

Omalizumab

Recommendations for use in the Australasian context

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Abbreviations and symbols used in this document

AE	adverse event
AQLQ	asthma quality of life questionnaire
FcεR1	Fc epsilon receptor one
FE _{NO}	forced exhaled nitric oxide
FEV ₁	forced expiratory volume in 1 second
IgE	immunoglobulin E
IL	interleukin
ICAM	intracellular adhesion molecule
ICS	inhaled corticosteroid
INCS	intranasal corticosteroid
NNT	number needed to treat
OCS	oral corticosteroid
PC ₁₅	provocative dose causing a 15% fall in FEV ₁
PC ₂₀	provocative dose causing a 20 % fall in FEV ₁
PEF	peak expiratory flow
QOL	quality of life
RCT	randomized controlled trial

Introduction

This position paper was commissioned by the Executive of The Thoracic Society of Australia and New Zealand (TSANZ) in order to meet a perceived need for its members for guiding information regarding the use of this potentially effective, yet expensive novel medication in managing patients with difficult to control asthma.

A working party was established comprising members of the Society who have experience with omalizumab either in clinical use or research. Some members are also members of the Australasian Society of Clinical Immunology & Allergy (ASCIA), and paediatric representation was ensured.

The review was produced after careful consideration of all available published data at the time of preparation, along with consideration of the clinical use of the drug by members of the working group.

The costs of production of this paper were born by TSANZ.

Conflicts of Interest Statement

C Katelaris and P van Asperen have no conflicts of interest in relation to this paper.

P Gibson has participated in scientific symposia organised and funded by Novartis in 2007 and 2008, and his institution has participated in an investigator initiated clinical trial of omalizumab.

B Heddle has an offer, post-dating any involvement in the manuscript, to extend the use of omalizumab to facilitate a small clinical proof of concept trial. The Novartis offer has been limited to supply of omalizumab.

J Rimmer via the Woolcock Institute was involved in a Novartis trial in 2007/8 developing a model of allergen challenge in allergic rhinitis.

J Douglass in the past 5 years has been sponsored to attend international meetings by GSK, Astra-Zeneca and Altana Pharma. Over the past 2 years has accepted speakers' fees for national meetings from GSK, Altana Pharma, Astra-Zeneca and Pfizer and has undertaken contracted research as an investigator for Novartis, GSK, Astra-Zeneca and Pulmosonix.

D Ruffin has received funding from GSK for peak flow meters for an unrelated asthma study, an honorarium for participation in GP education and was on a panel advising GSK regarding a survey.

Several authors (BH, JR, CK, JD) have cared for patients who have had omalizumab provided free by Novartis for their treatment.

Part I. Executive summary and recommendations

- Omalizumab is a humanised IgG₁ antibody constructed from the constant region of IgG₁ κ human framework with a variable sequence of mouse antibody – it is >95% human IgG and <5% mouse antibody.
- Omalizumab was first approved for use in Australia in 2002, in New Zealand in 2007, and is now registered for use in 55 different countries. In all countries the current indication for omalizumab is “*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 IgE levels corresponding to the recommended dose range*” (>30 to 700 IU/ml).
- Following the first dose of omalizumab, free serum IgE drops substantially with reductions of >95% and then remains constant.
- The dosing strategy for omalizumab is for an injection to be given every two to four weeks. Body weight is the only significant factor affecting pharmacokinetic behaviour; hence its inclusion in calculation of drug dosage.
- Early clinical findings showed that efficacy was most pronounced when free IgE was reduced to below 16.7 IU/ml (40 ng/ml).
- Treatment with omalizumab attenuates early and late phase responses to inhaled allergen challenge.
- **Clinical studies** in patients with asthma have provided convincing evidence that omalizumab is effective in patients with severe asthma and that it may be particularly useful in patients whose asthma is inadequately controlled despite GINA step 4 therapy, usually termed ‘difficult-to-treat asthma’.
- **Study outcomes** in asthma trials with omalizumab show:
 - Reduced rates of asthma exacerbations (usually primary outcome measure in trials)
 - Reduction in dose of ICS
 - Improvement in daily symptom scores
 - Reduction in short-acting bronchodilator use
 - Improvement in quality of life
 - Improved FEV₁ (usually modest)
- The **safety profile** of omalizumab, as available from early controlled studies and post-marketing

experience, appears favourable. However, the occurrence of anaphylactic reactions and concerns regarding the possibility of increased rates of malignancy should lead to cautionary measures in obtaining consent and managing subjects.

- A recent review of the available trial and post marketing data suggests a rate of **anaphylaxis** of 0.2%. Worrying features are that in 26% of cases the onset of the reaction was more than two hours post injection and that around 8% of reactions have been protracted.
- In **paediatric** patients data on the use of omalizumab are limited with only one RCT in children between six and 12 years of age and none in the pre-school age group. This RCT does provide evidence that omalizumab can reduce inhaled corticosteroid dosage as well as exacerbation rates and also improve quality of life without major side effects, although the recent report of anaphylaxis did include paediatric cases.
- There is a **need to identify individual responders** to this drug, rather than recommend widespread use in difficult asthma. It is possible to identify individual responders to omalizumab using **single patient controlled trials** conducted in the setting of a specialised clinic.
- **Strict criteria for selection** must be applied, the most important of which are to confirm the diagnosis of asthma, to exclude masquerading conditions and to ensure that optimal conventional therapy has been tried.
- **Careful clinical assessment of response** is required using validated tools such as the Juniper Asthma Control Questionnaire[®].
- Omalizumab may be **continued** in those whose asthma has improved on treatment and deteriorated off treatment and will be ongoing unless new information becomes available to alter this view.
- This is an **expensive** medication. The actual costs are relative to the dose required, but range from about AU\$ 7,800 to 50,000 (NZ\$ 14,500 to 94,000) per annum.

Part II. Omalizumab – Basic Science Overview

1. Structure

Omalizumab is a humanised IgG₁ antibody constructed from the constant region of IgG₁κ human framework with a variable sequence of mouse antibody – it is >95% human IgG and <5% mouse antibody.

