# XOLAIR®
**Omalizumab (rch)**

## NAME OF THE MEDICINE

The active ingredient of Xolair is omalizumab.

**CAS no.:** 0242138-07-4

## 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 75 mg powder for solution contains 75 mg of omalizumab. A reconstituted single-use vial delivers 75 mg omalizumab per 0.6 mL (125 mg/mL).

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).

Each pre-filled syringe of 0.5 mL contains 75 mg of omalizumab.

Each pre-filled syringe of 1 mL contains 150 mg of omalizumab.

Excipients:

**Powder vial and solvent for solution for injection**

Xolair vial: sucrose, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20.

Solvent ampoule: water for injections

**Solution for injection in pre-filled syringe**

L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injection.

## PHARMACOLOGY

### General Characteristics

### Pharmacodynamics

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody is an $IgG_1$ kappa that contains human framework regions with the complementary-determining regions of a humanised murine antibody that binds to IgE.

## Patients with Allergic Asthma

The allergic cascade is initiated when IgE bound to the high affinity IgE receptor FcεRI, 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.

Clinical studies in asthma patients' showed that, 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.

### Patients with Chronic Idiopathic Urticaria (CIU)

There are several theories for the etiology of CIU, including one that suggests an autoimmune origin. Autoimmune antibodies to IgE and its receptor, FcεRI, have been isolated from the serum of some patients with CIU. These autoantibodies can activate basophils or mast cells leading to release of histamine.

One hypothesis for the mechanism of action of omalizumab in CIU is that it lowers free IgE levels in the blood and subsequently in the skin. This leads to down-regulation of surface IgE receptors, thereby decreasing downstream signaling via the FcεRI pathway, resulting in suppressed cell activation and inflammatory responses. As a consequence, the frequency and severity of symptoms of CIU are lessened. Another hypothesis is that lowering circulating free IgE levels leads to a rapid and non-specific desensitization of cutaneous mast cells. Down-regulation of FcεRI may help to sustain the response.

In clinical studies in CIU patients, omalizumab treatment led to a dose-dependent reduction of free IgE and an increase of total IgE levels in serum, similar to the observations in allergic asthma patients. Maximum suppression of free IgE was observed 3 days after the first subcutaneous dose. After repeated dosing once every 4 weeks, pre-dose serum free IgE levels remained stable between 12 and 24 weeks of treatment. Total IgE levels 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. After repeated dosing once every 4 weeks at 75 mg to 300 mg, average predose serum total IgE levels at week 12 were two-to three-fold higher compared with pre-treatment levels, and remained stable between 12 and 24 weeks of treatment. After discontinuation of Xolair, free IgE levels increased and total IgE levels decreased towards pre-treatment levels over a 16-week treatment-free follow-up period ].

## Pharmacokinetics

### General characteristics

#### Absorption

Administration of Xolair manufactured as a lyophilized or liquid formulation resulted in similar serum concentration-time profiles of omalizumab.

#### 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 $^{125}$I-omalizumab by any organ or tissue.

#### Biotransformation/Metabolism:

No circulating metabolites were detected after intravenous administration of $^{125}$I-omalizumab to cynomolgus monkeys.

#### Elimination

Since omalizumab is a recombinant humanised $IgG_1$, 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. In studies in mice and monkeys, the omalizumab:IgE complexes were eliminated by interactions with $Fc_i$ receptors within the liver and the reticuloendothelial system, at rates which were generally faster than IgG clearance.

### Patients with Allergic Asthma and seasonal allergic rhinitis patients

#### Absorption:

Following single, subcutaneous bolus administration, omalizumab is absorbed slowly, reaching mean peak serum 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:

Distribution volumes were 110 ± 14 mL/kg and typical of distribution volumes seen with large macromolecules.

#### Elimination:

Omalizumab has a long serum half-life (mean 22 $\pm$ 8.2 days). The long half-life is characteristic of IgG class immunoglobulins and a result of IgG recycling via its salvage receptor (FcRn). 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).

### Age, Gender, Race

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

### Patients with Chronic Idiopathic Urticaria (CIU)

### Absorption

Following a single subcutaneous dose in adult and adolescent patients with CIU, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 6 to 8 days.

In patients with CIU, omalizumab exhibited linear pharmacokinetics across the dose range of 75 mg to 600 mg given as a single subcutaneous dose. Following doses of 75 mg, 150 mg or 300 mg every 4 weeks, trough serum concentrations of omalizumab increased proportionally with the dose level.

