XOLAIR®
Omalizumab (rch)

NAME OF THE DRUG

The active ingredient of Xolair is omalizumab.

DESCRIPTION

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody produced in Chinese hamster ovary cells that selectively binds to human immunoglobulin E (IgE).

Xolair is a sterile, white, preservative-free lyophilised powder that is reconstituted with water for injections and administered as a subcutaneous (SC) injection.

One vial of Xolair 150 mg contains 150 mg of omalizumab. A reconstituted single-use vial delivers 150 mg omalizumab per 1.2 mL (125 mg/mL).

Excipients:
Xolair vial: sucrose, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20.
Solvent ampoule: water for injections

PHARMACOLOGY

Pharmacodynamics

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 humanised murine antibody that binds to IgE.

The allergic cascade is initiated when IgE bound to high affinity FcεRI 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 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 asthma such as bronchoconstriction, mucous production, wheezing, dyspnoea and chest tightness.

Omalizumab binds to IgE at the same site as the high-affinity FCεRI receptor, thereby reducing the amount of free IgE that is available to bind to the receptor. Treatment with omalizumab also reduces the number of FCεRI receptors on basophils in atopic subjects and histamine release was reduced in response to allergen challenge in those subjects.
Serum free IgE levels (e.g. unbound IgE) are reduced in a dose dependent manner within 2 hours of subcutaneous dosing. Average decreases were 84-99% of baseline. Serum total IgE levels (e.g. bound or unbound) increased an average of 4-fold post-dosing due to formation of omalizumab-IgE binding. Following discontinuation of omalizumab dosing, increases in total IgE and decreases in free IgE were reversible with no rebound in IgE levels after drug washout.

**Pharmacokinetics**

The pharmacokinetic parameter values cited in the following sections are estimates from data obtained from allergic asthma and seasonal allergic rhinitis patients. (See ‘PRECAUTIONS’)

**Absorption:**
Following single, subcutaneous bolus administration, omalizumab is absorbed slowly, reaching mean peak plasma concentrations after 6 to 10 days. Although not precisely defined, the mean absolute bioavailability after subcutaneous administration in humans is estimated to be approximately 53 - 71%.

**Distribution:**
In vitro, omalizumab forms complexes of limited size with IgE. The composition and molecular weight of the complexes are dependent on the molar ratio of omalizumab to IgE. Precipitating complexes and complexes larger than 1 million molecular weight were not observed in vitro. Complexes formed in vitro were similar to those studied in vivo. Tissue distribution studies in cynomolgus monkeys showed no specific uptake of 125I-omalizumab by any organ or tissue. Distribution volumes were 110 ± 14 mL/kg and typical of distribution volumes seen with large macromolecules.

**Biotransformation:**
No circulating metabolites were detected after intravenous administration of 125I-omalizumab to cynomolgus monkeys.

**Elimination:**
Since omalizumab is a recombinant humanised IgG1, its mechanism of clearance from the serum involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, free serum IgE. Omalizumab has a long serum half-life (mean 22 ± 8.2 days). The long half-life is characteristic of IgG class immunoglobulins and a result of IgG recycling via its salvage receptor (FcRn). In studies in mice and monkeys, the omalizumab:IgE complexes were eliminated by interactions with Fcγ receptors within the liver and the reticuloendothelial system, at rates which were generally faster than IgG clearance. At the doses recommended for therapeutic use, average clearance is expected to represent dominantly IgG clearance and to be relatively slow (2.27-4.12 mL/kg/day).

**Characteristics in patient populations:**
There are no clinically important differences in pharmacokinetic and pharmacodynamic data within the 12-75 age range or by gender or race.