2. Binding

Omalizumab binds to an area of the C3 domain of human IgE, very close to the binding sites for high- and low-affinity receptor binding. Thus omalizumab binds free IgE in serum or interstitium but cannot bind IgE bound to cell membrane as the binding site is already occupied. For this reason, it is non anaphylactogenic. Binding of free IgE of any specificity results in complex formation- either trimeric or hexameric. These are small and non complement- binding and are removed by the reticuloendothelial system. ¹

3. Effect on IgE

Following the first dose of omalizumab, free serum IgE drops substantially with reductions of >95% and then remains constant. At this time there is no readily available means to measure free IgE. As IgG-IgE complexes are removed more slowly from the circulation than free IgE, the appearance of the complexes adds more IgE to the circulation explaining why serum total IgE rises after administration of omalizumab. ²

4. Effect on high affinity IgE receptor

Reduction of FcεR1 from the surface of basophils, mast cells and dendritic cells is an interesting consequence of omalizumab treatment demonstrated in a number of studies. ³ it appears that elimination of serum IgE causes down regulation of the IgE receptors. This FcεR1 reduction from the surface of effector cells contributes to the sustained clinical effect of omalizumab treatment.

However there may be other explanations as to why omalizumab works, with newer data suggesting an effect on the B cell. ⁴

5. Dosing rationale – pharmacokinetics

The dosing strategy for omalizumab is for an injection to be given every two to four weeks. This takes into account the long terminal half life of omalizumab (19 - 22 days) due to the fact that the

IgG framework causes slow removal of the complexes through the reticuloendothelial system. Body weight is the only significant factor affecting pharmacokinetic behaviour; hence its inclusion in calculation of drug dosage.

6. Factors determining efficacy

Early clinical findings showed that efficacy was most pronounced when free IgE was reduced to below 16.7 IU/ml (40 ng/ml). Decline in free IgE is dependent on both the dose of omalizumab and the individual's baseline IgE. Calculations suggest that omalizumab needs to be given at a molar excess of 15-20:1 relative to baseline total IgE⁵ to achieve the minimum dose needed to suppress free IgE to this necessary level.

7. Time course for beneficial effect

The reduction in free serum IgE is only a marker of its true activity because free IgE does not bind allergen with usual physiological consequences. As a consequence of binding free IgE, there are fewer IgE molecules available for binding to the high affinity receptor and in turn there is down regulation of receptor expression. Omalizumab does not cause forcible dissociation of IgE from the high affinity receptor, rather it binds IgE once it becomes dissociated spontaneously. This dissociation occurs slowly over two to three weeks so disarming mast cells already bound with IgE also occurs slowly. Unlike basophils, mast cell survival in the tissues lasts for months so removal of cells already binding IgE is dependent entirely on the spontaneous rate of dissociation of IgE from its receptor and subsequent binding of that molecule by omalizumab; therefore, benefits from omalizumab therapy in mast cell dependent disorders such as allergic rhinitis and asthma take many weeks to occur.² Evidence for the removal of IgE from the surface of human airway mucosal mast cells was obtained from a study by Djukanovic *et al.*⁶ Immunohistological examination of bronchial biopsy samples revealed reduction in IgE+ cells of 90%.

8. Mechanism of action in asthma

Treatment with omalizumab attenuates early and late phase responses to inhaled allergen challenge.

From numerous studies⁷ we can see a differential response in the various organs:

- reduction in both the early phase response and late phase reaction can be seen in the nose, skin and bronchi;
- early phase response in the nose & bronchi appears to be suppressed earlier than the skin;

- the late phase response in the bronchi and the skin is suppressed earlier and more dramatically than the early phase response;
- chronic inflammation is reduced in patients with allergic asthma – suppression of the effects of natural allergen exposure.

Fahy *et al*⁸ studied 19 subjects with mild non-steroid-treated allergic asthma and performed bronchial challenge tests before and after treatment with omalizumab. They found that there was a decrease in the FEV₁ fall post challenge in the omalizumab treated group with an increase in the allergen concentration required to produce bronchoconstriction.

The late phase response to allergen was significantly reduced following omalizumab treatment with significant reduction in the fall in FEV₁ post allergen challenge. Induced sputum examination revealed non-significant reduction in ECP levels and eosinophil numbers. There was a non-significant improvement in PC₂₀ with methacholine.

Djukanovic⁶ showed the following anti inflammatory effects of omalizumab in a study examining markers of inflammation assessed by induced sputum and bronchial biopsy:

- Significant decrease in sputum eosinophilia
- Significant decrease in epithelial and submucosal eosinophils on biopsy
- Significant decrease in submucosal IgE+ cells, FcεR1+ cells, IL4+ cells

9. Observations from clinical studies in asthma

Study outcomes in asthma trials with omalizumab show:

- Reduced rates of asthma exacerbations (usually primary outcome measure in trials)
- Reduction in dose of ICS
- Improvement in daily symptom scores
- Reduction in short-acting bronchodilator use
- Improvement in quality of life
- Improved FEV₁ (usually modest). This may be a consequence of the fact that all patients enrolled in omalizumab studies were already on large doses of ICS so the component of airway responsiveness available for anti-inflammatory treatment manipulation is small. It may be that the remaining obstruction is due to fixed changes in the airway and not amenable to alteration.

- No significant change in airway hyperresponsiveness. In Djukanovic's study, significant changes in airway eosinophilia were seen; yet there was no significant effect on airway hyperresponsiveness to methacholine. This implies that the two observations are not related. Other studies have provided similar outcomes with regards to non-effect on airway hyperresponsiveness. Longer treatment periods may alter this finding.