### Distribution

Based on population pharmacokinetic, distribution of omalizumab in CIU patients was similar to that in patients with allergic asthma.

### Elimination

In patients with CIU, based on population pharmacokinetic simulations, omalizumab serum elimination half-life at steady state averaged 24 days and apparent clearance at steady state averaged 240 mL/day (corresponding to 3.0 mL/kg/day for an 80 kg patient).

### Age, Race/Ethnicity, Gender, Body Weight, Body Mass Index, Baseline IgE, anti-FcεRI autoantibodies, co-medications

The effects of demographic covariates and other factors on omalizumab exposure were evaluated using population pharmacokinetics. In addition, covariate effects were evaluated by analyzing the relationship between omalizumab concentrations and clinical responses. These analyses suggest that no dose adjustments are necessary in patients with CIU for age (12 to 75 years), race/ethnicity, gender, body weight, body mass index, baseline IgE, anti-FcεRI autoantibodies or concomitant use of H2 antihistamines or leukotriene receptor antagonists (LTRAs).

### Patients with renal and hepatic impairment

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

## CLINICAL TRIALS

### Allergic Asthma

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 ≥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 ³ 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 ≤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**

| | Omalizumab exacerbations/year | Placebo exacerbations/year | P-value for rate ratio | Treatment difference in annual rate |
|---|---|---|---|---|
| Study 2306 | 1.357 | 1.847 | 0.039 | 0.49 |
| Study 2304 | 0.491 | 0.785 | 0.027 | 0.29 |

| | | | | |
|---|---|---|---|---|
| Study 008 | 0.592 | 0.992 | <0.001 | 0.40 |
| Study 009 | 0.514 | 1.212 | <0.001 | 0.70 |
| Study IA04 | 0.989 | 2.470 | <0.001 | 1.48 |
| Study 011 | 1.176 | 1.600 | 0.165 | 0.42 |

Study 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 (≥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**

| | Proportion of patients with a clinically meaningful improvement in QOL | | Mean difference in change from baseline compared to placebo/control |
|---|---|---|---|
| | Omalizumab (%) | Placebo/Control (%) | |
| Study 2306 | 60.8* | 47.8 | 0.45* |
| Study 2304 | 78.8* | 69.8 | 0.25* |
| Study 008 | 74.6* | 65.5 | 0.28* |
| Study 009 | 68.4 | 69.3 | 0.32* |
| Study IA04 | 71.8* | 43.2 | 0.48* |
| Study 011 | 52.3* | 35.7 | 0.28* |

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

## Chronic Idiopathic Urticaria (CIU)

The efficacy and safety of Xolair were demonstrated in two randomised, placebo-controlled phase III studies (study Q4881g, Q4882g) in patients with CIU who remained symptomatic despite H1 antihistamine therapy at the approved dose. All patients received Xolair or placebo in addition to H1 antihistamines. A third study (Q4883g) primarily evaluated the safety of Xolair in patients with CIU who remained symptomatic despite treatment with H1 antihistamines at increased doses and H2 antihistamine and/or leukotriene receptor antagonist (LTRA) treatment. All patients received Xolair or placebo in addition to H1 antihistamines up to 4 times the approved dose, and/or H2 antihistamines and/or LTRAs.

CIU patients with external triggers were excluded from these trials. The three studies enrolled 975 patients aged between 12 and 75 years (mean age 42.3 years; 39 patients 12-17 years, 54 patients ≥65 years; 259 males and 716 females). All patients were required to have inadequate symptom control, as assessed by a weekly urticaria activity score (UAS7, range 0 42) of ≥16, and a weekly itch severity score (which is a component of the UAS7; range 0 21) of ≥8 for the 7 days prior to randomisation, despite having used an antihistamine for at least 2 weeks beforehand.

In studies Q4481g and Q4882g, patients had a mean weekly itch severity score of between 13.7 and 14.5 at baseline and a mean UAS7 score of 29.5 and 31.7 respectively. Patients in safety study Q4883g had a mean weekly itch severity score of 13.8 and a mean UAS7 score of 31.2 at baseline. Across all three studies, patients reported receiving on average 4 to 6 medications (including H1 antihistamines) for CIU symptoms prior to study enrolment. Patients received Xolair at 75 mg, 150 mg or 300 mg or placebo by subcutaneous injection every 4 weeks for 24 and 12 weeks in studies 1 and 2, respectively, and 300 mg or placebo by subcutaneous injection every 4 weeks for 24 weeks in study 3. All studies had a 16 week treatment-free follow-up period.