There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment. (see PRECAUTIONS)
**CLINICAL TRIALS**

The efficacy and safety of Xolair were demonstrated in a 28-week pivotal, placebo-controlled study (study 2306) involving 419 severe allergic asthmatics, ages 12-79 years, who had reduced lung function (FEV1 40–80% predicted) and poor asthma symptom control despite receiving >1000 micrograms of beclomethasone dipropionate (or equivalent) plus long-acting beta-2-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 beta-2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1000 micrograms inhaled beclomethasone dipropionate (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 systemic corticosteroids was the primary endpoint. The exacerbation rate was 0.74 on omalizumab and 0.92 on placebo and these did not differ significantly (p=0.153), however there was a difference between groups in this baseline exacerbation rate. When the analysis was adjusted for this baseline imbalance, the exacerbation rate was 0.68 on omalizumab and 0.91 on placebo (p=0.042). This approximates to a 74% (95% CIs 55%-99%) treatment effect ratio favouring omalizumab over the 28-week treatment period. Severe exacerbations (lung function less than 60% of personal best) were halved (49 omalizumab vs 100 placebo, p=0.008) resulting in 43.9% fewer asthma-related emergency visits comprised of hospitalisations, emergency room, and unscheduled doctor visits (p=0.038). The reduction in exacerbations in omalizumab-treated patients was seen in the context of statistically significant improvements in asthma symptoms, quality of life and lung function.

There were four large placebo-controlled supportive studies in adults and adolescents (>90% meeting global criteria of severe persistent asthma) (Studies 2304, 008, 009 and 011) and one further randomised standard therapy controlled study (study IA04) which most closely matched the population in study 2306. Studies 2304, 008, 009 and IA04 used exacerbation as primary endpoint, whereas study 011 primarily evaluated inhaled corticosteroid sparing.

In study 2304 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 ≥400 micrograms of inhaled budesonide. Inhaled long-acting beta2 agonists (39%) and nasal corticosteroids (17%) were allowed.

The co-primary endpoints for study 2304 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 ≥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 two identical 16-week studies (008 and 009), 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 008 and 009, respectively). Fewer omalizumab-treated patients experienced asthma exacerbations (14.6% vs 23.3%, \( p=0.009 \) in study 008 and 12.8% vs 30.5%, \( p<0.001 \) in study 009).

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.

Study IA04 was a randomised, controlled, open-label study for 52 weeks in 312 adult and adolescent patients with poorly controlled allergic asthma. Patients received omalizumab as add-on to current asthma treatment (median dose of inhaled corticosteroids was 2000 micrograms/day, 78% were receiving a long-acting beta2-agonist) or current asthma treatment alone. Patients had to have at least one asthma-related hospitalisation or emergency room visit and at least one additional course of oral corticosteroids due to asthma in the previous year.

Treatment with omalizumab led to a 61% reduction in clinically significant asthma exacerbation rate (\( p<0.001 \)) compared to current asthma therapy alone. This reduction in exacerbations was seen in the context of statistically significant improvements in asthma symptoms, lung function and rescue medication use.

In study 011 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).

The clinically meaningful treatment differences in exacerbation rates were comparable for all studies. Table 1 provides annualised exacerbation rates for each study.

### Table 1: Comparison of annualised asthma exacerbations rates per patient across studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Omalizumab exacerbations/year</th>
<th>Placebo exacerbations/year</th>
<th>P-value for rate ratio</th>
<th>Treatment difference in annual rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2306</td>
<td>1.357</td>
<td>1.847</td>
<td>0.039</td>
<td>0.49</td>
</tr>
<tr>
<td>Study 2304</td>
<td>0.491</td>
<td>0.785</td>
<td>0.027</td>
<td>0.29</td>
</tr>
<tr>
<td>Study 008</td>
<td>0.592</td>
<td>0.992</td>
<td>&lt;0.001</td>
<td>0.40</td>
</tr>
<tr>
<td>Study 009</td>
<td>0.514</td>
<td>1.212</td>
<td>&lt;0.001</td>
<td>0.70</td>
</tr>
<tr>
<td>Study IA04</td>
<td>0.989</td>
<td>2.470</td>
<td>&lt;0.001</td>
<td>1.48</td>
</tr>
<tr>
<td>Study 011</td>
<td>1.176</td>
<td>1.600</td>
<td>0.165</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Studies 008 and 009 rates based on one year treatment period. Study 011 includes an oral-steroid-dependent population (n=95) not included in the primary population that assessed inhaled corticosteroid reduction.