Part III. Omalizumab in Asthma

1. Pivotal studies in asthma

Omalizumab was first approved for use in Australia in 2002, in New Zealand in 2007, and is now registered for use in 55 different countries. In all countries the current indication for omalizumab is *“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 IgE levels corresponding to the recommended dose range” (>30 to 700 IU/mL).*

Pivotal studies can be grouped as follows:

- a. Proof of concept
 - b. Mechanistic trials
 - c. Clinical usage
- a. **Proof of concept** trials were conducted in the late 1990s and examined the effect of intravenous omalizumab on the early and late responses to inhaled allergen in atopic subjects with mild asthma^{8,9}. In Boulet *et al*⁹ 10 subjects were treated with fortnightly injections of 2mg/kg. Mean serum-free IgE fell by 89%, and there was a significant increase in allergen PC15 measured between three to seven weeks after treatment. In the Fahy study nine weekly injections of 0.5mg/kg were administered, with attenuation of early and late phase responses and a reduction in the magnitude of the fall in FEV₁ as well as an increase in the PC₂₀. There was no difference in skin test reactivity to allergen. Serum free IgE levels were reduced and this effect was maximal after six weeks treatment. This study measured blood and sputum eosinophil numbers and found non significant reduction in numbers compared to placebo. No effect on baseline lung function was seen. Subsequently aerosolised omalizumab was trialled and found to be ineffective. Subcutaneous administration has now been adopted.
 - b. **Mechanistic studies:** Mechanistic data are limited to three clinical trials^{6,8,10}. (See Part 11.8)
 - c. **Clinical Usage:** Milgrom *et al*¹¹ 1999, used high and low dose intravenous omalizumab for 12

weeks in 212 atopic subjects with moderate asthma (FEV₁ 71% predicted), all on inhaled and/or oral steroids. There were significant improvements in asthma scores, quality of life scores, exacerbation rates, ability to reduce steroid therapy but no clear improvement in lung function or beta 2 agonist usage. These results were confirmed by another large placebo controlled study, this time using subcutaneous omalizumab in a dose calculated by weight and serum IgE level.¹² In this study 274 subjects with moderate to severe asthma were treated for seven months, fewer exacerbations were noted in both the steroid stable (58%) and steroid reduction (52%) phases of the trial. Secondary outcome measures showed significant improvements in the asthma symptom score, rescue medication use, morning PFR and FEV₁.

Subsequent trials are well summarised in the Cochrane database which chronicles the use of omalizumab in mild to severe allergic asthmatics up to 2006 (14 trials).¹³ A total of approximately 1740 subjects (including paediatric subjects) were treated with the active drug. All subjects were atopic. The trials lasted up to 32 weeks. Asthma severity was defined by the BTS Guide to Asthma Management (2005) and ranged from mild,^{6,8,9,14,15,16,17} to moderate/severe^{11,12,18,19,20} and severe.^{21,22}

The summary of overall outcomes was:

- Reduction in serum IgE by 89 - 99% from the baseline value
- Reduction from baseline ICS use (-119mcg/day BDP equivalent) compared with placebo injections
- Increased numbers able to reduce ICS by over 50% or able to stop ICS
- Less likely to suffer an asthma exacerbation with either a steroid stable or steroid tapering trial
- There were no consistent effects on lung function.

The data were separately analysed in the subgroups of omalizumab versus placebo as add on therapy to stable dose inhaled or oral steroids or during steroid tapering with reduced exacerbations in both phases. In terms of NNT 10 asthmatics are treated to avoid one exacerbation. The INNOVATE study specifically looked at the population of asthmatics using omalizumab as add on therapy in patients with severe persistent asthma, inadequately controlled despite GINA 2002 step 4 treatment.²² There were reductions in clinically significant, severe exacerbations and emergency visits for asthma. The NNT to prevent one exacerbation was 2.2. Bousquet *et al*²³ have analysed data from several trials to examine predictors of response of omalizumab as add on therapy in severe asthma. They found that the response rate was 65% at 16 weeks and a minimum trial of 12

weeks was recommended. Responders in this trial were defined by a composite measure of one of four criteria with no asthma exacerbation over 16 weeks therapy; these criteria are:

- Reduced symptoms ≥ 1 mean total asthma score with no increase in beta 2 agonist use
- Reduction ≥ 1 mean number of puffs rescue medication/day with no increase in total symptom score
- Mean increase am PEF $\geq 15\%$
- Increase overall score ≥ 1 Juniper Asthma QOL questionnaire.

The predictors of response included a history of ED treatment in the last 12 months, high dose of inhaled BDP and low FEV₁.

2. Safety data – early trials and post marketing experience

a. Introduction

Although the “new biological agents” offer the prospect of greater selectivity than conventional small chemical compounds, they also bring special challenges. Monoclonal antibody therapeutics, such as omalizumab, are proteins allowing the prospect for allergenicity, lessened but not abrogated to the extent that the agent is humanised. Their selective but profound biological effects may achieve not only the desired actions but have the potential to produce unanticipated effects. As new medications that interfere with the immune system, which by definition meets qualitatively and quantitatively different challenges over a lifetime, some drug side effects may be delayed in their development, onset, and/or recognition. This emphasises the need for phase IV surveillance of all new therapeutics.

b. Overview

The safety profile of omalizumab, as available from early controlled studies and post-marketing experience, appears favourable. However, the occurrence of a varied profile of anaphylactic reactions and concerns regarding the possibility of increased rates of malignancy should lead to cautionary measures in obtaining consent and managing subjects. Adverse events (AE) will be considered under the following headings:

- i. AE reported at rates significantly above those seen with placebo
- ii. Serious AE or potential AE
- iii. Miscellaneous reported AE where causal relationship is doubtful

- iv. Risks based upon rationale rather than reported events
- v. Predictable laboratory abnormality

i. AE reported at rates significantly above those seen with placebo.

- a. *Local reaction*; the Product Information (PI; E MIMS 2007) lists local reactions as occurring at rate of 1.7% of patients treated with omalizumab versus 1.3% with placebo. The rates in specific studies vary enormously, possibly reflecting differing criteria and observers^{12,18,22,24} but the reactions appear to have been tolerable, self-limiting and not a cause for treatment withdrawal.
- b. *Weight increase*; the PI cites this as an uncommon side effect occurring in 0.7% of treated subjects vs. 0.2% on placebo, but it appears not to have been a cause for treatment withdrawal.
- c. *Urticaria*; the PI gives rates of 0.4% for omalizumab vs. 0.1% for placebo. Although an uncommon effect, the urticaria was severe and led to treatment withdrawal in at least one subject²⁵ and on retrospective analysis of the Genetech Xolair clinical trials and post-marketing surveillance data by the Omalizumab Joint Task Force of AAAAI and ACA, some of the cases experienced anaphylaxis rather than simple urticaria.²⁶

ii. Serious AE or potential AE

- a. *Anaphylaxis*; omalizumab cannot cross link IgE molecules on the surface of mast cells and basophils, <5% of the molecule is murine and its Fc component does not activate complement^{26,27} but anaphylaxis following injection of omalizumab has proven an issue of concern. Estimates based on early experience were that 0.1% of subjects experience anaphylaxis. A more recent review of the available trial and post marketing data suggests a rate of 0.2%.²⁸ Worrying features are that in 26% of cases the onset of the reaction was more than two hours post injection, that around 8% of reactions have been protracted,²⁸ that risk factors for anaphylaxis and the delayed onset have not been defined²⁸ and that the responsible ingredient (murine component, allotypic or idiotypic determinants, glycosylated hamster component, polysorbate, aggregates/complexes) and mechanism (IgE, IgG, complexes) have not been determined.²⁶

Practical implications include; need for fully informed consent and education on risk and nature of anaphylaxis; assessment of clinical status including FEV₁ before each injection; administration only in circumstances able to detect and deal with anaphylaxis; holding for two hours post-injection (European recommendation. Cox, Platts-Mills *et al*²⁶ suggest one half

hour for fourth and subsequent injections but the data is numerically slight) and having subject always carry an automated adrenaline syringe which they know how to use.

