**PUBLIC SUMMARY DOCUMENT**
**Product:** Omalizumab (rch), powder for injection, 150 mg, Xolair®
**Sponsor:** Novartis Pharmaceuticals Australia Pty Ltd
**Date of PBAC Consideration:** November 2010

## 1. Purpose of Application

The re-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

At the November 2009 meeting, the PBAC rejected a submission for 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 because of a poorly targeted restriction, uncertain clinical benefit and a high and unacceptable cost-effectiveness ratio. A copy of the Public Summary Document (PSD) from this meeting is available at: www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Omalizumab-nov09.

## 3. Registration Status

Please refer to the November 2009 PSD.

## 4. Listing Requested and PBAC's View

*The following is an abbreviation of the requested restriction.*

Public and private hospital authority required
Initial PBS-subsidised treatment with omalizumab by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, 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 general physician experienced in the management of patients with severe asthma, 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 micrograms), or

ii. airway hyperresponsiveness defined as a > 20% decline in $FEV_1$ 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) $FEV_1 \leq 80\%$ 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) > 30 IU/mL, and the appropriate weight range for the IgE level, according to the Product Information; 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 (*defined in NOTE*). Optimised asthma therapy includes:

i. adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (budesonide 1,600 micrograms/day or fluticasone propionate 1,000 micrograms/day or equivalent), plus long-acting beta-2 agonist therapy (at least salmeterol 50 micrograms twice daily (bd) or eformoterol 12 micrograms bd) for at least 12 months, unless contraindicated or not tolerated (*defined in NOTE*), AND

ii. oral corticosteroids (at least 10 mg/day prednisolone (or equivalent)) for at least 6 weeks, unless contraindicated or not tolerated (*defined in NOTE*).

The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application:

(a) an Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month, AND

(b) while on oral corticosteroids and in the past 12 months, experienced at least 1 admission to hospital for a severe asthma exacerbation, OR 1 severe asthma exacerbation, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician.

Public and private hospital authority required

Continuing PBS-subsidised treatment with omalizumab, by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, 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.

An adequate response to omalizumab treatment is defined as:

(a) a reduction in the Asthma Control Questionnaire (ACQ-5) score of at least 0.5 from baseline, OR

(b) maintenance oral corticosteroid dose reduced by at least 25% from baseline, and no deterioration in ACQ-5 score from baseline.

Public and private hospital authority required *(Grandfather restriction)*

Initial PBS-subsidised supply for continuing treatment with omalizumab by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, of a patient with severe allergic asthma who 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 general physician experienced in the management of patients with severe asthma, 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 micrograms), or

ii. airway hyperresponsiveness defined as a > 20% decline in $FEV_1$ 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) past or current evidence of atopy, documented by skin prick testing or RAST; and

(e) 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 for grandfathered patients; and

(f) prior to omalizumab therapy had failed to achieve adequate control with optimised asthma therapy. Optimised asthma therapy includes:

i. adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (budesonide 1,600 micrograms/day or fluticasone propionate 1,000 micrograms/day or equivalent), plus long-acting beta-2 agonist therapy (at least salmeterol 50 micrograms bd or eformoterol 12 micrograms bd) for at least 12 months, and

ii. may have included maintenance dose oral corticosteroids; and

(g) has demonstrated an adequate response to treatment with omalizumab.

A review of the patient's records should be conducted to extract pre- and post-omalizumab data on symptoms, quality of life, medication doses, exacerbations and hospitalisations. Examples of parameters to establish response include:

i. a reduction in Asthma Control Questionnaire (ACQ-5) score of at least 0.5;

ii. an improvement of at least 0.5 in the Asthma Quality of Life Questionnaire (AQLQ or mini-AQLQ);

iii. maintenance oral corticosteroid dose reduced by at least 25% from baseline; and/or

iv. a reduction in the number of hospitalisations or severe exacerbations requiring use of systemic corticosteroids, compared to the 12 months prior to commencement of omalizumab.

Where baseline assessments are not available, please call Medicare Australia on 1800 700 270 to discuss.