In a subgroup analysis of study 2306 (conducted in subjects with severe asthma), patients with pre-treatment total IgE < 76 IU/mL were less likely to experience a clinically meaningful benefit. In these patients Xolair did not significantly reduce asthma exacerbation compared to placebo, whereas in patients with pre-treatment total IgE > 76IU/L, the rate of asthma exacerbations was reduced by 40% (p = 0.002).

There are no efficacy data in patients with mild asthma (eg. those not already on inhaled steroids).

In the clinical trials of Xolair, all subjects had a positive skin test or serum IgE RAST to a relevant Aeroantigen. The efficacy of Xolair in subjects who are negative for these tests is unknown.

### Quality of life

Asthma-related quality of life scores were measured using the Juniper Quality of Life assessments. For all six studies there was a statistically significant improvement from baseline in Quality of Life scores for omalizumab patients versus the placebo or control group (Table 2). Improvements were demonstrated in all four asthma-specific domains of the asthma quality of life questionnaire - symptoms, activities, emotional function and environmental exposure - as well as in the overall score. In five of the six studies, a statistically significantly higher number of omalizumab patients than control patients showed a clinically meaningful improvement (\( \geq 0.5 \) points) in total Quality of Life score.
**Table 2: Proportion of patients with a clinically meaningful improvement in QOL and mean change from baseline compared to placebo/control**

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion of patients with a clinically meaningful improvement in QOL</th>
<th>Mean difference in change from baseline compared to placebo/control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Omalizumab (%)</td>
<td>Placebo/Control (%)</td>
</tr>
<tr>
<td>Study 2306</td>
<td>60.8*</td>
<td>47.8</td>
</tr>
<tr>
<td>Study 2304</td>
<td>78.8*</td>
<td>69.8</td>
</tr>
<tr>
<td>Study 008</td>
<td>74.6*</td>
<td>65.5</td>
</tr>
<tr>
<td>Study 009</td>
<td>68.4</td>
<td>69.3</td>
</tr>
<tr>
<td>Study IA04</td>
<td>71.8*</td>
<td>43.2</td>
</tr>
<tr>
<td>Study 011</td>
<td>52.3*</td>
<td>35.7</td>
</tr>
</tbody>
</table>

* p<0.05 (comparison of omalizumab to placebo/control)

**INDICATIONS**

Xolair is indicated for the management of adult and adolescent patients with moderate to severe allergic asthma, who are already being treated with inhaled steroids, and who have serum immunoglobulin E levels corresponding to the recommended dose range (see Table 5 under “Dosage and Administration”).

**CONTRAINDICATIONS**

Hypersensitivity to omalizumab or any other component of the formulation.

**PRECAUTIONS**

**Allergic reactions:**
Local or systemic allergic reactions, including anaphylaxis, may occur. In post-marketing experience, anaphylaxis and anaphylactoid reactions have been reported following the first and subsequent administrations of Xolair. Although most of these reactions occurred within 2 hours after Xolair administration, some occurred beyond 2 hours and even beyond 24 hours after injections. Medications for the treatment of anaphylactic reactions should always be available for immediate use following administration of Xolair. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur (see “Adverse 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. Patients should be advised to report any suspected symptoms.
Immunogenicity:
As with all protein pharmaceuticals, a small percentage of patients may potentially develop antibodies to the protein (see ‘ADVERSE REACTIONS’)

Other IgE-associated disorders:
Xolair has not been studied in patients with anaphylaxis, hyperimmunoglobulin E syndrome, allergic bronchopulmonary aspergillosis, food allergy or atopic dermatitis. Parasitic infestation may also result in elevation of serum IgE concentrations. In a study of asthmatic patients who had been treated for gut parasites, the level of reinfection did not differ significantly between omalizumab and placebo groups and there were no serious or severe infections. There is no current evidence to suggest that parasitic infections are predisposed to by omalizumab.

Thrombocytopenia:
At serum concentrations in excess of maximum human exposure used in pivotal clinical trials, dose-related thrombocytopenia occurred in 2 out of 4 non-human primate species studied. The thrombocytopenia was more pronounced in juvenile animals. No Xolair-related thrombocytopenia has been observed in clinical trials.