- b. *Malignancy*; early data suggested an incidence of 0.5% compared to 0.2% in control patients²⁹ but a very large general population database showed cancer rates intermediate between those in the control and omalizumab groups. The chronology might be regarded as unusual for oncogenesis and the distribution of tumours, predominantly solid tissue tumours, not that seen with many drugs that predispose to malignancy (see also “Briefing document on safety, BLA STN 103976/0. US Food and Drug Administration. April 18, 2003”. Available at: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3952B1_02_FDA-Xolair-Safety.pdf. Accessed July 25, 2008). Nevertheless, there are concerns that IgE may be inhibitory of oncogenesis²⁷ and in practice it appears prudent to acknowledge these as unsubstantiated concerns in seeking consent, especially when long term therapy in younger subjects is planned.
- c. *Thrombocytopenia* was a feature in animal studies at doses far higher than used in humans. Whilst this concern is reflected in the CPI, thrombocytopenia in clinical use has been uncommon, mild, reversible and without sequelae²⁷ with the exception of one case of petechial rash.²² Omalizumab is not recommended in subjects with a history of thrombocytopenia or bleeding disorder. Monitoring of platelet counts pre-treatment and “periodically” during therapy are recommended (PI). In practice, patient education about early signs may be equally valuable.

iii. Miscellaneous reported AE where causal relationship is doubtful

These include headaches (circa 1% of subjects) and many other reactions which are classified as uncommon (<1% of subjects) - dizziness, fatigue, nausea, pharyngitis, URTI, viral infection, skin rashes other than urticaria and arm swelling. These AE appear no more common than in the placebo group.^{11,12,18,24,30}

iv. Risks based upon rationale rather than reported events

- 150 mg of omalizumab is presented with 108 mg of sucrose which may have implications for those with metabolic abnormalities in sugar handling, including theoretically, diabetes mellitus.
- Populations in which there is inadequate safety data; this includes children <12 years of age, pregnant and breast feeding women.
- Conditions that may demonstrate clinical features of asthma where safety and efficacy is unknown including allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome and

hyper IgE syndrome.

- Parasitic infestation see:
 - i. Cruz AA, Lima F, Sarinho E, et al. Safety of anti-immunoglobulin E therapy with omalizumab in allergic patients at risk of geohelminth infection. *Clin Exp Allergy* 2007;197-207.
 - ii. Cooper PJ, Ayre G, Martin C et al. Geohelminth infections: a review of the role of IgE and assessment of potential risks of anti-IgE treatment. *Allergy* 2008;63:409-417.
- Generation of antibodies to omalizumab, limiting efficacy or resulting in immune complex disorders; such a response appears to be rare and immune complex disorders have not been observed in the many trials that have looked for them ^{11,12,18,24,25,30,31} (see also US Food and Drug Administration. Briefing document on safety, 2003).
- Possible interactions with concurrent treatments other than usual treatments for asthma.
- Over-rapid corticosteroid withdrawal. Cessation or interruptions to therapy in a patient after OCS have been withdrawn also leads to loss of asthma exacerbation protection and the potential for a significant asthma exacerbation to occur.

v. Predictable laboratory abnormality

Despite rapid reduction in free IgE after omalizumab treatment, usual measures of IgE are falsely elevated for up to 12 months after treatment with omalizumab. ^{11,18}

Summary

Consistent with the expected selectivity of the agent, the safety profile of omalizumab appears favourable compared to traditional, less selective therapies, with the exception of anaphylactic reactions which merit a number of precautions, as above. Vigilance over decades will be needed before currently unsubstantiated concerns about long term effects such as the effect of omalizumab treatment on the incidence of malignancy can be dismissed.

3. Post marketing adult experience and use

This section is confined to post-marketing data in the following areas:

- a. Use of omalizumab
- b. Adverse Events with omalizumab in Adults

Omalizumab has been investigated in several studies using pooled data and by meta-analysis to provide evidence of benefit and exploit data from studies performed following initial marketing. The major weakness in the data presented is that only one trial (INNOVATE)²² uses omalizumab consistent with its indications for licensed use in Australasia i.e. severe asthma.

a. Use of Omalizumab

Three papers use pooled data from the same studies to examine:

- (i). Predicting and evaluating responses to omalizumab^{32,33}
- (ii). Effect of omalizumab on the need for systemic corticosteroid treatment³⁴
- (iii). Effect of omalizumab on quality of life³⁵.

(i). Predicting and evaluating responses to omalizumab.

In adults, the use of omalizumab has been investigated in studies of efficacy in an attempt to identify those patients most likely to benefit. This study by Bousquet and colleagues³² presents pooled data from seven studies; five blinded placebo-controlled plus inhaled corticosteroid, and two open label against current asthma treatment. Six of the studies were published independently, but the largest study was the “ALTO” study, containing 1,760 patients and has not been independently published. The total patient number was 4308. The studies attempted to identify a group of patients in whom the efficacy of omalizumab was most clearly established by observing exacerbation rates in subgroups of the pooled dataset. Most of the patients were in the severe persistent category of asthma severity by GINA guidelines. In the study overall, the annualized rates of emergency visits was 0.332 for the omalizumab group and 0.623 for control groups representing a 47% reduction in exacerbations. Correspondingly, hospital admissions were reduced by 52%, Emergency Room visits by 61% and unscheduled doctor visits by 47%. The following variables were examined to attempt to identify a subgroup who appeared to respond to a greater extent:

- Age less than 18
- Age 18 to 65
- Male
- Female
- FEV₁ less than 60% predicted
- FEV₁ between 60 and 80% predicted
- FEV₁ greater than 80% predicted

- IgE levels
- 2 or 4-weekly dosing schedule

The only group in which there was no significant response to omalizumab compared to control was the >65 year old group, but none of the studied variables could predict those who responded to omalizumab. Overall in subsequent meta-analysis 61% of patients were considered to respond to omalizumab therapy by physician assessment or by a clinically significant improvement in asthma quality of life score.

