

# DATA SHEET

## **XOLAIR<sup>®</sup>** **Omalizumab**

### **150 mg powder and solvent for solution for injection**

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#### **Qualitative and quantitative composition**

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One vial of Xolair 150 mg powder and solvent for solution for injection contains 150 mg of omalizumab. Reconstituted Xolair contains 125 mg/mL of omalizumab (150 mg in 1.2 mL).

Omalizumab is a humanized monoclonal antibody manufactured from a mammalian cell line.

For a full list of excipients, see List of excipients.

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#### **Pharmaceutical form**

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Powder vial and solvent for solution for injection.

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#### **Clinical particulars**

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##### ***Therapeutic indications***

Xolair (omalizumab) is indicated for the reduction of asthma exacerbations and control of asthma symptoms when given as add-on therapy for adult and adolescent patients, 6 years and older, with severe persistent allergic asthma who have 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 corticosteroids.

##### ***Dosage and method of administration***

The appropriate dose and dosing frequency of Xolair is determined by baseline immunoglobulin E (IgE) (IU/mL), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements 75–600 mg of Xolair in 1 to 4 injections may be needed for each administration. See Tables 1 for a conversion chart and Tables 2 and 3 for the dose determination charts in children (6 years to less than 12 years of age) and in adults and adolescents (12 years of age and older). For doses of 225, 375 or 525 mg Xolair 150 mg can be used in combination with Xolair 75 mg.

Patients whose baseline IgE levels or body weight in kilograms are outside the limits of the dosing table should not be given Xolair.

For subcutaneous administration only. Do not administer by the intravenous or intramuscular route.

**Table 1 Conversion from dose to number of vials, number of injections and total injection volume for each administration**

| Dose (mg) | Number of vials | Number of injections | Total injection volume (mL) |
|-----------|-----------------|----------------------|-----------------------------|
| 150 mg    |                 |                      |                             |
| 150       | 1               | 1                    | 1.2                         |
| 225       | 1.5             | 2                    | 1.8                         |
| 300       | 2               | 2                    | 2.4                         |
| 375       | 2.5             | 3                    | 3.0                         |
| 450       | 3               | 3                    | 3.6                         |
| 525       | 3.5             | 4                    | 4.2                         |
| 600       | 4               | 4                    | 4.8                         |

*1.2 ml = maximum delivered volume per vial (Xolair 150 mg) or use 0.6 mL from a 150 mg vial.*

### Treatment duration, monitoring and dose adjustments

In clinical trials there were reductions in asthma exacerbation events and rescue medication use with improvements in symptom scores during the first 16 weeks of treatment. At least 12 weeks of treatment is required to adequately assess whether or not a patient is responding to Xolair.

Xolair is intended for long-term treatment. Discontinuation generally results in a return to elevated free IgE levels and associated symptoms.

Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than one year should be based on serum IgE levels obtained at the initial dose determination. Total serum IgE levels may be re-tested for dose determination if treatment with Xolair has been interrupted for one year or more.

Doses should be adjusted for significant changes in body weight (see Tables 2 and 3).

**Table 2 ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 weeks**

| Baseline IgE (IU/ml) | Body weight (kg) |        |        |        |        |        |        |        |   |          |  |
|----------------------|------------------|--------|--------|--------|--------|--------|--------|--------|---|----------|--|
|                      | >20-25           | >25-30 | >30-40 | >40-50 | >50-60 | >60-70 | >70-80 | >80-90 | >90-125                                     | >125-150 |  |
| ≥30-100              | 75               | 75     | 75     | 150    | 150    | 150    | 150    | 150    | 300   | 300      |  |
| >100-200             | 150              | 150    | 150    | 300    | 300    | 300    | 300    | 300    | ADMINISTRATION EVERY 2 WEEKS<br>SEE TABLE 3 |          |  |
| >200-300             | 150              | 150    | 225    | 300    | 300    |        |        |        |   |          |  |
| >300-400             | 225              | 225    | 300    |        |        |        |        |        |   |          |  |
| >400-500             | 225              | 300    |        |        |        |        |        |        |   |          |  |
| >500-600             | 300              | 300    |        |        |        |        |        |        |   |          |  |
| >600-700             | 300              |        |        |        |        |        |        |        |   |          |  |