Xolair should be used with caution in patients with thrombocytopenia and patients with a history of thrombocytopenia. It is recommended that patients have a platelet count before commencing therapy with Xolair and then periodically during treatment with Xolair.

Malignancies:
During clinical trials, there was a numerical imbalance in cancers arising in the active treatment group (25 patients of 5015), compared with the control group (5 patients of 2854). The number of observed cases was uncommon (<1/100) in both the active and the control group, respectively 0.5% and 0.2%. The observed cases in Xolair-treated patients included breast, non-melanoma skin, prostate, melanoma and parotid malignancies. The overall observed incidence rate of malignancy in the Xolair clinical trial programme was comparable to that reported in the general population (0.4%). Since the majority of patients were observed for less than 1 year, the impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known.

Effects on ability to drive and use machines:
Patients receiving Xolair should be informed that if they experience dizziness, fatigue, faintness or somnolence they should not drive or use machines.

Use in children:
There are currently insufficient safety data to support the use of Xolair in children under the age of 12 years.

Use in the 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.

Renal or hepatic impairment
There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of Xolair. Xolair should be administered with caution in these patients.
Carcinogenicity
No long-term studies have been performed in animals to evaluate the carcinogenic potential of omalizumab.

Mutagenicity
There was no evidence of gene mutations in a bacterial gene mutation assay with omalizumab. The clastogenic potential of omalizumab has not been investigated.

Effects on fertility
Studies in cynomolgus monkeys showed no adverse effects of omalizumab on fertility or general reproductive performance of males or females at weekly doses up to 75 mg/kg SC (about 45 times the anticipated clinical exposure in adult patients, based on serum AUC).

Use in Pregnancy (Category B1)
No studies have been performed in pregnant or breast-feeding women. Studies in cynomologous monkeys do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or neonatal growth at weekly doses up to 75 mg/kg SC (about 45 times the anticipated clinical exposure in adult patients, based on serum AUC). Because immunoglobulins are known to cross the placenta and the potential for harm to the foetus is unknown, caution should be exercised when prescribing Xolair to pregnant women.

Use in Lactation
It is not known whether Xolair is excreted in human milk. Because human IgG is excreted in human milk, and because the potential for absorption and harm to the infant are unknown, caution should be exercised when Xolair is administered to breast-feeding women.

In order to assess the effect of omalizumab on late gestation, and to evaluate the placental transfer and milk excretion of omalizumab, doses of 75 mg/kg/week were administered subcutaneously to female cynomolgus monkeys. Transport of omalizumab into maternal milk was limited. The serum levels of omalizumab observed in dams, fetuses, and neonates are consistent with reported transport and distribution of IgG class immunoglobulins.

Interactions with Other Drugs
In clinical studies, Xolair was effectively and safely used in conjunction with inhaled corticosteroids, inhaled beta agonists and oral antihistamines. No formal drug interaction studies have been performed with Xolair.

Special precautions
Patients with diabetes mellitus, the glucose-galactose malabsorption syndrome, fructose intolerance or sucrose-isomaltase deficiency should be warned that one 150 mg Xolair dose contains 108 mg of sucrose.
ADVERSE REACTIONS

Clinical trial experience

Adverse reactions with Xolair were observed (all studies) at a frequency of 6.6 % of patients, treated with active drug, during clinical trials.
The most commonly associated adverse drug reactions were injection site reactions, including injection site pain, swelling, itching and redness (1.7%) and headaches (1%).

Other adverse reactions most frequently observed were weight increase (0.7%), urticaria (0.4%), fatigue, arm swelling, nausea, pharyngitis and skin rashes (all at 0.3%). Most of these events were mild or moderate in severity.

The adverse reactions listed in Table 3 were recorded in clinical studies in the total safety population treated with Xolair. Adverse reactions are ranked under headings of frequency using the following convention: common (>1/100; <1/10), uncommon (>1/1000; <1/100), rare (<1/1000).