*For PBAC's view, see Recommendation and Reasons*

## 5. Clinical Place for the Proposed Therapy

Please refer to the November 2009 PSD.

## 6. Comparator

The submission nominated placebo in addition to Optimal Asthma Therapy (OAT) as the main comparator. This was accepted by the PBAC, as previously.

## 7. Clinical Trials

The same trials presented in the November 2009 submission were presented in the re-submission, which included one direct randomised double blind trial with post-hoc adjustment for baseline differences in asthma exacerbations (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 plus OAT with OAT alone. However, data from the double blind Trial 2306 were presented as the key trial data and results from open label Trial 2425 presented as supporting evidence. The PBAC noted that the re-submission included new analyses stratified by oral corticosteroid (OCS) use at baseline. Additional post hoc analyses for patients eligible under the revised restriction (ACQ ≥ 2.0 and OCS ≥ 10 mg/day) were conducted for both Trial 2306 and Trial 2425.

Publication details of Trials 2306 and IA04 have been reported previously in the November 2009 PSD. Publication details for Trial 2425 as presented in the submission are shown in the table below.

| Trial ID / First author | Protocol title / Publication title | Publication citation |
|---|---|---|
| Trial 2425/ Magyar P et al | Persistency of treatment response to omalizumab in patients with severe allergic (IgE-mediated) asthma. | European Respiratory Journal, 2009; 34 (Suppl 53): Abs E1870. |
| Siergiejko Z et al | Omalizumab improves quality of life in adults and adolescents (>12 years) with uncontrolled severe allergic asthma. | Am J Respi Crit Care Med, 2010; 181: A6651 |
| Siergiejko Z et al | Omalizumab reduces health care resource utilization in adults and adolescents (>12 years) with uncontrolled severe allergic asthma. | Am J Respi Crit Care Med, 2010; 181: A5404. |

Since the PBAC's November 2010 consideration, Trial 2425 has been published online as follows:

| Trial ID / First author | Protocol title / Publication title | Publication citation |
|---|---|---|
| Trial 2425/ Bousquet et al | Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. | Allergy, 2011; DOI 10.1111/j.1398-9995.2010.02522.x |

## 8. Results of Trials

In Trial 2306, the rate of clinically significant asthma exacerbations over 28 weeks was lower for patients treated with omalizumab plus OAT compared with OAT alone, for OCS users and non-users, however the differences were not statistically significant.

There were statistically significantly lower rates of severe asthma exacerbations over 28 weeks (Trial 2306) and clinically significant asthma exacerbations over 32 weeks (Trial 2425) for omalizumab treated patients compared to patients treated with OAT alone for both OCS users and non-users.

The rates of hospital admissions, emergency department visits, unscheduled doctors' visits and total emergency visits due to asthma exacerbations in Trials 2306 and 2425 were lower in patients treated with omalizumab regardless of OCS use. However, there were no statistically significant differences between patients taking omalizumab plus OAT compared to OAT alone in Trial 2306 OCS-based subgroups, whereas these differences were statistically significant in OCS non-users in Trial 2425 and for total emergency visits in OCS users.

The change from baseline to endpoint in Asthma Quality of Life Questionnaire (AQLQ) was generally greater in omalizumab treated patients compared to patients treated with OAT. The difference was statistically significant in OCS non-users in Trial 2306, and in both OCS users and non-users in Trial 2425.

The Asthma Control Questionnaire (ACQ) was used in Trial 2425 and there was a statistically significant reduction in symptom score (on the 5 and 7 item version) in patients treated with omalizumab plus OAT compared to OAT alone, in OCS users and non-users.

*For PBAC's view of these results, see Recommendation and Reasons.*

The re-submission presented additional toxicity data from the most recent Periodic Safety Update Report (PSUR) and updated post-marketing study Q2948g (EXCELS study). The overall rates of cardiovascular and cerebrovascular serious adverse events were higher in the omalizumab cohort compared with the non-omalizumab cohort. Interpretation of these results may be limited by baseline confounders, very small numbers of events for some groupings and a lack of detailed information about the events. A U.S. Food and Drug Administration (FDA) black box warning issued on 2 February 2007 warned of post marketing reports of anaphylactic reactions in omalizumab treated patients.

