PUBLIC SUMMARY DOCUMENT
Product: Omalizumab (rch), powder for injection, 150 mg, Xolair®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) listing for the initial and continuing treatment of patients with uncontrolled severe allergic asthma, who are 12 years of age or older and who meet certain criteria.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Omalizumab was first TGA registered on 13 June 2002 for the management of adults and adolescent patients with moderate allergic asthma. Registration was extended on 13 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.

4. Listing Requested and PBAC's View

Public and private hospital authority required
Initial 1 (new patients or new treatment cycle)
Initial treatment of uncontrolled severe allergic asthma

Initial PBS-subsidised treatment with omalizumab by a respiratory physician, clinical immunologist, allergist or a consultant physician as specified in the NOTE below*, of a patient with uncontrolled severe allergic asthma who has been under the care of this physician for at least 12 months and satisfies the following criteria:
(a) age 12 years or older; and
(b) has a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or consultant physician as specified in the NOTE below, defined by standard clinical features, including:

i. forced expiratory volume (FEV_1) reversibility ≥12% and ≥200 mL at baseline within 30 minutes after administration of salbutamol (200 - 400 μg), or
ii. airway hyperresponsiveness defined as a >20% decline in FEV1 during a direct bronchial provocation test or >15% decline during an indirect bronchial provocation test, or
iii. peak expiratory flow (PEF) variability of >15% between the two highest and two lowest peak expiratory flow rates during 14 days; and

(c) duration of asthma of at least 1 year; and
(d) FEV1 ≤80% predicted, documented on 3 or more occasions in the previous 12 months; and
(e) past or current evidence of atopy, documented by skin prick testing or RAST; and
(f) total serum human immunoglobulin E (IgE) ranging from >30 IU/ml to ≤1,100 IU/ml and the appropriate weight range for that IgE level, according to the Product Information (see NOTE); and
(g) has signed a patient acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment; and
(h) has failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented (see NOTE). Optimised asthma therapy includes:

i. adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (budesonide 1600 μg/day or fluticasone propionate 1000 μg/day or equivalent), plus long-acting beta-2 agonist therapy (at least salmeterol 50 μg bd or eformoterol 12 μg bd) for at least 12 months, and
ii. if clinically appropriate (see NOTE), lowest maintenance dose oral corticosteroids.

Alternative PBS listing which excludes the requirement to be on oral corticosteroids as part of OAT.
The restriction would be the same as requested above, except that the corticosteroid criterion, h (ii) (and accompanying NOTES), would not be included.

NOTES:
Prescribers must be a respiratory physician, consultant physician [internal medicine physician practicing in respiratory medicine] or consultant physician [general medicine specialising in respiratory medicine]. [*this section to be finalised with the RWG*]

A re-assessment of free IgE can only be made at least 12 months after the last dose of omalizumab. For patients re-commencing omalizumab within 12 months of the last dose the previous pre-omalizumab IgE level should be used.

Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council Information Paper for Health Professionals on Inhaler Technique [see NAC form]; the assessment and adherence to correct technique should be documented in the patient's medical records.

If treatment with any of the drugs required for optimised standard therapy is contraindicated according to the relevant TGA-approved Product Information, please provide details at the time of application.

Oral corticosteroids may *not* be clinically appropriate if:

i. there are contraindications to oral corticosteroids; or
ii. age is 16 years or less (due to the risk of growth impairment), or
iii. there is documented evidence in the patient's medical records of side-effects that have required cessation of previous oral corticosteroids [see Toxicity criteria form], or
iv. there is documented evidence in the patient's medical records that the patient has used sufficiently high and/or prolonged doses of oral corticosteroids such that there is a significant risk of developing one or more side-effect [see Toxicity criteria form], or
v. there is documented evidence in the patient's medical records that the patient has used sufficiently high and/or prolonged doses of oral corticosteroids, but demonstrates a lack of therapeutic response (is unresponsive or resistant to oral corticosteroids).

If intolerance to the drugs required for optimised standard therapy develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, please provide details of the degree of this toxicity at the time of application. Details of the accepted toxicities including severity can be found on the Medicare Australia website (www.medicareaustralia.gov.au) [see Toxicity criteria form].