**Table 3 ADMINISTRATION EVERY 2 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 2 weeks**

|                      | Body weight (kg)             |        |        |         |   |   |         |         |         |          |          |
|----------------------|------------------------------|--------|--------|---------|---|---|---------|---------|---------|----------|----------|
| Baseline IgE (IU/ml) | >20- 25                      | >25-30 | >30-40 | >40- 50 | >50- 60   | >60- 70   | >70- 80 | >80- 90 | >90-125 | >125-150 | >150-200 |
| > 30-100             | ADMINISTRATION EVERY 4 WEEKS |        |        |         |   |   |         |         |         |          | 225      |
| > 100-200            | SEE ABOVE                    |        |        |         |   |   |         |         | 225     | 300      | 375      |
| > 200-300            |                              |        |        |         |   | 225   | 225     | 225     | 300     | 375      | 525      |
| > 300-400            |                              |        |        | 225     | 225   | 225   | 300     | 300     | 450     | 525      |          |
| > 400-500            |                              |        | 225    | 225     | 300   | 300   | 375     | 375     | 525     | 600      |          |
| > 500-600            |                              |        | 225    | 300     | 300   | 375   | 450     | 450     | 600     |          |          |
| > 600-700            |                              | 225    | 225    | 300     | 375   | 450   | 450     | 525     |         |          |          |
| > 700-800            | 225                          | 225    | 300    | 375     | 450   | 450   | 525     | 600     |         |          |          |
| > 800-900            | 225                          | 225    | 300    | 375     | 450   | 525   | 600     |         |         |          |          |
| > 900-1000           | 225                          | 300    | 375    | 450     | 525   | 600   |         |         |         |          |          |
| > 1000-1100          | 225                          | 300    | 375    | 450     | 600   | DO NOT ADMINISTER – data is unavailable for dose recommendation |         |         |         |          |          |
| > 1100-1200          | 300                          | 300    | 450    | 525     | 600   | DO NOT ADMINISTER – data is unavailable for dose recommendation |         |         |         |          |          |
| > 1200-1300          | 300                          | 375    | 450    | 525     | DO NOT ADMINISTER – data is unavailable for dose recommendation |   |         |         |         |          |          |
| > 1300-1500          | 300                          | 375    | 525    | 600     | DO NOT ADMINISTER – data is unavailable for dose recommendation |   |         |         |         |          |          |

Safety and efficacy in paediatric patients below the age of 6 have not been established and use of Xolair in such patients is therefore not recommended.

## **Use in Elderly**

There are limited data available on the use of Xolair in patients older than 65 years but there is no evidence that elderly patients require a different dosage from younger adult patients.

## **Contraindications**

Hypersensitivity to the active substance or to any of the excipients (see List of excipients).

## **Warnings and precautions for use**

### **General**

Xolair is not indicated for the treatment of acute asthma exacerbations, acute bronchospasm or status asthmaticus.

Xolair has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions.

Xolair has not been adequately studied in atopic dermatitis, allergic rhinitis or food allergy.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or those with pre-existing renal or hepatic impairment. Caution should be exercised when administering Xolair in these patient populations. Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of Xolair therapy is not recommended. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

Patients with diabetes mellitus, the glucose-galactose malabsorption syndrome, fructose intolerance or sucrose-isomaltase deficiency should be warned that one 150 mg Xolair powder vial and solvent for solution dose contains 108 mg of sucrose and one 75 mg Xolair powder vial and solvent for solution dose contains 54 mg of sucrose respectively. Among the different presentations, only Xolair powder vial contains sucrose.

### **Anaphylaxis**

Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials the frequency of anaphylaxis attributed to Xolair use was estimated to be 0.1%. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment.

Xolair should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Patients should be closely observed for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports (see Adverse Effects). Patients should be informed of the signs and symptoms of anaphylaxis, and instructed to seek immediate medical care should signs or symptoms occur.

Xolair should be discontinued in patients who experience a severe hypersensitivity reaction (see Contraindications).