**Table 3 Efficacy endpoints**

| | |
|---|---|
| Change from baseline to week 12 in weekly Itch Severity Score (ISS, range 0-21) | Primary endpoint in studies Q4881g and Q4882g<br>Secondary endpoint in safety study Q4883g |
| Time to MID [a] response (decrease from baseline of ≥5 points) in weekly ISS up to week 12 | Secondary endpoints in all three studies Q4881g, Q4882g and Q4883g |
| Change from Baseline to week 12 in Urticaria Activity score during a 7 day period (UAS7 [b], range 0-42) | |
| Proportion of patients with Urticaria Activity Score during a 7-Day Period ≤ 6 (UAS7 [b] ≤ 6) at week 12 | |
| Proportion of patients with Urticaria Activity Score during a 7-Day Period = 0 (UAS7 [b] = 0) at week 12 [c] | |
| Changes from baseline in the weekly number of hives score at week 12 | |
| Change from baseline to week 12 in overall Dermatology Life Quality Index (DLQI) | |
| Proportion of patients with angioedema-free days from week 4 to week 12 [d] | |

[a] *MID: Minimally Important Difference*

[b] *UAS7: Composite of itch severity and number of hives measured daily and totalled over one week*

[c] *Post hoc analysis for study Q4882g*

[d] *Mean proportion of angioedema-free days from week 4 to week 12 was calculated for the entire study population, including patients asymptomatic for angioedema.*

In studies Q4881g and Q4882g the 75 mg dose did not consistently meet either the primary efficacy endpoint or a number of secondary endpoints. It was deemed not efficacious and therefore not further presented.

### Change from baseline to week 12 in weekly itch severity score

The primary efficacy endpoint, change from baseline to week 12 in weekly itch severity score was met by both the 150 mg and 300 mg doses in studies Q4881g and Q4882g and by the 300 mg dose in Q4883g (see Table 4).

**Table 4 Change from baseline to week 12 in weekly itch severity score, Studies Q4881g, Q4882g and Q4883g (mITT population*)**

| | Placebo | Omalizumab 150mg | Omalizumab 300mg |
|---|---|---|---|
| **Study Q4881g** | | | |
| N | 80 | 80 | 81 |
| Mean (SD) | -3.63 (5.22) | -6.66 (6.28) | -9.40 (5.73) |
| Difference in LS means vs. placebo[1] | - | -2.95 | -5.80 |
| 95% CI for difference | - | −4.72,−1.18 | −7.49,−4.10 |
| P-value vs. placebo[2] | - | 0.0012 | <0.0001 |
| **Study Q4882g** | | | |
| N | 79 | 82 | 79 |
| Mean (SD) | -5.14 (5.58) | -8.14 (6.44) | -9.77 (5.95) |
| Difference in LS means vs. placebo[1] | - | -3.04 | -4.81 |
| 95% CI for difference | - | −4.85,−1.24 | −6.49,−3.13 |
| P-value vs. placebo[2] | - | 0.0011 | <0.0001 |
| **Study Q4883g** | | | |
| n | 83 | - | 252 |
| Mean (SD) | -4.01 (5.87) | - | -8.55 (6.01) |
| Difference in LS means vs. placebo[1] | - | - | -4.52 |
| 95% CI for difference | - | - | −5.97, −3.08 |
| P-value vs. placebo[2] | - | - | <0.0001 |

**Modified intent-to-treat (mITT) population: Included all patients who were randomized and received at least one dose of study medication.*