The following initiation criterion indicates *failure to achieve adequate control* and must be demonstrated in all patients at the time of the application:
(a) an Asthma Control Questionnaire (ACQ) Score of at least 1.5, as assessed in the previous month, and either:

i. experienced at least two independent (at least 1 month apart) severe asthma exacerbations in the past 12 months, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician, or
ii. experienced at least one admission to hospital for a severe asthma exacerbation in the past 12 months.

Applications for authorisation must be made in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Severe Allergic Asthma PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] [Application form] which includes the following:

i. the completed current 5 item Asthma Control Questionnaire (ACQ) [Approved questionnaire] calculation sheet including the date of assessment of the patient's symptoms; and
ii. details of prior optimised standard drug therapy [dosage, date of commencement and duration of therapy]; and
iii. the signed patient acknowledgement.

A maximum quantity and number of repeats to provide for an initial course of omalizumab consisting of the recommended number of doses for the baseline IgE level and body weight (see Table 5 in the PI) to be administered every 2 or 4 weeks, will be authorised.

Where fewer than the required number of repeats to complete 20 weeks of treatment are requested at the time of the application, authority approvals for sufficient repeats to complete 20 weeks of omalizumab therapy may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Under no circumstances will telephone approvals be granted for initial authority applications, or for treatment that would otherwise extend the initial treatment period beyond 20 weeks.

The Asthma Control Questionnaire assessment of the patient's response to this initial course of treatment must be made at around 16 weeks after the first dose so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed.

This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to Medicare Australia within 4 weeks of the date of assessment, and no later than 2 weeks prior to the patient completing their current treatment course, to avoid an interruption to supply. Where a response assessment is not undertaken and submitted to Medicare Australia within this timeframe, the patient will be deemed to have failed to respond to treatment with omalizumab.

It is recommended that an application for continuing treatment is posted to Medicare Australia at the time of the 16 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised omalizumab treatment.

Public and private hospital authority required
First assessment for continuing treatment
Continuing treatment of uncontrolled severe allergic asthma

Continuing PBS-subsidised treatment with omalizumab, by a respiratory physician, clinical immunologist, allergist or a consultant physician as specified in the NOTE below*, of a patient who:
(a) has a documented history of severe allergic asthma; and
(b) has demonstrated or sustained an adequate response to treatment with omalizumab.

NOTES:
Prescribers must be a respiratory physician, consultant physician [internal medicine physician practicing in respiratory medicine] or consultant physician [general medicine specialising in respiratory medicine]. [*this section to be finalised with the RWG*]

The first assessment should occur at around 16 weeks (4 months) after commencing omalizumab and should, where possible, be completed by the same physician who initiated treatment with omalizumab. If the same physician cannot assess the patient please call Medicare Australia on 1800 700 270.

An adequate response to omalizumab treatment at the first assessment is defined as:
(a) a reduction in Asthma Control Questionnaire (ACQ) score of at least 0.5 compared to baseline.

Applications for authorisation must be made in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Severe Allergic Asthma PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes the following:
i. the completed Asthma Control Questionnaire (5 item) score calculation sheet including the date of the assessment of the patient's condition.

The Asthma Control Questionnaire assessment of the patient's response to this initial course of treatment must be made at around 16 weeks after the first dose so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed.

This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to Medicare Australia within 4 weeks of the date of assessment, and no later than 2 weeks prior to the patient completing their current treatment course, to avoid an interruption to supply. Where a response assessment is not undertaken and submitted to Medicare Australia within this timeframe, the patient will be deemed to have failed to respond to treatment with omalizumab.

It is recommended that an application for continuing treatment is posted to Medicare Australia at the time of the 16 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised omalizumab treatment.

Where an assessment is not submitted to Medicare Australia within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response, to treatment with omalizumab.

Patients are eligible to receive a second course of omalizumab treatment of up to 20 weeks providing the demonstrate an adequate response to treatment. A confirmatory assessment will need to be conducted at around 32 weeks (8 months) after commencing omalizumab, and ongoing assessments will need to be undertaken every 6 months thereafter.

At the time of the authority application, medical practitioners should request the appropriate number of vials, based on the baseline IgE level and weight of the patient, to provide sufficient for 20 weeks of therapy.