This study also used this pooled dataset to attempt to identify components of physician assessment which could be used to identify response. Pooled physician assessment appeared to be the most reliable tool, with no one item appearing more reliable than global assessment. Importantly, lung function improvement only identified approximately half of those who “responded” to omalizumab.

(ii). Effect of omalizumab on need for systemic corticosteroid treatment

Busse and co-workers³⁴ used the same dataset as in the Bousquet paper to determine the effect of omalizumab on the need for rescue treatment with corticosteroids. The rate of courses of systemic corticosteroids was reduced in omalizumab-treated patients relative to control with an OR of 0.57 (0.48 - 0.66). This reduction closely correlated with both physician and patient global assessments.

(iii). Effect of omalizumab on quality of life

In a pooled patient population from six published papers, 1342/ 2548 patients receiving omalizumab there was an improvement in the asthma quality of life as measured by the Juniper AQLQ.

Patients receiving omalizumab experienced an improvement of 1.01 in the AQLQ, a “moderate” improvement which was statistically significant ($p < 0.001$) compared to placebo. However, patients receiving placebo also improved 0.61 points.

b. Adverse Events

- i. The most common side effect of omalizumab reported is injection site redness and discomfort.
- ii. A major concern regarding the use of omalizumab is the description of anaphylaxis occurring with a prevalence of 0.09%²⁶. See Part III.2.b.ii.a
- iii. Malignancy. The NICE report on omalizumab has reported the findings on malignancies related to omalizumab.³⁶ The Committee noted that in 35 completed trials of omalizumab,

malignancies were reported in 25 of 5015 (0.50%) omalizumab-treated patients compared with five of 2854 (0.18%) standard therapy-treated patients. (see Part III.2.b.ii.b)

Despite substantial post-marketing data on the use of omalizumab, the initial concerns remain: that the indications for the drug were not clearly established in the pre-marketing studies. Post-marketing surveillance does not entirely address this issue and further trials similar to the “Innovate” trial are necessary to establish both efficacy in the severe asthma group, according to GINA guidelines, and cost-effectiveness.

4. Paediatric experience and use

There are limited data available on the use of omalizumab in the paediatric age group with the most recent Cochrane review of omalizumab for chronic asthma in adults and children in 2006¹³ identifying only one RCT performed in the paediatric age group.¹⁹ This 28 week RCT involved 334 children (omalizumab n=225; placebo n=109) between six and 12 years with moderate to severe allergic asthma requiring treatment with inhaled corticosteroids. All children were positive on skin prick testing to at least one of five common aero-allergens and had a total serum IgE level between 30-1300 IU/ml. During a four to six week run in phase all patients were switched to beclomethasone dipropionate (BDP) [42 µg/puff] which was administered twice a day (daily dose 168-420µg BDP). The BDP dose was kept stable for 16 weeks, then reduced over eight weeks to the minimum effective dose and then kept stable for the final four weeks. Patients randomised to omalizumab received doses of either 150mg or 300mg every four weeks or 225mg, 300mg or 375mg every two weeks, administered subcutaneously with a minimum dose of 0.016 mg/kg/IgE (IU/ml) per four weeks.

- More participants in the omalizumab group decreased their BDP dose (p=0.02), and their reduction was greater than that of the placebo group (median reduction 100% vs. 66.7%; p=0.001). BDP was withdrawn completely in 55% of the omalizumab group versus 39% of the placebo group (p=0.004).
- The incidence and frequency of asthma exacerbations requiring treatment with doubling of BDP dose or systemic corticosteroids were lower in the omalizumab group, but reached statistical significance only in the steroid-reduction phase (asthma exacerbations 18.2% vs. 38.5%; p<0.001 and mean number of episodes 0.42 vs. 2.72; p<0.001).
- There was little change in asthma symptom scores or spirometry measurements during either the stable-steroid or steroid dose-reduction phase with minimal differences between groups.

- There was also a statistically significant benefit on mean school days lost (0.65 vs. 1.21; $p=0.04$) and mean unscheduled asthma-related medical contacts (0.15 vs. 5.35; $p=0.001$).
- Median reduction in serum free IgE was 95-99% among omalizumab treated children.
- Improvement in asthma-related quality of life (using the Paediatric Asthma Quality of Life Questionnaire) was found to be significantly better at the end of the steroid-reduction phase in the omalizumab group compared to the placebo groups for overall quality of life and also the “activities” and “symptoms” domains.³⁷
- A significantly lower FE_{NO} (measured as area under the curve) in the omalizumab group (0.88 ± 0.69 vs 1.65 ± 1.06 ; $p=0.031$) was reported in a small subset of patients ($n=29$, 18 omalizumab, 11 placebo).³⁸ A reduction in FE_{NO} was also reported in the placebo group at the end of an additional open label phase of 24 weeks of omalizumab therapy, but this did not reach statistical significance.
- Omalizumab was well tolerated in the RCT¹⁹ and there were no serious treatment related adverse events.
- The frequency and types of all adverse events were similar in the omalizumab and placebo groups, although study drug-related adverse events occurred more frequently in the omalizumab group (6.2% vs. 0.9%; $p=0.029$).
- No adverse events suggestive of serum sickness or immune complex formation were observed.
- Urticaria was reported in nine (4%) omalizumab patients vs. one (0.9%) placebo patient. A subsequent report including the 24 week open extension phase of the study²⁵ confirmed these findings with a similar rate of urticaria (4.9%) and no reports of anaphylaxis. However, the recent report documenting anaphylaxis after omalizumab administration did include cases in the paediatric age group.²⁸

In summary, data on the use of omalizumab in paediatric patients are limited with only one RCT in children between six and 12 years of age and none in the pre-school age group. This RCT does provide evidence that omalizumab can reduce inhaled corticosteroid dosage as well as exacerbation rates and also improve quality of life without major side effects, although the recent report of anaphylaxis did include paediatric cases.