*BOCF (Baseline Observation Carried Forward) was used to impute missing data.*

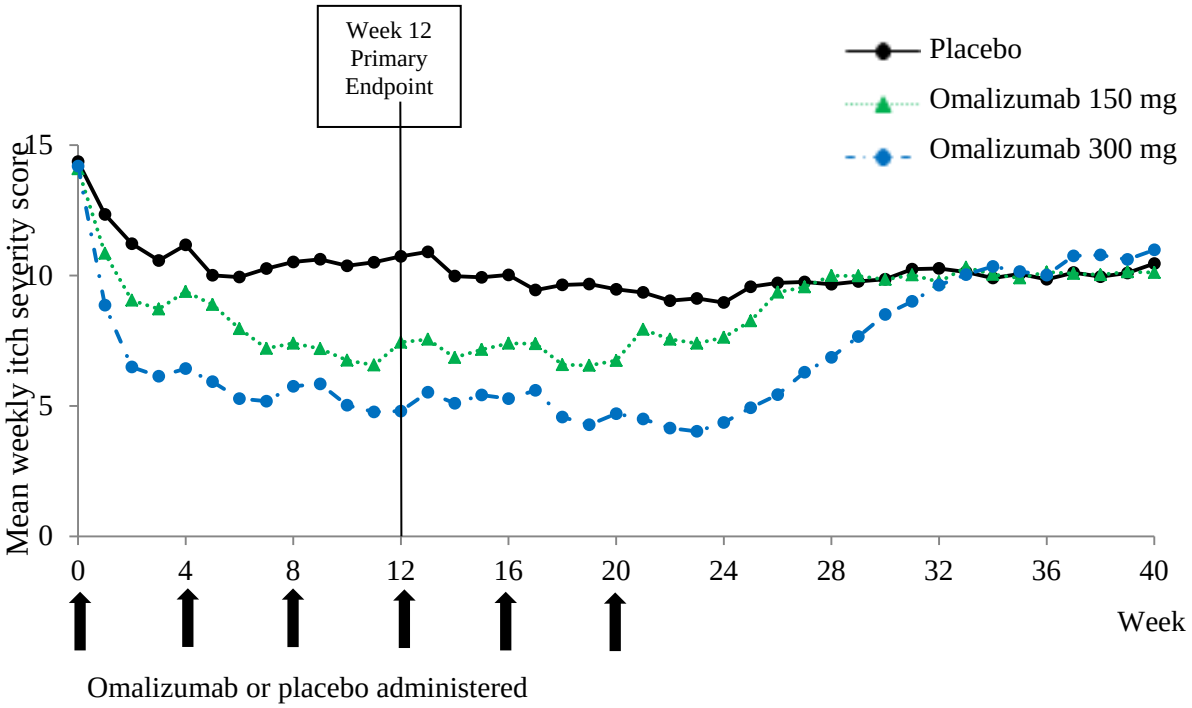
*[1] The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (< 13 vs. ≥13) and baseline weight (< 80 kg vs. ≥ 80 kg).*

*[2] p-value is derived from ANCOVA t-test*

Figure 1 shows the mean weekly itch severity score over time in study Q4881g. The mean weekly itch severity scores significantly decreased in both treatment groups with a maximum effect around week 12 that was sustained over the 24-week treatment period. In studies Q4883g (300 mg over the 24-week treatment period) and Q4882g (150 mg and 300 mg over the 12-week treatment period) the results were similar to those of study Q4881g.

In all three studies (see Figure 1 for study Q4881g), the mean weekly itch severity score for both doses increased gradually during the 16-week treatment-free follow-up period, consistent with symptom re-occurrence. Mean values at the end of the follow-up period were similar to the placebo group, but lower than respective mean baseline values.

**Figure 1 Mean weekly itch severity score over time, Study Q4881g (BOCF, mITT population)**




BOCF=baseline observation carried forward; mITT=modified intention-to-treat population

Secondary endpoints for studies **Q4881g, Q4882g and Q4883g** are presented in Table 5