Where fewer than the required number of repeats to complete 20 weeks of treatment are requested at the time of the application, authority approvals for sufficient repeats to complete 24 weeks of omalizumab therapy may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Public and private hospital authority required
Confirmatory and ongoing assessment
Continuing treatment of uncontrolled severe allergic asthma

Continuing PBS-subsidised treatment with omalizumab, *in consultation with* a respiratory physician, clinical immunologist, allergist or consultant physician as specified in the NOTE below, of a patient who:
(a) has a documented history of severe allergic asthma; and
(b) has demonstrated or sustained an adequate response to treatment with omalizumab.

NOTES:
Omalizumab must be prescribed in consultation with a respiratory physician, consultant physician [internal medicine physician practicing in respiratory medicine] or consultant physician [general medicine specialising in respiratory medicine]. [*this section to be finalised with the RWG*]

A confirmatory assessment with the Asthma Control Questionnaire plus additional criteria is required at around 32 weeks (8 months) after commencing omalizumab, and ongoing assessments using the same criteria are required every 6 months thereafter.

An adequate response to omalizumab treatment at the confirmatory and ongoing assessments is defined as:
(a) a reduction in Asthma Control Questionnaire (ACQ) score of at least 0.5 compared to baseline, and either:
   i. at least a 50% reduction in the number of clinically significant exacerbations requiring documented use of systemic corticosteroids, compared to the 12 months prior to commencement of omalizumab, or
   ii. 3 fewer clinically significant exacerbations requiring documented use of systemic corticosteroids, compared to the 12 months prior to commencement of omalizumab, or
   iii. one less hospitalisation for asthma compared to the 12 months prior to commencement of omalizumab, or
   iv. at least a 25% reduction in the daily dose of maintenance oral corticosteroids, compared to the baseline dose (for patients on oral corticosteroids at baseline).

Applications for authorisation must be made in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Severe Allergic Asthma PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes the following:
   ii. the completed Asthma Control Questionnaire (5 item) score calculation sheet including the date of the assessment of the patient's condition, and
   iii. details of the additional criteria to satisfy an adequate response to omalizumab.

The assessment of the patient's response to a continuing course of therapy must be made no later than 4 weeks before the date of completion of that course and posted to Medicare Australia no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criterion.

Where an assessment is not submitted to Medicare Australia within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response, to treatment with omalizumab.

Patients are eligible to receive continuing omalizumab treatment in courses of up to 24 weeks providing they continue to sustain the response.

At the time of the authority application, medical practitioners should request the appropriate number of vials, based on the baseline IgE level and weight of the patient, to provide sufficient for 24 weeks of therapy.

Where fewer than the required number of repeats to complete 24 weeks of treatment are requested at the time of the application, authority approvals for sufficient repeats to complete 24 weeks of omalizumab therapy may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

A grandfather restriction was also requested for patients who have previously received non-PBS-subsidised therapy with omalizumab prior to a PBAC positive recommendation.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Asthma is "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment". (National Asthma Handbook, NAC, 2006, p 4)

Allergic asthma is caused by allergens to which a person has been sensitised which result in over-producing IgE antibodies directed against the allergen. Subsequent expose to the allergen, after sensitisation, elicits an allergic response.

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.

6. Comparator

The submission nominated placebo as the comparator for patients using maintenance dose oral corticosteroids (OCS) whose asthma remains uncontrolled; patients unable to use OCS due to intolerance (includes those patients with contraindications, existing side-effects or a high risk of side-effects due to past exposure) or because they are unresponsive to, or resistant to, OCS. This was considered appropriate by the PBAC.

The submission also nominated oral corticosteroids as the comparator for patients who could conceivably use OCS, however it is recognised that there are risks associated with long-term use, and the clinical preference is to use omalizumab in place of OCS. The PBAC agreed the appropriate comparator for this group is OCS.

7. Clinical Trials

The submission presented one direct randomised double blind trial with post-hoc adjustment for primary outcome (Trial 2306), one direct randomised open label trial (Trial 2425), and one supporting post-hoc subgroup analysis of severe uncontrolled asthmatics from a direct randomised open label trial (Trial IA04 subgroup), each comparing omalizumab + optimised asthma therapy (OAT) with OAT with or without placebo. OAT included high dose inhaled corticosteroids and long-acting beta-2 agonists with or without OCS. Meta-analyses of secondary outcomes from the included trials were also conducted.