## **Allergic reactions**

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have rarely been seen in patients treated with humanized monoclonal antibodies including omalizumab. The onset has typically been 1-5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgia, rash (urticaria or other forms), fever and lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder, and patients should be advised to report any suspected symptoms.

## **Malignancies**

During clinical trials for adults and adolescents 12 years of age and older, there was a numerical imbalance in cancers arising in the Xolair treatment group compared with the control group. The frequency of observed cases was uncommon (<1/100) in both the active and the control group, i.e. 25 cancers in 5,015 patients treated with Xolair (0.5%) and 5 cancers in 2,854 patients in the control group (0.18%). The diversity in the type of cancers observed, the relatively short duration of exposure and the clinical features of the individual cases render a causal relationship unlikely. The overall observed incidence rate of malignancy in the Xolair clinical trial program was comparable to that reported in the general population.

## **Parasitic infections**

IgE may be involved in the immunological response to some infections. In patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight increase in infection rate with omalizumab, although the course, severity, and response to treatment of infection were unaltered. The helminth infection rate in the overall clinical program, which was not designed to detect such infections, was less than 1 in 1,000 patients. However, caution may be warranted in patients at high risk of helminth infection, in particular when travelling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of Xolair should be considered.

## **Renal or hepatic impairment**

There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of Xolair. Because omalizumab clearance at clinical doses is dominated by the reticular endothelial system (RES) it is unlikely to be altered by renal or hepatic impairment. While no particular dose adjustment is recommended, Xolair should be administered with caution in these patients.

## ***Interaction with other medicinal products and other forms of interaction***

Cytochrome P450 enzymes, efflux pumps and protein binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions. No formal drug or vaccine interaction studies have been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medications used in the treatment of asthma will interact with omalizumab.

In clinical studies Xolair was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta2-agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used asthma medications. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy).

## ***Pregnancy and lactation***

### **Pregnancy**

There are no adequate and well-controlled studies of omalizumab in pregnant women. IgG molecules are known to cross the placental barrier. Because animal reproduction studies are not always predictive of human response, Xolair should only be used during pregnancy if clearly needed.

Reproduction studies in cynomolgus monkeys have been conducted with omalizumab. Subcutaneous doses up to 75 mg/kg (12-fold the maximum clinical dose) of omalizumab did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on foetal or neonatal growth when administered throughout late gestation, delivery and nursing.

Although no clinically significant effects on platelets have been observed in patients, doses of omalizumab in excess of the clinical dose have been associated with age-dependent decreases in blood platelets in nonhuman primates, with a greater relative sensitivity in juvenile animals. In reproduction studies in cynomolgus monkeys, there was no clinical evidence of thrombocytopenia in neonatal monkeys from mothers treated with up to 75 mg/kg omalizumab; however, platelet counts were not measured in these offspring.

### **Nursing Mothers**

While Xolair presence in human milk has not been studied, IgG is excreted in human milk and therefore it is expected that Xolair will be present in human milk. The potential for Xolair absorption or harm to the infant are unknown; caution should be exercised when administering Xolair to a nursing woman.

The excretion of omalizumab in milk was evaluated in female cynomolgus monkeys receiving subcutaneous doses of 75 mg/kg/week. Neonatal plasma levels of omalizumab after *in utero* exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of omalizumab were 1.5% of the maternal blood concentration.

### ***Effects on ability to drive and use machines***

Patients receiving Xolair should be informed that if they experience dizziness, fatigue, syncope or somnolence they should not drive or use machines.

### ***Adverse effects***

#### **Clinical trials experience**

The most serious adverse reactions occurring in clinical trials with Xolair were anaphylaxis and malignancies (see Warnings and precautions for use). Anaphylaxis was reported in 3 of 3507 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

During clinical trials with adult and adolescent patients 12 years of age and older, the most commonly reported adverse reactions were injection site reactions, including injection site pain, swelling, erythema and pruritus and headaches. In clinical trials with patients 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the events were mild or moderate in severity.

Table 6 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by system organ class and by frequency. Frequencies are defined as: Very common ( $\geq 1/10$ ), common ( $> 1/100$ ;  $< 1/10$ ), uncommon ( $> 1/1000$ ;  $< 1/100$ ), rare ( $< 1/1000$ ).