## 9. Clinical Claim

The submission described omalizumab as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo. However, the PBAC considered that omalizumab was inferior to placebo in terms of safety.

## 10. Economic Analysis

The submission presented an updated stepped economic evaluation, based on data from both the double-blind Trial 2306 and the open label Trial 2425 and implemented an updated modelled economic evaluation. The types of economic evaluation presented were cost-effectiveness (trial-based costs per exacerbation avoided and per additional patient free of exacerbation) and cost-utility analyses.

The incremental costs per quality adjusted life-year (QALY) gained of omalizumab versus placebo in Trial 2306 and in Trial 2425 were in the range of $45,000 - $75,000.

The PBAC noted that the results of sensitivity analyses indicated that the model was most sensitive to the risk of death due to exacerbations, the relative risk of death associated with OCS use, model duration, the price of omalizumab and the use of EQ-5D utilities.

*For PBAC's view, see Recommendation and Reasons.*

## 11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the re-submission to be less than 1,000 per year, while the financial cost per year to the PBS was estimated to be less than $10 million in any of the first 5 years.

## 12. Recommendation and Reasons

The PBAC noted that a revised restriction had been requested, which was maintained to be consistent with the recommendations from the stakeholder meeting on the appropriate target population. The PBAC recommended that if listing is recommended, the restriction should stipulate that a patient's asthma should be uncontrolled with a dose of at least 10 mg prednisolone equivalent; should mandate the use of Asthma Control Questionnaire (ACQ: 7 item version) as the two extra domains in this version are less subjective than the five domains in the ACQ: 5 item version, and should mandate a total serum immunoglobulin E (IgE) ≥ 76 as the TGA-approved Product Information notes that patients with a lower IgE were less likely to experience a clinically meaningful benefit..

As previously, the PBAC accepted placebo in addition to Optimal Asthma Therapy (OAT) as the appropriate comparator. In addition, it was noted that post hoc analyses for patients eligible under the revised restriction (ACQ ≥ 2.0 and OCS ≥ 10 mg/day) were conducted for both Trial 2306 and Trial 2425.

No new clinical data were presented, although the re-submission focussed appropriately on the double-blind randomised Trial 2306 with the data from the open label randomised Trial 2425 as supportive evidence. The PBAC noted that the submission presented new analyses stratified by OCS use.

In the double blind Trial 2306, there were no statistically significant differences in the rates of clinically significant asthma exacerbations in omalizumab treated patients compared to patients treated with OAT alone for either OCS users or non-users (unadjusted and adjusted for differences in baseline exacerbation rates).

The rates of severe asthma exacerbations were statistically significantly lower in the double blind Trial 2306 patients treated with omalizumab compared to patients treated with OAT alone for both OCS users and non-users.

In the open label Trial 2425, there were statistically significantly lower rates of clinically significant exacerbations for omalizumab treated patients compared to patients treated with OAT alone for both OCS users and non-users (with and without data imputation).

The PBAC noted that there were no statistically significant differences in emergency visits for omalizumab treated patients compared to patients treated with OAT alone when the data

were analysed for OCS user and non-user subgroups in the double blind Trial 2306. However, there were statistically significantly lower frequencies of total emergency visits in omalizumab treated patients compared to patients treated with OAT alone for OCS users and non-users in the open label Trial 2425.

Changes in Asthma Quality of Life Questionnaire (AQLQ) scores were only statistically significant for omalizumab treated patients compared to patients treated with OAT alone for OCS non-users in double blind Trial 2306. The PBAC noted the proportion of patients achieving improvement of ≥ 0.5 from baseline in the control arm of the trial (patients treated with OAT only) was much lower in the unblinded Trial 2425 than the blinded Trial 2306.

The PBAC concluded that these results and other results for differences in outcomes such as percentage predicted $FEV_1$ and Investigator Global Evaluation of Treatment Effectiveness did not suggest a consistent pattern of greater response to omalizumab treatment in patients taking maintenance OCS at baseline. However, the PBAC considered it would be reasonable to conclude that omalizumab was more effective than OAT in some patients and that continuation criteria would assist to minimise continued use of the drug in patients who were not responding to omalizumab.