The table below details the published trials presented in the submission. Trial 2425 was completed just prior to the submission to the PBAC and has not yet been published.

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
Trial 2306/ Humbert M, et al.	Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy.	Allergy 2005; 60:309-316
Trial IA04/	Efficacy and tolerability of IgE therapy with	Allergy 2004

Ayres JG, et al.	omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma.	Jul;59(7):701-8
Trial IA04/ Niven R, et al	Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: An open-label study.	Respiratory Medicine 2008 Oct;102(10):1371-8
Supportive Meta-analyses		
Bousquet J, et al.	The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma.	Allergy 2005; 60(3):302-308

8. Results of Trials

The primary outcomes presented are the rate of clinically significant asthma exacerbations (requiring systemic corticosteroids), and response to and persistency of response to omalizumab. Key secondary outcomes are the rate of severe exacerbations, the rates of hospitalisation, emergency department visits and unplanned outpatient department visits, and changes from baseline in forced expiratory volume in one second (FEV1), symptom scores (including the Asthma Control Score (ACQ)) and EQ-5Dscore. In addition, the AQL-5D score was mapped from the Asthma Quality of Life Questionnaire (AQLQ).
The rates of clinically significant asthma exacerbations in Trial 2306 (PITT) are shown below.

	OAT + OM N=209 n (%)	**OAT + PBO N=210 n (%)**
Adjusted baseline exacerbations		
Rate of clinically significant asthma exacerbations 28 weeks	0.68	0.91
Ratio of exacerbation rate (95% CI)	0.738 (0.552, 0.988)	
p value	0.042	
Rate of clinically significant asthma exacerbations 28 weeks	0.74	0.92
Not adjusted for baseline exacerbations		
Ratio of exacerbation rate (95% CI)	0.806 (0.600, 1.083)	
p value	0.153	

OM = omalizumab; OAT = optimised asthma therapy; PBO = placebo, PITT = Primary-Intention-to-Treat.

There were statistically significant differences in the number of clinically significant asthma exacerbations experienced by patients treated with omalizumab + OAT versus those treated with OAT + placebo for the PITT population adjusted post-hoc for variations in baseline pre-trial exacerbations rates (with and without imputation for missing data). However, in the analyses unadjusted for variations in baseline pre-trial exacerbations rates, no statistically significant differences were observed with respect to clinically significant exacerbations.

Trial 2306 defined a severe asthma exacerbation as an exacerbation resulting in a peak expiratory flow (PEF) or FEV1 less than 60% of personal best or breathlessness at rest and

requiring treatment with systemic corticosteroids. The rates of severe asthma exacerbations in Trial 2306 (PITT) are shown below.

	Severe asthma exacerbation rate (without imputation)		
Nº of severe asthma exacerbations	**OAT + OM N=*209***	**OAT + PBO N=*210***	**p value**
Total exacerbations	49	100	
Rate of severe asthma exacerbations over 28 weeks	0.24	0.48	
Ratio of exacerbation rate (95% CI)	0.499 (0.321, 0.777)		0.002

OM = omalizumab; OAT = optimised asthma therapy; PBO = placebo, PITT = Primary-Intention-To-Treat.

There was a statistically significant difference in the number of severe asthma exacerbations experienced by patients treated with omalizumab + OAT versus those treated with OAT alone [ratio 0.499, 95% CI (0.321, 0.777), p = 0.002].

The results of investigator and patient assessment of Global Evaluation of Treatment Effectiveness (GETE) dichotomised to responder/non-responder in Trial 2306 (PITT) are shown below.

	Responders			
	Investigator's GETE		**Patient's GETE**	
	OAT + OM N=209 n (%)	**OAT + PBO N=210 n (%)**	**OAT + OM N=209 n (%)**	**OAT + PBO N=210 n (%)**
Responder	60.5%	42.8.0%	64.3%	43.3%
Non-responder	39.5%	57.3%	35.7%	56.7%

OM = omalizumab; OAT = optimised asthma therapy; GETE = Global Evaluation of Treatment Effectiveness; PITT = Primary-Intention-To-Treat.

While the proportion of responders and non-responders appears to favour treatment with omalizumab, no statistical analysis of the results was reported in the submission.