**Table 6 Adverse reactions in clinical trials**

|   |  |
|---|--|
| <b>Infections and infestations</b>                          |  |
| Uncommon  | Pharyngitis  |
| Rare  | Parasitic infections   |
| <b>Immune system disorders</b>                              |  |
| Rare  | Anaphylactic reaction and other allergic conditions, anti-therapeutic antibody development |
| <b>Nervous system disorders</b>                             |  |
| Common  | Headache**   |
| Uncommon  | Dizziness, somnolence, paresthesia, syncope  |
| <b>Vascular disorders</b>                                   |  |
| Uncommon  | Postural hypotension, flushing   |
| <b>Respiratory , thoracic and mediastinal disorders</b>     |  |
| Uncommon  | Coughing, allergic bronchospasm  |
| Rare  | Laryngoedema   |
| <b>Gastrointestinal disorders</b>                           |  |
| Common  | Abdominal pain upper*  |
| Uncommon  | Nausea, diarrhoea, dyspeptic signs and symptoms  |
| <b>Skin and subcutaneous tissue disorders</b>               |  |
| Uncommon  | Urticaria, rash, pruritus, photosensitivity  |
| Rare  | Angioedema   |
| <b>General disorders and administration site conditions</b> |  |
| Very common   | Pyrexia*   |
| Common  | Injection site reactions such as pain, erythema, pruritus, swelling                        |
| Uncommon  | Weight increase, fatigue, swelling arms, influenza-like illness                            |

\*: In 6 to <12 year old children

\*\* : Very common in 6 to <12 year old children

The frequencies of adverse reactions in the active treatment group patients were very similar to those observed in the control group.

### Post-marketing observations

The following reactions have been identified through spontaneous reporting.

**Anaphylaxis:** Based on spontaneous reports and an estimated exposure of about 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis attributed to Xolair use as estimated to be at least 0.2% of patients. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to Xolair administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases.

Of the reported cases of anaphylaxis attributed to Xolair, 39% occurred with the first dose, 19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). The time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were unknown.

Twenty-three patients who experienced anaphylaxis were rechallenged with Xolair and 18 patients had a recurrence of similar symptoms of anaphylaxis. In addition, anaphylaxis occurred upon rechallenge with Xolair in 4 patients who previously experienced urticaria only.

**Immune system disorders** (see Warnings and precautions for use): Serum sickness.

**Skin and subcutaneous disorders:** Alopecia.

**Blood and lymphatic system disorders:** Idiopathic severe thrombocytopenia.

**Respiratory, thoracic and mediastinal disorders:** Allergic granulomatous angiitis (i.e. Churg Strauss syndrome).

**Musculoskeletal and connective tissue disorders:** Arthralgia, myalgia, joint swelling.

## **Malignancies**

During clinical trials in adults and adolescents 12 years of age and older, there was a numerical imbalance in cancers arising in the active treatment group, compared with the control group. The number of observed cases was uncommon (<1/100) in both the active and the control group. The overall observed incidence rate of malignancy in the Xolair clinical trial programme was comparable to that reported in the general population (see Warnings and precautions for use).

There were no cases of malignancy in the clinical trials in the 6 to <12 years of age group with omalizumab; there was a single case of malignancy in the control group.

## **Arterial Thromboembolic Events (ATE)**

In controlled clinical trials and an ongoing observational study, a numerical imbalance of ATEs was observed. ATE included stroke, transient ischemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). The rate of ATE in patients in the controlled clinical trials was 6.29 for Xolair-treated patients (17/2703 patient years) and 3.42 for control patients (6/1755 patient years). In Cox proportional hazards model, Xolair was not associated with ATE risk (hazard ratio 1.86; 95% confidence interval 0.73-4.72). In the observational study, the rate of ATE was 5.59 (79/14140 patients years) for Xolair-treated patients and 3.71 (31/8366 patient years) for control patients. In a multivariate analysis controlling for baseline cardiovascular risk factors, Xolair was not associated with ATE risk (hazard ratio 1.11; 95% confidence interval 0.70-1.76)

## **Platelets**

In clinical trials few patients experienced platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in haemoglobin. No pattern of persistent decrease in platelet counts has been reported in humans (patients greater than 6 years of age), as was observed in non-human primates (see Preclinical safety data).