Table 3: Adverse reactions listed in Table 3 recorded in clinical studies in the total safety population treated with Xolair

<table>
<thead>
<tr>
<th>Body as a whole disorders</th>
<th>Common: injection site reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: weight increase, fatigue, swelling arms, post-injection phenomena</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Uncommon: syncope and vasovagal syncope</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon: Postural hypertension, flushing</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon: nausea, diarrhoea, dyspeptic signs and symptoms</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare: anaphylactic reactions, anti-therapeutic antibody development</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Uncommon: moniliasis</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common: headache</td>
</tr>
<tr>
<td>Uncommon: dizziness, somnolence, paresthesia</td>
<td></td>
</tr>
<tr>
<td>Respiratory system</td>
<td>Uncommon: pharyngitis, coughing, allergic bronchospasm</td>
</tr>
<tr>
<td>Rare: laryngoedema</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon: urticaria, rash, pruritus, photosensitivity</td>
</tr>
<tr>
<td>Rare: angioedema</td>
<td></td>
</tr>
<tr>
<td>Adverse event special categories (causality not established)</td>
<td>Uncommon: asymptomatic platelet decreases, parasitic infections</td>
</tr>
</tbody>
</table>
The frequencies of adverse reactions in the active treatment group patients were very similar to those observed in the placebo group. Weight increase (0.7% vs 0.2%, placebo), urticaria (0.4% vs 0.1%, placebo) and local injection site reactions (1.7% vs 1.3%, placebo) were slightly more commonly observed in the active treatment group than in placebo group patients.

**Adverse Events (AEs):** The commonest adverse events observed (frequency of ≥20%) in this patient population, were headaches, viral infections and upper respiratory tract infections. The frequencies of all adverse events for both treated (N = 1763) and placebo group patients (N =1278) for all studies were very similar.

**Serious Adverse Events (SAEs):** were reported for 2.6% of Xolair treated patients and 2.8% of placebo-treated patients. The most frequently reported SAE’s were appendicitis and fractures (0.2% for both treatment groups and both events). Frequencies of all SAEs by body system were comparable for both treatment groups.

**Allergic events:** As with any protein, local or systemic allergic or Type I hypersensitivity events can occur. Frequencies of all allergic-type events were similar for both treatment groups of the total study population (4%, Xolair, 6%, placebo). Events such as vasovagal syncope, postural hypotension, allergic bronchospasm and photosensitivity occurred in <1% of patients in each treatment group. (see “ Precautions”)

**Parasitic infections:** In patients at chronic high risk of helminth infection, a placebo-controlled trial showed a numerical increase in infection rate with omalizumab that was not statistically significant. The course, severity, and response to treatment of infections were unaltered (see PRECAUTIONS - “Other IgE associated disorders”).

**Malignancies:** During clinical trials, there was a numerical imbalance in cancers arising in the active treatment group (25 patients of 5015), compared with the control group (5 patients of 2854). The number of observed cases was uncommon (<1/100) in both the active and the control group, respectively 0.5% and 0.2%. The observed cases in Xolair-treated patients included breast, non-melanoma skin, prostate, melanoma and parotid malignancies. The overall observed incidence rate of malignancy in the Xolair clinical trial programme was comparable to that reported in the general population (0.4%). Since the majority of patients were observed for less than 1 year, the impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known.

**Platelets:** In clinical trials 0.6% of patients experienced platelet counts below the lower limit of the normal laboratory range. None of these changes was associated with bleeding episodes or a decrease in haemoglobin. No pattern of persistent decrease in platelet counts has been reported in humans, as observed in non-human primates. (See ‘Precautions’)

**Other laboratory data:** There was no evidence of clinically relevant changes in laboratory safety tests during clinical trials.

**Allergic asthma (adult and adolescent study population):** The most frequently observed adverse events in this population (N = 716 Xolair patients, N = 694 placebo patients) were viral infections, upper respiratory tract infections, sinusitis and headaches (frequency ≥20%).
Adverse reactions occurred in 5.6% of Xolair-treated patients and in 5.2% of patients receiving placebo. The most frequently reported events of this type were headaches (1.3% vs 1.2%, placebo) and fatigue (0.6% vs 0%, placebo). All other suspected Xolair drug related adverse events occurred with a frequency of <0.5%.

Serious episodes of asthma related events requiring hospitalisation were observed in 0.2% of Xolair-treated patients and 1.3% of placebo-treated patients, in the asthma studies.