There were statistically significant differences in the number of clinically significant asthma exacerbations favouring treatment with omalizumab + OAT versus OAT with or without placebo in Trial 2306 and Trial IA04 (post-hoc subgroup analysis). Adjustment for baseline exacerbations (during the year prior to screening) in Trial 2306 had the effect of making the difference in exacerbation rates between omalizumab + OAT and placebo + OAT statistically significant.

In the double - blind Trial 2306 there was no statistically significant differences between trial arms for hospital admissions, ED visits and other unscheduled visits in the analyses unadjusted for baseline exacerbation rates.

The rate of serious adverse events (excluding asthma exacerbations) was similar across trial arms.

The incidence of 'all adverse events' reported in Trial 2306 appeared to include asthma related events. Consequently the lower rate of asthma related events in patients treated with

omalizumab resulted in a lower rate of adverse events for patients receiving omalizumab + OAT compared to those receiving OAT + placebo.

Gastrointestinal disorders, musculoskeletal and connective tissue disorders and skin and subcutaneous tissue disorders were more common in patients receiving omalizumab.

Anaphylactic reactions, while very rare, have been reported to occur predominantly within the first few hours after administration of omalizumab and on occasion up to 36 hours after administration.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The submission described omalizumab as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The submission presented a stepped economic evaluation. The model has 10 health states, incorporating whether the patient is a responder to omalizumab treatment or not and whether the patient currently uses, has previously used, or never used maintenance OCS. Patients are cycled through the model in 32 week cycles over 50 years.

The possible events in the model are non-asthma death, response/non-response, discontinue OCS, return to maintenance OCS and exacerbations (clinically significant, severe, hospitalised severe, or fatal).

From the results of the sensitivity analyses, the model is most sensitive to the utilities applied to the health states in the model. Using the EQ-5D utilities recommended in The Guidelines, rather than the AQL-5D values derived using the AQLQ, increases the incremental cost per QALY gained for the OCS population and the non-OCS population. The incremental cost per QALY gained for the OCS population was between $45,000 - $75,000, and between $75,000 - $105,000 for the non-OCS population.

The model is also sensitive to the probability of maintaining response to omalizumab in the long-term, the risk of death associated with a severe, hospitalised exacerbation, the relative risk of death in OCS users and the model duration.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 600 in Year 5 for OCS patients only, or less than 1,200 in Year 5 for all patients. The submission's estimate was considered to be underestimated.

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5 for OCS patients only, or less than $20 million in Year 5 for all patients. The submission's estimate was considered to be underestimated.

12. Recommendation and Reasons

The PBAC noted from the hearing that there is a high clinical need for an effective treatment for patients with severe asthma who are uncontrolled on, or intolerant to, oral corticosteroids and that such a patient group is difficult to define. The PBAC is sympathetic to these patients and indicated its willingness to work with the sponsor in order to target patients with the highest clinical need, as well as to try to address the other issues that have arisen with the submission, including the use of the appropriate trial data in the model, calibration of the trial data to the model, the time horizon and utilities in the model.

The PBAC agreed with the ESC that the definition of patients who would qualify for treatment matched neither the entry criteria for the trials nor the sub-group upon which the economic evaluation was based. In particular, the requested restriction includes patients with IgE greater than 30, but the TGA-approved Product Information states that patients with IgE less than 76 are less likely to experience benefit. The clinician at the hearing indicated that the patients treated at his hospital had an IgE significantly higher than 30.

Further, despite its complexity, the requested restriction did not target the patients with the most severe form of asthma nor those who would necessarily need to be treated in hospital outpatient clinics. This was supported by the Highly Specialised Drugs Working Party that did not recommend Section 100 PBS listing.

As noted by the ESC, in the requested restriction, the qualifying Asthma Control Questionnaire (ACQ) Score is at least 1.5 on a 7-point scale, and either:

> (i) experienced at least two independent (at least 1 month apart) severe asthma exacerbations in the past 12 months, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician, or
> (ii) experienced at least one admission to hospital for a severe asthma exacerbation in the past 12 months.

Whereas in its criteria for patients not controlled with inhaled corticosteroids, the John Hunter Hospital Difficult Airways Clinic (July 2009), for example, uses an ACQ score of at least 2.0, and at least one of the following criteria:

> (i) at least 2 hospital admissions for a severe asthma exacerbation in the last 12 months, or
> (ii) at least 3 asthma exacerbations in the past 12 months defined by worsening in asthma symptoms requiring a course of intravenous or OCS or an increase in the patient's usual dose of OCS, each course lasting for at least 5 days.