Part IV. Pharmacoeconomics of omalizumab

Cost effectiveness estimations for the use of drugs in Australasia require assumptions that:

- (i). clinical trial data can be transferred to real life,
- (ii). the frequency and severity of events are correct for the patient population under consideration, and
- (iii). the models used provide reliable estimates for the Australian and New Zealand settings.

If omalizumab is considered for use in Australasia in the more severe persistent asthma group, several estimates of cost effectiveness are available from overseas data.

Oba and Salzman³⁹ examined data from clinical trials of omalizumab vs. placebo in moderate to severe asthma. They arrived at figures of US\$378 / day to achieve a 0.5 increase in Asthma Quality of Life Questionnaire Point score. They were unable to derive a cost / Quality Adjusted Life Year (QALY) gained. Asche *et al*⁴⁰ raised issues about underestimation of costs. The inference of these papers was that omalizumab was not considered to be cost effective. DeWilde *et al*⁴¹ modelled the results of the INNOVATE 28 week study of standard therapy versus standard therapy plus omalizumab in patients with severe asthma in a Swedish context and arrived at an estimate of €56,091 per additional QALY. The authors discussed issues around incorporating mortality in their model as a comparison of the biological therapies for rheumatoid arthritis in Sweden (€43,500 to €44,500 / QALY) to suggest omalizumab may be cost effective within the assumptions of that model.

Brown *et al*⁴² used data from an open label Canadian study of omalizumab to estimate the cost effectiveness of omalizumab in severe persistent asthma. They estimated €31,209 / QALY for omalizumab used for five years in addition to standard therapy. Campbell *et al*⁴³ criticised some of the assumptions in this study.

Wu *et al*⁴⁴ estimated the cost effectiveness of omalizumab by modelling data from the Cochrane Airway Group review. They arrived at a figure of US\$821,000 per QALY gained. This is in the context of the dialysis threshold in the US of \$93,500. An editorial by Krishnan and Gould⁴⁵ supported the methodology of Wu *et al*⁴⁴ and the conclusion of poor cost-effectiveness ratio for the community.

Walters *et al*⁴⁶ have put the discussion into an Australian context and highlighted the large placebo effect noted in the Cochrane review where the cost of omalizumab in Australia for 12 months treatment for an average 450 mg dose two weekly would be almost \$50,000.

The manufacturer has run a “Xolair Responder Programme”. The data from this programme suggests the range in dose is from 150 mg/month (1 vial) to 750 mg/month (6 vials), with the mean dose being 459 mg/month (requiring 4 vials).

The equivalent annual costs are \$7,800 for those requiring the lowest dose and \$50,700 for those requiring the highest dose, with a mean annual cost of \$33,800. At the maximal dose of 750 mg/month this is given as 375 mg two weekly, and with wastage (the drug comes as 150 mg/vial) requires the use of 3 vials each fortnight.

In NZ the cost to the pharmacy is NZ\$700.00/vial, but with GST & mark-ups the patient cost is NZ\$1,207.50, thus the drug costs significantly more than in Australia (NZ\$14,490 to NZ\$94,185 with a mean annual cost of NZ\$62,790).

Given the observed placebo effect and the varied overseas estimates of cost-effectiveness, a pragmatic approach of undertaking studies in experienced severe asthma clinics and assessing responders using a modified n=1 trial design is indicated. This offers the best option to accrue the benefits of omalizumab to the current patients and afford the whole community the best outcome. A strategy for this type of assessment has been described by Gibson *et al.*⁴⁷

Part V. Application of omalizumab in the Australasian context

1. Clinical indications

Omalizumab is registered by the Therapeutic Goods Administration in Australia for the “*management of adult and adolescent patients with moderate to severe allergic asthma, who are already being treated with inhaled corticosteroids and who have serum IgE levels corresponding to the recommended dose range*”. In New Zealand the Medsafe registered indication is: “*the reduction of asthma exacerbations and control of asthma symptoms when given as add-on therapy for adult and adolescent patients, 12 years and older, with severe persistent allergic asthma who have an IgE \geq 30 IU/ml, a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled steroids.*”

Clinical studies in patients with asthma have provided convincing evidence that omalizumab is effective in patients with severe asthma and that it may be particularly useful in patients whose asthma is inadequately controlled despite GINA step 4 therapy (medium or high dose inhaled corticosteroid plus long acting β_2 -agonist), usually termed ‘difficult-to-treat’ asthma’. The underlying conceptual framework is that the majority of patients with asthma can achieve satisfactory levels of control with standard therapy. There is a small group of patients who, in order

to achieve control, require therapy that results in unacceptable side effects, or who remain uncontrolled despite maximal doses of inhaled therapy. These patients have asthma that is ‘difficult-to-control’ with conventional therapy. There are several reasons why asthma may be difficult to control with conventional therapy. These include misdiagnosis, non-adherence, inadequate self-management skills, and persistent treatment resistant asthma. Following careful assessment over several months, patients with difficult-to-control asthma due to persistent disease that is resistant to conventional therapy can be considered for add-on therapy, such as omalizumab.

2. Patient selection

Patients with difficult asthma exhibit varying individual responses to omalizumab. A Cochrane review¹³ of the efficacy of omalizumab in asthma identified a significant placebo effect that has an important impact on the pharmacoeconomic assessment of the use of omalizumab. Also, there is limited experience with the use of this treatment within Australasia. These factors emphasise the need to identify individual responders to this drug, rather than recommend widespread use in difficult asthma.

For these reasons the criteria set out below are recommended to ensure the most cost-effective and rational use of a high cost drug.