**Table 5 Secondary efficacy endpoints in Studies Q4881g, Q4882g and Q4883g (mITT population*)**

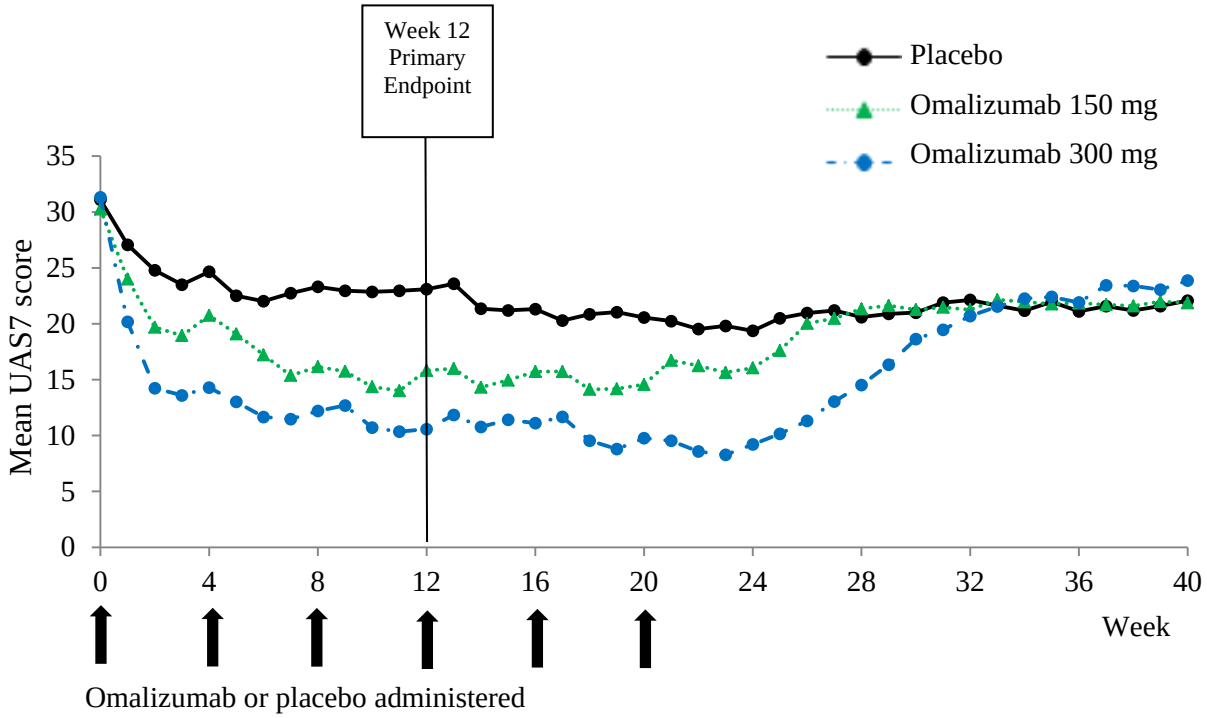
| | Placebo | Omalizumab 150mg | Omalizumab 300mg |
|---|---|---|---|
| **Time to MID response in weekly ISS up to week 12 (median weeks)** | | | |
| Q4881g | 4 | 2 (p=0.0301) | 1 (p<0.0001) |
| Q4882g | 4 | 2 (p=0.0101) | 1 (p<0.0001) |
| Q4883g | 5 | NA | 2 (p<0.0001) |
| **Change from baseline to week 12 in UAS7 (mean)** | | | |
| Q4881g | -8.01 | -14.44 (p = 0.0008) | -20.75 (p<0.0001) |
| Q4882g | -10.36 | -17.89 (p = 0.0001) | -21.74 (p<0.0001) |
| Q4883g | -8.50 | NA | -19.01 (p<0.0001) |
| **Changes from baseline in the weekly number of hives score at week 12 (mean)** | | | |
| Q4881g | -4.37 | -7.78 (p=0.0017) | -11.35 (p<0.0001) |
| Q4882g | -5.22 | -9.75 (p<0.0001) | -11.97 (p<0.0001) |
| Q4883g | -4.49 | NA | -10.46 (p<0.0001) |
| **Change from baseline to week 12 in overall Dermatology Life Quality Index (DLQI) (mean)** | | | |
| Q4881g | -6.13 | -8.00 (p=0.2286) | -10.29 (p<0.0001) |
| Q4882g | -6.09 | -8.29 (p=0.0215) | -10.15 (p=0.0004) |
| Q4883g | -5.11 | NA | -9.69 (p<0.0001) |
| **Proportion of angioedema-free days from week 4 to week 12 (mean)** | | | |
| Q4881g | 88.2% | 89.6% (p=0.1747) | 96.1% (p<0.0001) |
| Q4882g | 89.2% | 91.6% (p=0.0905) | 95.5% (p<0.0001) |
| Q4883g | 88.1% | NA | 91.0% (p<0.0006) |
| **Proportion of patients with UAS7 ≤ 6 at week 12 (% patients)** | | | |
| Q4881g | 11.3 | 40.0 (p<0.0001) | 51.9 (p<0.0001) |
| Q4882g | 19.0 | 42.7 (p=0.0010) | 65.8 (p<0.0001) |
| Q4883g | 12.0 | NA | 52.4 (p<0.0001) |
| **Proportion of patients with UAS7 = 0 at week 12 (% patients)** | | | |
| Q4881g | 8.8 | 15.0 (p=0.2087) | 35.8 (p<0.0001) |
| Q4882g | 5.1 | 22.0 (p=0.0019) | 44.3 (p<0.0001) |
| Q4883g | 4.8 | NA | 33.7 (p<0.0001) |