There is variability in the use of ACQ scores as a measure of asthma control. Gibson et al. (2007), reporting on a small study of 12 uncontrolled severe allergic asthma patients (n of 1 trials of omalizumab), found an average baseline ACQ score of 3.0 in both ICS dependent and OCS dependent patients.

The requested listing proposed the use of the ACQ5 as a measure of response to determine eligibility for continuing treatment with omalizumab. However, this was not the measure used in the included trials, which was the Global Evaluation of Treatment Effectiveness,

GETE). Furthermore, the two domains omitted from the ACQ7 to form the ACQ5 were the only objective outcomes (FEV_1 changes and use of rescue medication) in the questionnaire.

The PBAC also considered the patients defined as those who could conceivably use OCS, however it is recognised that there are risks associated with long-term use, and the clinical preference is to use omalizumab in place of OCS, to be problematic and agreed that the appropriate comparator for this group would be OCS.

From the double blind Trial 2306, omalizumab, in combination with optimised asthma therapy (OAT), appears to provide some numerical improvement in the remission of symptoms of severe, uncontrolled, allergic asthma compared to placebo plus OAT . However, these improvements are not consistent across all trial outcomes and not statistically significant in the primary outcome of the trial (rate of clinically significant asthma exacerbations), until the trial data were re-analysed post-hoc, adjusting for variation between trial arms for the rate of baseline asthma exacerbations. There is no statistically significant difference between omalizumab + OAT compared to placebo + OAT in the number of hospitalisations, ED visits and unplanned outpatient visits due to exacerbations (unadjusted for rate of baseline asthma exacerbations) in Trial 2306. The PBAC considered it inappropriate to apply a baseline adjustment to the exacerbations in Trial 2306 given that the variability in exacerbations between the treatment and placebo arms was not significant. Further, the number of patients with exacerbations would have been a more relevant measure than the number of exacerbations for the economic evaluation.

The PBAC considered use of the results of the unblinded 2425 trial in the economic analysis to be unjustified and inappropriate. The PBAC noted the results for the incremental cost per QALY would be less favourable if the submission had based the economic evaluation on Trial 2306.

The PBAC considered there were a number of other issues of uncertainty about the economic model, as identified by the ESC, all of which favoured omalizumab:
- The economic analysis does not model the recommencement of omalizumab after 6 months, which is permitted under the proposed restriction;
- The model is not adequately calibrated to the trial data given the large difference in outcomes between the trial-based results;
- The use of AQL-5D (an instrument that is not validated nor widely used) as the source of utilities in the modelled evaluation when utilities from EQ-5D were directly measured in the trial;
- The application of a disutility for exacerbations may not be reasonable and may result in double-counting because the utility estimates measured directly from the trial already capture the impact on utility of exacerbations;
- Post hoc subgroup analyses of patients with baseline ACQ score at least 1.5 stratified by OCS use results in small patients numbers (N=41 for the 'with OCS' subgroup) on which model estimates of response, exacerbations, resource use and utilities are based.

The PBAC thus considered the incremental cost per QALY gained from $45,000 - $75,000 in the base case for the OCS population and $75,000 - $105,000 in the non-OCS population to be high and uncertain.

The PBAC therefore rejected the submission because of a poorly targeted restriction, uncertain clinical benefit and a high and unacceptable cost-effectiveness ratio.

13. 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.

14. Sponsor's Comment

Novartis acknowledges that aspects of the submission, including the wording of the patient eligibility criteria, can be further refined. The company would like to emphasise that the intention of the submission and restrictions was to seek PBS-subsidy for patients with a high medical need – those who, despite using oral corticosteroids and maximal doses of inhaled therapy, continue to experience asthma symptoms and exacerbations. However Novartis acknowledges the views of the PBAC and is committed to working with the committee, physicians and other stakeholders to address the restrictions and other issues of concern.

Novartis would also like to note (as these results are not included in the PSD) that in Trial 2306 there were significant improvements in the mean symptom score, quality of life score and lung function, and a significantly lower rate of total emergency visits in patients treated with omalizumab.