## Parasitic infections

In patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight numerical increase in infection rate with omalizumab that was not statistically significant. The course, severity, and response to treatment of infections was unaltered (see Warnings and precautions for use).

## Overdose

No case of overdose has been reported. Maximum tolerated dose of Xolair has not been determined. Single intravenous doses up to 4,000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period and this dose did not result in any untoward acute effects.

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# Pharmacological properties

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## *Pharmacodynamic properties*

Pharmacotherapeutic group: other systemic drugs for obstructive airway diseases, ATC code: R03DX05

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

The allergic cascade is initiated when IgE bound to high affinity Fc $\epsilon$ RI (high affinity IgE receptor) receptors on the surface of mast cells and basophils is crosslinked by allergen. This results in the degranulation of these effector cells and the release of histamines, leukotrienes, cytokines and other mediators. These mediators are causally linked to the pathophysiology of allergic asthma including airway oedema, smooth muscle contraction and altered cellular activity associated with the inflammatory process. They also contribute to the signs and symptoms of allergic disease such as bronchoconstriction, mucus production, wheezing, dyspnoea, chest tightness, nasal congestion, sneezing, itchy, runny nose and itchy, watery eyes.

Omalizumab binds to IgE and prevents binding of IgE to the high-affinity Fc $\epsilon$ RI receptor, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of Fc $\epsilon$ RI receptors on basophils. Furthermore, the *in vitro* histamine release from basophils isolated from Xolair treated subjects was reduced by approximately 90% following stimulation with an allergen compared to pre-treatment values.

In clinical studies, free IgE levels in serum were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. Mean decrease in free IgE in serum was greater than 96% using recommended doses. Total IgE levels (i.e., bound and unbound) in serum increased after the first dose due to the formation of omalizumab: IgE complexes which have a slower elimination rate compared with free IgE. At 16 weeks after the first dose, average serum total IgE levels were five-fold higher compared with pre-treatment levels when using standard assays. After discontinuation of Xolair dosing, the Xolair-induced increase in total IgE and decrease in free IgE were reversible, with no observed rebound in IgE levels after drug washout. Total IgE levels did not return to pre-treatment levels for up to one year after discontinuation of Xolair.

## ***Clinical Experience***

### **Adults and adolescents > 12 years of age**

The safety and efficacy of Xolair were evaluated in five randomised, double-blind, placebo controlled, multi-centre trials.

In identical 16-week studies 1 and 2, the safety and efficacy of omalizumab as add-on therapy were demonstrated in 1,071 allergic asthmatics, who were symptomatic despite treatment with inhaled corticosteroids (beclomethasone dipropionate 500 to 1,200 micrograms/day).

In both trials omalizumab was superior to placebo with respect to the primary variable of asthma exacerbation (worsening of asthma requiring systemic corticosteroids or a doubling of the patient's baseline beclomethasone dose). The number of asthma exacerbations was significantly lower in the omalizumab group ( $p=0.006$  and  $p<0.001$  in studies 1 and 2, respectively). Fewer omalizumab-treated patients experienced asthma exacerbations (14.6% vs 23.3%,  $p=0.009$  in study 1 and 12.8% vs 30.5%,  $p<0.001$  in study 2).

In double-blind extension phases of both studies out to one year the reduction in the frequency of asthma exacerbations for omalizumab-treated patients compared to placebo-treated patients was maintained.

In studies 1 and 2, clinically meaningful improvement in asthma-related quality of life, measured by the validated Juniper's Asthma Quality of Life Questionnaire, was demonstrated in the Xolair group at the end of the 28-week core trial compared to that observed in the placebo treated group (difference from placebo  $p \leq 0.001$  in studies 1 and 2).