The most frequently observed (≥5%) adverse events in studies with asthma patients 12 years of age and older are provided in Table 4.

**Table 4:** Most frequently reported adverse events regardless of causality in adult/adolescent asthma population (≥ 5% in either treatment group)

<table>
<thead>
<tr>
<th>Body system/preferred term</th>
<th>Xolair (N=716)</th>
<th>Placebo (N=694)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Pain</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Digestive system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Pain abdominal</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection, viral</td>
<td>37%</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain back</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Sprains and strains</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Nervous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>27%</td>
<td>27%</td>
</tr>
</tbody>
</table>

**Post-marketing observations:**

The following reactions have been identified through spontaneous reporting.

**Immune system disorders**
Anaphylaxis and anaphylactoid reactions have been reported following the first or subsequent administrations, serum sickness (see section “Precautions” and “Allergic events” in the “Clinical trial experience” section).
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

**DOSAGE AND ADMINISTRATION**

150 to 375 mg of Xolair 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 (Table 5).

<table>
<thead>
<tr>
<th>Baseline IgE (IU/mL)</th>
<th>Total milligrams of Xolair required per 4-week interval</th>
<th>Body Weight (kg)</th>
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<td>&gt;30–40</td>
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<td>&gt;1200–1300</td>
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</tbody>
</table>

Note:
Doses ≤300 mg per 4-week interval are administered once per 4 weeks.

Doses >300 mg per 4-week interval are split into 2 equal doses administered every 2 weeks (i.e. 600 mg total = 300 mg every 2 weeks).

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:

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

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.

**Measurement of serum IgE levels:**

Any commercial serum total IgE assay may be used for determination of serum total IgE for initial dose assignment. However, Xolair can interfere with accurate quantitation of serum IgE levels. The total IgE levels while on active treatment of Xolair increased an average of 4-fold post-dose as a result of omalizumab-IgE binding. If it is necessary to measure serum total IgE in subjects currently on Xolair treatment or who have discontinued within the last 12 months, the Abbott IMX assay has been shown to demonstrate reliable serum total IgE measurements.

**Treatment duration, monitoring and dose adjustments:**

Doses do not need to be adjusted for variations in serum IgE over time. Data from clinical studies suggest that, in the absence of omalizumab treatment, there is no significant temporal variation in serum total IgE levels.

Dose assignment after treatment interruptions or discontinuations should be based on serum IgE levels obtained at initial dose assignment. Serum IgE should only be re-determined for dose assignment if treatment has been discontinued for six months or more.

Doses will need to be increased for body weight gains. No data are currently available to support dose adjustments based on changes in serum total IgE with increasing age.

Discontinuation of Xolair treatment generally results in a return to elevated free IgE levels and associated symptoms.

At 16 weeks after commencing Xolair therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue Xolair should be based on whether a marked improvement in overall asthma control is seen (see CLINICAL TRIAL).

Reduction of inhaled corticosteroids may be attempted after 16 weeks of treatment with Xolair in patients with stable, well-controlled asthma. The dose of corticosteroid should be reduced gradually under medical supervision. In some patients, inhaled corticosteroids can be tapered off completely. Xolair should not be abruptly substituted for inhaled corticosteroids.

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.
Administration of Xolair

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

For Xolair 150 mg:

1. Draw 1.4 mL of water for injections 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 injections 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:
Xolair 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:
Xolair should not be mixed with any other medicinal product or diluent other than water for injections.
**OVERDOSAGE**

No cases of overdose have been reported. A maximum tolerated dose of Xolair has not been determined. Single intravenous doses up to 4000 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.

**PRESENTATION**

Xolair is supplied as a pack containing 1 single-use vial of 150 mg sterile, lyophilised powder and 1 ampoule of water for injections for use as diluent. Upon reconstitution, Xolair 150 mg contain 150 mg omalizumab per 1.2 mL (125 mg/mL of omalizumab).

**Storage:** Store at 2° to 8°C. Do not freeze. Store in the original package. Medicines should be kept out of the reach of children.

**Poison schedule:** 4

**SPONSOR**

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