It is possible to identify individual responders to omalizumab using single patient controlled trials conducted in the setting of a severe asthma clinic or similar highly specialised unit using the following criteria: ⁴⁷

a. Patient eligibility

- age equal to or greater than 12 years old
- duration of asthma \geq 1 year,
- poor control as evidenced by the presence of 2/6 asthma symptoms most days per week over at least a 3 months period:
(breathlessness, wheezing, limitation in activities, relief by bronchodilators, night awaking, morning asthma symptoms),
- objective confirmation of asthma: forced expiratory volume (FEV₁) reversibility \geq 12% at baseline within 30 minutes after administration of salbutamol (100-200ug) or equivalent, airway hyperresponsiveness or increased peak expiratory (PEF) variability, previously documented,

- adherent to maximal inhaled therapy: treatment with budesonide 1600ug/day or fluticasone propionate 1000ug/day or equivalent, plus long-acting beta agonist, for 3 months.
- total serum IgE ranging from $\geq 30\text{IU/ml}$ to $\leq 700\text{IU/ml}$.

b. Exclusion criteria:

- current smoker or stopped smoking less than 3 month ago,
- evidence for masquerading or complicating asthma conditions such as: vocal cord dysfunction, chronic obstructive pulmonary disease, allergic bronchopulmonary aspergillosis or Churg-Strauss syndrome,
- any respiratory related illness (excluding upper airway disease) other than asthma,
- acute upper respiratory tract infection within 1 month,
- pregnant or lactating,
- unable to attend clinic regularly

When a single patient trial-of-therapy is used to identify responders to omalizumab, then the patient undergoes baseline assessment over 1 month, assessment during omalizumab dosing for 4 months, and then assessment after drug withdrawal for between 1 and 3 months. Definite responders improve on omalizumab and deteriorate when therapy is withdrawn.

c. Clinical assessment

Follow up clinical assessment involves the measurement of asthma symptoms, asthma control scores, for example using the Juniper asthma control questionnaire (ACQ) ^{48,49} quality of life using the Asthma Quality of Life questionnaire (AQLQ), ⁵⁰ rescue beta 2-agonist use, spirometry with FEV₁, FVC and PEF, maintenance oral corticosteroid dose, asthma exacerbations (frequency, type), health care utilization(e.g. hospitalisations). An outcome measure such as the ACQ is highly desirable being a validated and calibrated measure with a change in score of 0.5 representing the minimum clinically significant difference in asthma status.

3. Assessment of response

- i) for patients on oral steroids – a reduction of 25% or greater in steroid dosage with improvement in one or more parameters listed above and similar deterioration on withdrawal.
- ii) for patients not on oral steroids at commencement of omalizumab trial, an improvement in ACQ by 0.5 and deterioration in asthma control off omalizumab treatment by ACQ of 0.5.

4. Continuing treatment

Omalizumab may be continued in those whose asthma has improved on treatment and deteriorated off treatment by one or more criteria listed above.

Treatment may be ongoing unless new information becomes available to alter this view.

5. Omalizumab use in New Zealand

Omalizumab has been approved for use in New Zealand, but clinical experience with it in New Zealand is very limited. Although precise figures are not available, it appears that only a handful of patients have been treated outside of clinical trials (data from Novartis). The main reason for this is lack of funding. Currently the drug is not funded by Pharmac (the New Zealand Drug funding agency) and, although an application for funding has been made, there is no indication that this is likely to happen in the near future (data from Pharmac).

Funding has been obtained for some patients with occupational asthma through the Accident Compensation Corporation. It is possible that District Health Boards may fund the drug for individual patients in exceptional circumstances, particularly if it could be shown to reduce their admissions to hospital and reduce overall costs.

6. Use of omalizumab in remote areas

In the real case of subjects being in remote rural areas the following is suggested:

- They still need review in a specialist clinic experienced in the treatment of difficult asthma and with omalizumab. If this is judged to be an appropriate option then they would embark on the same assessment as for patients as described above.
- Treatment administration and routine clinic reviews could be undertaken by the GP or non-respiratory specialist after appropriate education. Progress is monitored in association with the sponsoring specialist/clinic, both for treatment and withdrawal. The site needs to be prepared to monitor and treat for anaphylaxis and resuscitate in the event of an arrest.
- The patient returns to the specialist clinic for final assessment and discussion. If they fail then other options can be considered.
- If they succeed then ongoing treatment is continued locally.
- Specialist clinic review is undertaken, 6 or 12 monthly.

7. Administration of omalizumab

See Appendices I & III

8. Adverse effects

For detailed discussion see Part 111.2.b

a. Local injection site reactions

b. Anaphylaxis

- reported in 0.1 - 0.2% of treated patients after omalizumab administration.
- The effect is unpredictable.
- It may occur after any dose (even the first dose), and may occur if there has not been a reaction to prior doses.
- The reaction may be delayed up to 24 hours.
- The reported symptoms have included generalized pruritus, urticaria, angioedema of the throat or tongue, bronchospasm, dyspnoea, cough, chest tightness, hypotension, syncope. In the cases reported to the US FDA, most (96%) had pulmonary involvement, 13% had hypotension or syncope, and 15% required hospitalization.
- **Therapy should be discontinued if a severe anaphylactic reaction occurs.**

Management of anaphylaxis risk:

- need for fully informed consent.
- education on risk and nature of anaphylaxis.
- assessment of clinical status including FEV₁ before each injection. FEV₁ is measured as a baseline for monitoring in the case of an adverse event. If it is significantly reduced compared to usual (e.g. < 80%), caution should be exercised in deciding whether to administer the drug or not.
- administration only in circumstances able to detect and deal with anaphylaxis.
- holding for two hours post-injection (European recommendation. Cox, Platts-Mills *et al* ²⁶ suggest one half hour for fourth and subsequent injections but the data is numerically slight).
- provision of an automated adrenaline syringe with instructions on how and when to use.

- provision of a written anaphylaxis management plan (e.g. ASCIA plan - www.allergy.org.au).

Part VI. Unanswered questions & future research directions

Clinical experience with omalizumab is slowly increasing, more so in USA than in Australasia, where it is used in allergic rhinitis as well as in asthma, often in combination with allergen injection immunotherapy. A number of questions regarding use of omalizumab await answers.