In study 3 the safety and corticosteroid-sparing effect of omalizumab was demonstrated in 246 patients with severe allergic asthma requiring daily treatment with high-dose inhaled corticosteroids (fluticasone  $\geq 1000$  micrograms/day) and in whom long-acting beta2-agonists were allowed. The study included a 16-week steroid stable phase with study medication added, followed by a 16-week steroid reduction phase. The percent reduction in inhaled corticosteroid dose at the end of the treatment phase was significantly greater in omalizumab-treated patients versus placebo patients (median 60% vs. 50%,  $p=0.003$ ). The proportion of omalizumab patients who were able to reduce their fluticasone dose to  $\leq 500$  micrograms/day was 60.3% versus 45.8% in the placebo group ( $p>0.05$ ).

In study 4 the safety and efficacy of omalizumab were demonstrated in 405 patients with co-morbid allergic asthma and perennial allergic rhinitis. Eligible patients had both symptomatic allergic asthma and perennial allergic rhinitis. Patients were treated with omalizumab or placebo for 28 weeks as add-on therapy to  $\geq 400$  micrograms of Budesonide Turbohaler. Inhaled long-acting beta2-agonists (39%) and nasal corticosteroids (17%) were allowed.

The co-primary endpoints for study 4 were the incidence of asthma exacerbations (worsening of asthma requiring systemic corticosteroids or a doubling of the patient's baseline budesonide dose) and the proportion of patients in each treatment group with a  $\geq 1.0$  improvement from baseline at the end of the treatment phase in both asthma and rhinitis specific quality of life assessments (Juniper Quality of Life Assessment).

Patients treated with omalizumab had a significantly lower incidence of asthma exacerbations than patients receiving placebo (20.6% omalizumab vs 30.1% placebo,  $p=0.02$ ) and there was a significantly higher proportion of omalizumab-treated than placebo patients that improved by  $\geq 1.0$  points in both asthma and rhinitis specific quality of life assessments (57.7% omalizumab vs 40.6% placebo,  $p < 0.0001$ ).

The reduction in exacerbations and improvements of quality of life in omalizumab-treated patients were seen in the context of statistically significant improvements in both rhinitis and asthma symptoms, and lung function, compared to placebo.

In study 5 the efficacy and safety of Xolair were demonstrated in a 28-week study involving 419 severe allergic asthmatics, ages 12–79 years, who had reduced lung function (Forced Expiratory Volume/1 second: FEV<sub>1</sub> 40–80% predicted) and poor asthma symptom control despite receiving >1000 micrograms of beclomethasone dipropionate (or equivalent) plus long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1000 micrograms (or equivalent) plus long-acting beta2-agonist. Oral corticosteroid (22%), theophylline (27%) and anti-leukotriene (35%) maintenance therapies were allowed. In the treatment phase concomitant asthma therapy was not changed.

The rate of asthma exacerbations requiring treatment with bursts of systemic corticosteroids was the primary endpoint. Omalizumab reduced the rate of asthma exacerbations by 19% (p = 0.153). Further evaluations which did show statistical significance (p<0.05) in favour of Xolair included reductions in severe exacerbations (where patient's lung function was reduced to below 60% of personal best and requiring systemic corticosteroids) and asthma-related emergency visits (comprised of hospitalisations, emergency room, and unscheduled doctor visits), and improvements in Physician's overall assessment of treatment effectiveness, Asthma-related Quality of Life (AQL), asthma symptoms and lung function. A physician's overall assessment was performed in the five above mentioned studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account Peak Expiratory Flow (PEF), day and night time symptoms, rescue medication use, spirometry and exacerbations. In all five studies a significantly greater proportion of Xolair treated patients were judged to have achieved either a marked improvement or complete control of their asthma compared to placebo patients.

### **Children 6 to < 12 years of age**

The primary support for safety and efficacy of Xolair in the 6 to < 12 years of age group comes from one randomised, double-blind, placebo controlled, multi-centre trial (study 6) and an additional supportive study (study 7).

Study 6 was a 52 week study that evaluated the safety and efficacy of Xolair as add-on therapy in 628 allergic asthmatics who were uncontrolled despite treatment with regular inhaled corticosteroids (fluticasone DPI  $\geq$  200 mcg/day or equivalent) with or without other controller asthma medications. Eligible patients were those with a diagnosis of asthma > 1 year and a positive skin prick test to at least one perennial aeroallergen and a history of clinical features of moderate to severe persistent asthma including daytime and/or night-time symptoms along with a history of experiencing exacerbations within the year prior to study entry. Long-acting beta2-agonists (67.4%), anti-leukotriene (36.6%) and oral corticosteroid (1.3%) maintenance therapies were allowed. During the first 24 weeks of treatment, a patient's steroid doses remained constant from baseline and this was followed by a 28 week period during which inhaled corticosteroid adjustment was allowed.