The PBAC noted that a potentially higher incidence of cardiovascular and cerebrovascular events in patients using omalizumab was raised with the TGA and FDA by the sponsor. Thus it could not be concluded that omalizumab was as safe as placebo when added to OAT. Further, the submission did not include the cost of treating the adverse events associated with omalizumab in the financial implications, including anaphylaxis, Epicutaneous Patch Testing and the requirement for adrenaline auto-injector devices. However, it was noted that the Sponsor proposed a rebate directly to hospitals and pharmacies that dispense an adrenaline auto-injector device to any patient on omalizumab.

The PBAC agreed with the Economics Sub-Committee concerning the following issues in relation to the economic modelling:

- Time horizon: The model was sensitive to the duration of the model. The extrapolation to 50 years may not be reasonable, and was highly uncertain.
- Resource use: Outpatient visits were not costed according to the Manual of Resource Items and their Associated Costs. Further, not all costs for testing were included. The assumption that 49% of all omalizumab injections would be administered by a nurse and not a medical practitioner was also uncertain.
- Assumptions in relation to the re-initiation of omalizumab following treatment failure where it was assumed to have the same probability of response as the initial attempt. There were no data presented in the submission to support this assumption.
- Reliance on the sub-group analysis, which were generally based on small numbers and small numbers of events, to populate the probabilities of exacerbations, hospitalisations and other parameters in the model.
- In particular, use of mapped rather than directly measured EQ-5D utility values when the latter were available (for Trial 2425 only). The mapped results favour omalizumab, and also tend to be larger than many in the literature.

The results of sensitivity analyses indicated that the model was most sensitive to the risk of death due to exacerbations, the relative risk of death associated with OCS use, model duration, the price of omalizumab and the use of EQ-5D utilities.

The PBAC considered that in the context of the uncertainties raised above, the base incremental cost per QALY in the range of $45,000 - $75,000 was too high (and was likely to be higher) for the Committee to recommend listing. The PBAC noted a sensitivity analysis which used the EQ-5D utility values direct from Trial 2425, which produced a higher incremental cost-effectiveness ratio (ICER) in the range of $45,000 - $75,000. The PBAC, however, acknowledged the high clinical need for patients who were not responding to OAT and considered, given the uncertainty, that if the sponsor was prepared to offer a price reduction to give an ICER of less than $45,000, it would be prepared to recommend listing.

The PBAC therefore deferred its decision on the listing of omalizumab to seek a further price reduction from the sponsor. Should such an offer be forthcoming, the PBAC would be prepared to consider the matter out-of-session.

**Further out-of-session PBAC consideration:**
Subsequent to the November 2010 meeting, the PBAC received an offer of a price reduction sufficient for the PBAC to recommend the listing of omalizumab. The PBAC recommended out of session the listing of omalizumab on the basis of an acceptable cost effectiveness ratio in a severe patient group with limited treatment options, whose asthma was uncontrolled while on at least 10 mg per day prednisolone equivalent.

The resulting base case ICER was reduced to in the range of $40,000 - $45,000 per QALY. This was considered acceptable in the context of the clinical and economic uncertainties raised by the PBAC in both the previous and current submissions. The sponsor accepted the PBAC proposal to use the Asthma Control Questionnaire (ACQ: 7 item version) in the restriction to determine eligibility for treatment and to assess eligibility for continuing treatment with omalizumab. The sponsor also accepted the PBAC proposal to limit PBS-subsidised access to patients with total serum immunoglobulin E (IgE) ≥ 76 (the submission proposed IgE > 30 IU/mL).

***Recommendation***:
OMALIZUMAB (rch), powder for injection, 150 mg

Restriction: Section 100 (Highly Specialised Drugs Program)
Public and Private Hospital Authority Required
Restriction to be finalised

## 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 welcomes the PBAC decision to recommend listing of omalizumab on the PBS for patients with a high medical need. We would like to thank the PBAC and Secretariat for convening the Stakeholder meeting in April 2010, at which the patient eligibility and response criteria for treatment with omalizumab were defined.