- How long should omalizumab be used and what are the end points? This appears to be the major stumbling block for funding bodies faced with granting approval for use. At present the available data suggests ongoing treatment in responders.
- Can omalizumab be successfully used in patients with IgE levels outside the manufacturer's range of 30-600 IU/ml (note the above recommendation is for treatment in the 30–700 IU/ml range)?
- What about the use of omalizumab in pregnancy? Omalizumab is rated as a category B drug. Birth defects associated with omalizumab have not been reported. However, there is insufficient experience with omalizumab in pregnancy and abundant evidence for safe options.
- What is the risk in parasitic disease? There is evidence of a lack of danger from this point of view. A study was conducted in Brazil ⁵¹ with 137 patients at high risk of ascaris infection followed for one year. While there was a slightly higher rate of infestation in the omalizumab treated group compared to placebo, the course, severity and treatment response was the same for the two groups.
- Is omalizumab a cost-effective treatment compared with other management approaches in children with difficult to control asthma?
- Is there any risk of malignancy with long term use of this monoclonal? Long term follow up to monitor for this possibility is necessary and patients receiving treatment need to be made aware that this remains an unknown risk at present.

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Appendix I

Administration of Omalizumab

Eligible patients with baseline IgE level between 30 to 700 IU/ml receive omalizumab subcutaneously at 2 or 4 week intervals for a total of 12 weeks. A dosing chart incorporating body weight and total IgE at baseline is used to assure a minimum omalizumab administration of $\geq 0.0016\text{mg/kg IgE (IU/ml)}$ per 4 weeks (see appendix II). For patients requiring 150-300mg omalizumab, the drug is administered at 4 week intervals. For patients requiring 450-750mg omalizumab, the dose is divided into 2 portions administered at 2 week intervals, to minimise the number of injections at one time and still maintain adequate drug levels. For patients requiring doses of 300mg or greater each fortnight, it is recommended that the dose be divided and administered as two injections into the left and right arm.

The medication should be administered to the patient using a disposable 25-gauge needle and a disposable plastic tuberculin-type syringe. The injections are administered in the deltoid region on the right arm and/or left arm. Alternatively, the injections can be administered in the thigh if reasons preclude administration in the deltoid region. The injections are administered by subcutaneous injection after aspiration of the plunger of the syringe. If blood is withdrawn, the needle is removed without administration of the dose and the injection site is changed.

The drug is administered according to the manufacturers instructions (appendix III). Each dose should be administered in a setting where there is adequate clinical support and access to emergency resuscitation equipment. Patients are observed for 2 hours after dosing, and advised on the recognition and emergency management of adverse effects including anaphylaxis.

Concomitant medications

The maximal doses of inhaled or inhaled plus intranasal corticosteroids are maintained during the assessment period. Rescue medications include salbutamol 100ug as needed (maximum 8 puffs/day) for bronchospasm and a non sedating antihistamine daily for uncontrolled rhinitis symptoms.

Appendix II

DOSAGE AND ADMINISTRATION

150 to 375 mg of omalizumab is administered subcutaneously every two or four weeks. Doses (mg) and dosing frequency are determined by baseline serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination chart below. No more than 150 mg should be administered to a single injection site.

ADMINISTRATION EVERY 4 WEEKS (Milligrams)					ADMINISTRATION EVERY 2 WEEKS (Milligrams)				
Pre-treatment serum IgE (IU/ml)	Body weight (kg)				Pre-treatment serum IgE (IU/ml)	Body weight (kg)			
	30-60	61-70	71-90	91-150		30-60	61-70	71-90	91-150
30-100	150	150	150	300	101-200				225
101-200	300	300	300		201-300		225	225	300
201-300	300				301-400	225	225	300	X
					401-500	300	300	375	X
					501-600	300	375	X	X
					601-700	375	X	X	X
X = DO NOT DOSE									

Table: Omalizumab (Xolair) doses for adults and adolescents (12 years of age and older) with allergic asthma, subcutaneous administration.

Doses greater than 750 mg were not studied in the pivotal clinical studies and are not recommended. The maximum single dose based on clinical studies is 20 mg/kg. In phase III clinical studies, the following formula was used for patients whose bodyweight and IgE levels fell outside the dosing table:

$$BW \text{ (kg)} \times \text{baseline IgE (IU/mL)} \times 0.008 \text{ mg/kg/(IU/mL)} = \text{Individual dose (mg)/two week interval.}$$

When using this formula, select the dose that will provide at least the minimum individual dose per two week intervals.

Patients with severe asthma and a baseline IgE lower than 76 IU/mL were less likely to experience benefit (see CLINICAL TRIALS). Prescribing physicians should ensure that patients with IgE below 76 IU/ml have unequivocal in vitro reactivity (RAST) to a perennial allergen before starting therapy.

Appendix III

MANUFACTURER'S INSTRUCTIONS FOR THE ADMINISTRATION OF OMALIZIUMAB

To prepare omalizumab for subcutaneous administration, please follow the following instructions:

For omalizumab 150 mg:

1. Draw 1.4 mL of water for injection from the ampoule into a 3 mL syringe equipped with a 1-inch, large-bore 18-gauge needle.
2. With the vial placed upright on a flat surface, insert the needle and transfer the water for injection into the omalizumab vial using standard aseptic techniques, directing the water for injections directly onto the powder.
3. Keeping the vial in the upright position, vigorously swirl the vial (do not shake) for approximately 1 minute to evenly wet the powder.
4. To aid dissolution, continue to swirl the upright vial for 5 – 10 seconds approximately every 5 minutes in order to dissolve any remaining solids. The powder typically takes 15 to 30 minutes to dissolve completely, although it may take longer. When the product is fully dissolved, there should be no visible gel-like particles in the solution. It is safe and acceptable to have small bubbles or foam around the edge of the vial. The reconstituted product will appear clear or slightly opaque. Do not use if foreign particles are present.
5. Invert the vial for 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3 mL syringe equipped with a 1-inch, large-bore, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.

Note: As the reconstituted product is somewhat viscous, care must be taken to withdraw all of the product from the vial before expelling any air or excess solution from the syringe in order to obtain the full 1.2 mL dose.

6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection. The usual site of administration is the deltoid region of the arm or the thigh. However, any anatomical site suitable

for subcutaneous injection may be used.

7. Expel air, large bubbles and any excess solution in order to obtain the required 1.2 mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, the injection may take 5-10 seconds to administer.

The vial delivers 1.2 mL (150 mg) of omalizumab.

Stability after reconstitution:

Omalizumab is for single use in one patient only and contains no antimicrobial agent. To reduce microbiological hazard, use as soon as practicable after reconstitution. Discard any residue. If storage is necessary, store at 2° to 8°C for not more than 8 hours.

Incompatibilities:

Omalizumab should not be mixed with any other medicinal product or diluent other than water for injections.