A clinically significant exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose for at least 3 days and/or treatment with rescue systemic (oral or iv) corticosteroids for at least 3 days.

Exacerbation rates during the 52-week double-blind treatment period in Xolair patients with FEV<sub>1</sub> >80% at baseline had relative decreases of 43% in asthma exacerbations compared with placebo (p<0.001). Xolair patients had statistically significant reduction in the rate of asthma exacerbations irrespective of concomitant long-acting beta2-agonist use at baseline compared with placebo patients, representing a 45% decrease for long-acting beta2-agonist users and a 42% decrease for long-acting beta2-agonist non-users (p<0.001 and p=0.011, respectively).

Study 7 was a 28 week double blind controlled study primarily evaluating safety in 334 patients who were well controlled with inhaled corticosteroids. During the first 16 weeks, patients' steroid doses remained constant from baseline and this was followed by a 12 week steroid dose reduction period. The study assessed percent reduction in the dose of beclomethasone dipropionate (BDP) and the proportion of patients with a reduction in the dose of BDP at 28 weeks. The percent reduction in the dose of BDP at 28 weeks was higher in the Xolair group than in the placebo group (median reduction 100% vs. 66.7%,  $p=0.001$ ) as well as the proportion of patients with a reduction in the dose of BDP ( $p=0.002$ ). Frequency and incidence of asthma exacerbation episodes during the steroid dose-reduction phase were also lower in the omalizumab group (mean rate 0.42 vs. 0.72,  $p<0.001$ ; percent patients with exacerbations 18% vs. 39%,  $p<0.001$ ). A trend for superiority of omalizumab with respect to reduction of exacerbation frequency and incidence was evident during the first 16 weeks of the 24 week treatment period. 55.7% omalizumab patients had a complete (100%) reduction in corticosteroid dose at the end of the 28 week treatment period compared with a 43.2% of placebo patients. In addition, more omalizumab patients had a  $\geq 50\%$  reduction in corticosteroid dose compared with placebo (80.4% vs. 69.5%,  $p=0.017$ ).

A physician's overall assessment was performed in the two above mentioned studies (6 and 7) as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF, day and night time symptoms, rescue medication use, spirometry and exacerbations. In both studies a significantly greater proportion of Xolair treated patients were judged to have achieved either a marked improvement or complete control of their asthma compared to placebo patients.

### **Pharmacokinetic properties**

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma.

#### **Absorption**

After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single subcutaneous dose in adult and adolescent patients with asthma, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7-8 days. The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg. Following multiple doses of omalizumab, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose.

#### **Distribution**

*In vitro*, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than one million Daltons in molecular weight are not observed *in vitro* or *in vivo*.

Tissue distribution studies in cynomolgus monkeys showed no specific uptake of  $^{125}\text{I}$ -omalizumab by any organ or tissue. The apparent volume of distribution in patients following subcutaneous administration was  $78 \pm 32$  mL/kg.

#### **Elimination**

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the liver reticuloendothelial system (RES) and endothelial cells. Intact IgG is also excreted in bile. In studies with mice and monkeys, omalizumab: IgE complexes were eliminated by interactions with Fc $\gamma$  receptors within the RES at rates that were generally faster than IgG clearance. In asthma patients omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging  $2.4 \pm 1.1$  mL/kg/day. In addition, doubling of body weight approximately doubled apparent clearance.

## Characteristics in patient populations

### **Age, Race/Ethnicity, Gender, Body Mass Index**

The population pharmacokinetics of Xolair were analysed to evaluate the effects of demographic characteristics. Analyses of these data suggest that no dose adjustments are necessary for age (6-76 years), race, ethnicity, gender or body mass index.

### **Renal and hepatic impairment**

There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment (see Warnings and precautions for use).

