% applied in the estimates is not justified.
- The extent of current cyclosporin use to treat CIU may be overestimated and it is improbable that omalizumab would entirely substitute cyclosporin use for CIU. The cost offsets for cyclosporin may not be realised.
- There is a risk of possible use outside the restriction in milder disease and as earlier line treatment, particularly because the test used to determine severity is subjective. However, people may be deterred from using omalizumab to treat mild disease because it is administered as an injection.

Table 10: Estimated usage and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS/RPBS (less co-payment, drug cost-offset and rebate) as per the submission	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to PBS/RPBS (less co-payment, drug cost-offset and rebate), cyclosporin cost-offset updated during the evaluation	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to PBS/RPBS (less co-payment, drug cost-offset and rebate), updated in the PSCR	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS (less co-payment, drug cost-offset and rebate), updated to exclude patients continuing in subsequent years of treatment	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Quality Use of Medicines

- 6.41 The submission stated that Australian CIU patients have a high unmet clinical need and would benefit from access to an effective targeted therapy.
- 6.42 Omalizumab is associated with a risk of anaphylaxis. Post-administration observation of up to two hours is recommended in the Australian Medicines Handbook (2015). The submission claimed that general practitioners with resuscitation facilities are administering omalizumab under the guidance of the initiating specialist given the increased familiarity with omalizumab, i.e. not limited to the hospital setting.

Financial Management – Risk Sharing Arrangements

- 6.43 The sponsor proposed a [REDACTED]% confidential rebate on net Commonwealth expenditure under the requested listing. This does not mitigate the risk of use beyond the requested PBS population.
- 6.44 DUSC noted the comments in the PSCR (pp4-5) that uncertainties such as the dose proportion, discontinuation rule and the adjustment of the estimates to be a cost to

Government could be handled using a risk share arrangement, which the sponsor is prepared to discuss with the Department following a positive recommendation.

- 6.45 The PBAC considered that there was a risk of use outside the requested restriction, in particular in milder disease and earlier line treatment. The PBAC noted the revised estimates of usage in the DUSC advice and considered that a risk share arrangement based on these figures would be appropriate to address the potential leakage and manage the financial implications for any use beyond the restriction.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of omalizumab for the treatment of chronic idiopathic urticaria, on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program). The recommendation was formed on the basis of a cost-minimisation analysis compared with cyclosporin. The equi-effective doses are omalizumab 300mg and cyclosporin 3mg/kg.
- 7.2 The PBAC accepted that cyclosporin was the appropriate comparator.
- 7.3 The PBAC noted that formal non-inferiority testing was not conducted in the analysis presented in the submission, and 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.
- 7.4 The PBAC accepted that omalizumab was non-inferior to cyclosporin and superior to placebo in terms of clinical effectiveness.
- 7.5 The PBAC considered the sponsor's claim of superior comparative safety over cyclosporin was difficult to quantify due to differences in the safety profiles and the limited data available. The PBAC acknowledged that the risk of anaphylaxis with omalizumab treatment remained a concern, but noted that this risk is known and, as advised in the Sponsor hearing, manageable.
- 7.6 The PBAC noted the cost-effectiveness analysis against placebo, and the issues raised by ESC in regard to the model presented in the submission, but considered that the cost-minimisation analysis against cyclosporin was the appropriate comparison to use as the basis for listing. The PBAC noted that in determining the equi-effective doses of omalizumab and cyclosporin the submission allowed downward titration for omalizumab but applied the trial-based dose of cyclosporin without titration. The PBAC consider this inconsistency was inadequately justified and biased the cost-minimisation analysis in favour of omalizumab. The PBAC considered that the dose of cyclosporine 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 300mg and cyclosporin 3mg/kg.

- 7.7 The PBAC considered that a continuation rule would be difficult to implement in clinical practice, and instead recommended that usage should be reviewed after listing. The PBAC requested the Department to finalise a restriction wording.
- 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: *Restrictions to be finalised*

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
OMALIZUMAB omalizumab 150 mg/mL injection, 1 x 1 mL syringe	2	2	Xolair	Novartis

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Severe
Condition:	Chronic idiopathic urticaria
PBS Indication:	Severe chronic idiopathic urticaria
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a clinical immunologist; OR Must be treated by an allergist; OR Must be treated by a dermatologist; OR Must be treated by a general physician with expertise in the management of chronic idiopathic urticaria (CIU).

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<p>Clinical criteria:</p>	<p>The condition must be based on both physical examination and patient history (to exclude any factors that may be triggering the urticaria)</p> <p>AND</p> <p>Patient must have itch and hives that persist on a daily basis for at least 6 weeks despite treatment with H1 antihistamines</p> <p>AND</p> <p>Patient must have failed to achieve an adequate response after a minimum of 2 weeks treatment with H1 antihistamines at maximally tolerated doses in accordance with clinical guidelines, and/or H2 receptor antagonist (150 mg twice per day) and/or leukotriene receptor antagonist (LTRA)(10 mg per day) and/or doxepin (up to 25mg three times a day).</p>
<p>Population criteria:</p>	<p>-</p>
<p>Prescriber Instructions</p>	<p>If the requirement for treatment with H1 antihistamines, H2 receptor antagonists, leukotriene receptor antagonists and doxepin cannot be met because of contraindications according to the relevant TGA-approved Product Information and/or intolerances of a severity necessitating permanent treatment withdrawal, details of the contraindication and/or intolerance must be provided in the authority application.</p> <p>The following initiation criteria indicates failure to achieve an adequate response to standard therapy and must be demonstrated at the time of the initial application: A current Urticaria Assessment Score 7 (UAS7) score of ≥ 28 with an itch score of greater than 8, as assessed while still on standard therapy. The current UAS7 assessment must be no more than 1 month old at the time of the application.</p> <p>A maximum of 12 weeks of treatment with omalizumab will be authorized under this restriction.</p> <p>The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Chronic Idiopathic Urticaria PBS Authority Application - Supporting Information Form which must include the following: (i) a completed current Urticaria Assessment Score Form completed for 7 consecutive days including the dates of assessment of the patient's condition; and (ii) a signed patient acknowledgment.</p>
<p>Administrative Advice</p>	<p>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).</p> <p>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</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
OMALIZUMAB omalizumab 150 mg/mL injection, 1 x 1 mL syringe	1	5	Xolair	Novartis

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Severe
Condition:	Chronic idiopathic urticaria
PBS Indication:	Severe chronic idiopathic urticaria
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a clinical immunologist; OR Must be treated by an allergist; OR Must be treated by a dermatologist; OR Must be treated by a general physician with expertise in the management of chronic idiopathic urticaria (CIU).
Clinical criteria:	Patient must have a documented history of severe chronic idiopathic urticaria (CIU), AND Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND Patient must not receive more than 24 weeks of treatment under this restriction.
Prescriber Instructions	At the time of the authority application, medical practitioners should request the appropriate maximum quantity to provide for a continuing course of omalizumab consisting of the number of doses sufficient for 24 weeks of therapy.

Administrative Advice	<p>A proportion of patients respond to 150mg 4-weekly so where a substantial improvement has been obtained with a 300mg dose it is reasonable to back-titrate dose after initial treatment.</p> <p>Cessation of therapy should be considered after the patient has demonstrated clinical benefit with omalizumab to re-evaluate the need for continued therapy. Any patient who ceases therapy and whose CIU relapses will need to re-initiate omalizumab as a new patient on the PBS.</p> <p>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).</p>
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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

The Sponsor had no comment.