### ***Preclinical safety data***

There was no evidence of a systemic anaphylactic response due to mast-cell degranulation in either adult or juvenile cynomolgus monkeys. Circulating omalizumab: IgE antibody complexes were present in all monkey studies, however there was no evidence of immune complex-mediated disease in any organ (including the kidney) following omalizumab administration. Omalizumab: IgE complexes do not fix complement or mediate complement-dependent cytotoxicity.

Chronic administration of omalizumab was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related decrease in platelet counts that occurred in several non-human primate species, at serum concentrations generally in excess of maximum human exposure in pivotal clinical trials. Juvenile monkeys were more sensitive to the platelet effects than adult monkeys. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys, consistent with a localised immune response to repeated subcutaneous administration of a heterologous protein. Formal carcinogenicity studies have not been conducted with omalizumab.

Antibodies to omalizumab were detected in some monkeys following subcutaneous or intravenous administration. This was not unexpected based on administration of a heterologous protein. Some animals could not be evaluated because of high serum omalizumab concentrations, high IgE levels, or both. However, the animals maintained high serum omalizumab concentrations throughout the treatment periods of the studies, and there was no apparent toxicity due to the presence of anti-omalizumab antibodies.

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## Pharmaceutical particulars

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### ***List of excipients***

Powder vial: Sucrose, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20

Solvent: Water for injection

### ***Incompatibilities***

Xolair should not be mixed with any medication or diluents other than sterile water for injection.

### ***Shelf life***

4 years

After reconstitution, the solution must be administered in accordance with the requirements outlined below (see Special precautions for disposal).

### ***Special precautions for storage and shipping***

Xolair must be stored in a refrigerated condition at 2°C–8°C. Do not freeze. Store in the original package. Do not use beyond the expiration date stated.

Xolair powder vial and solvent can be shipped at controlled ambient temperature ( $\leq 30^{\circ}\text{C}$ ) or at 2°C–8°C.

Xolair must be kept out of the reach and sight of children.

### ***Nature and contents of container***

Xolair is supplied as packs containing one vial of powder for solution for injection and one ampoule of water for injection.

Powder vial: Clear, colourless type I glass vial with stopper and blue flip-off seal.

Solvent ampoule: Clear, colourless type I glass ampoule containing 2 mL water for injection.

### ***Special precautions for disposal and other handling***

The lyophilized product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted product will appear clear or slightly opaque and may have a few small bubbles or foam around the edge of the vial. Because 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 0.6 mL or 1.2 mL dose.

**To prepare Xolair for subcutaneous administration, please adhere to the following instructions:**

#### **Xolair 150 mg vials**

1. Draw 1.4 mL of water for injection from the ampoule into a syringe equipped with a large-bore 18-gauge needle.
2. With the vial placed upright on a flat surface, insert the needle and transfer the water for injections into the omalizumab vial using standard aseptic techniques, directing the water for injections directly onto the powder.
3. Keeping the vial in an upright position, vigorously swirl the upright vial (do not shake) for approximately 1 minute to evenly wet the powder.
4. To aid in dissolution after completing step 3, gently swirl the upright vial for 5-10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

\* Note that in some cases it may take longer than 20 minutes for the powder to dissolve completely. If this is the case, repeat step 4 until there are no visible gel-like particles in the solution.

When the product is fully dissolved, there should be no visible gel-like particles in the solution. It is 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-cc syringe equipped with a 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.

6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.
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 Xolair.
8. The injections are administered subcutaneously in the deltoid region of the arm or the thigh.

Xolair 150 mg powder for solution for injection are supplied in a single-use vial and contain no antibacterial preservatives. Chemical and physical stability of the reconstituted product has been demonstrated for 8 hours at 2°C to 8°C and for 4 hours at 30°C. From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 8 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. Any unused product or waste material should be disposed of in accordance with local requirements.

### ***Medicine classification***

Prescription Medicine

### ***Name and address***

Novartis New Zealand Limited  
Private Bag 65904  
Mairangi Bay  
Auckland 0754  
Building G, 5 Orbit Drive  
Rosedale  
Auckland 0632

Telephone: 09 361 8100

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