**Modified intent-to-treat (mITT) population: included all patients who were randomised and received at least one dose of study medication*
*p-value was derived using Cox proportional hazard model, ANCOVA, stratified Wilcoxon, and stratified CMH, as appropriate, comparing between active treatment and placebo*
*NA: Not applicable.*
*BOCF: Baseline Observation Carried Forward*

Figure 2 shows mean UAS7 over time in study Q4881g, displaying a significant decrease from baseline in both treatment groups with a maximum effect around week 12. The magnitude of the effect was maintained during the 24-week treatment period. In studies Q4882g (150 mg and 300 mg over the 12-week treatment period) and Q4883g (300 mg over 24-week treatment period) the results were similar to those of study Q4881g.

In all three studies (see Figure 2 for study Q4881g), the UAS7 for both omalizumab treatment groups increased gradually during the 16-week treatment-free follow-up period, consistent with symptom re-occurrence. Mean values at the end of the follow-up period were similar to the placebo group but lower than respective mean baseline values.

**Figure 2 Mean UAS7 over time, Study Q4881g (BOCF, mITT population)**




*BOCF=baseline observation carried forward; mITT=modified intention-to-treat population; UAS7= urticaria activity score over 7 days*

**Efficacy after 24 weeks of treatment**

Table 6 shows the results after 24 weeks of treatment. Similar magnitudes of response are seen as at 12 weeks.

**Table 6 Efficacy results after 24 weeks of treatment, Studies Q4881g and Q4883g (mITT population*)**

| Parameter<br>Study | Week | Placebo | Omalizumab 150 mg | Omalizumab 300 mg |
|---|---|---|---|---|
| Change from baseline in weekly itch severity score (BOCF), mean | | | | |
| Study Q4881g | Week 24 | −5.41 | −6.47 | −9.84** |
| Study Q4883g | Week 24 | −4.03 | NA | −8.60** |
| Change from baseline in UAS7 (BOCF), mean | | | | |
| Study Q4881g | Week 24 | −11.73 | −14.21 | −22.11** |
| Study Q4883g | Week 24 | −8.85 | NA | −19.15** |
| Proportion of patients with UAS7 ≤ 6, % patients | | | | |
| Study Q4881g | Week 24 | 25.0 | 36.3 | 61.7** |
| Study Q4883g | Week 24 | 16.9 | NA | 55.6** |
| Proportion of patients with UAS7 = 0, % patients | | | | |
| Study Q4881g | Week 24 | 12.5 | 20.0 | 48.1** |
| Study Q4883g | Week 24 | 3.6 | NA | 42.5** |

**Modified intent-to-treat (mITT) population: included all patients who were randomised and received at least one dose of study medication*
*** p-value≤0.0001 for the corresponding test statistics between the treatment and the placebo*
*NA: Not applicable.*
*BOCF: Baseline Observation Carried Forward*

The treatment duration in the studies were 12 weeks (Q4882g) and 24 weeks, respectively (Q4881g and Q4883g), therefore the Clinical trial experience of long-term treatment beyond 6 months in this indication is limited.

# INDICATIONS

### Allergic Asthma

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 9 under “Dosage and Administration”).

### Chronic Idiopathic Urticaria (CIU)

Xolair is indicated for adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment.

# 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 EFFECTS").

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.

**Churg-Strauss syndrome and hypereosinophilic syndrome:**

Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids. In rare cases, patients on therapy with anti-asthma agents, including omalizumab, may present or develop systemic eosinophilia and vasculitis. A causal association between Xolair and these underlying conditions has not been established. These events are commonly associated with the reduction of oral corticosteroid therapy. In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy. Discontinuation of omalizumab should be considered in all severe cases with the above mentioned immune system disorders.

**Immunogenicity:**

As with all protein pharmaceuticals, a small percentage of patients may potentially develop antibodies to the protein. (see 'ADVERSE EFFECTS')

**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, but it has been reported in the post-market setting.

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.

**Arteriothrombolic Events (ATE)**

In controlled clinical trials, interim and final analyses of an observational study, a numerical imbalance of ATE was observed. See 'ADVERSE EFFECTS'.

**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.

**Pre-filled syringe, latex-sensitive individuals**

The removable needle cap of Xolair solution for injection in pre-filled syringe contains a derivative of natural rubber latex. Although no natural rubber latex is detected in the removable needle cap, the safe use of Xolair solution for injection in pre-filled syringe in latex-sensitive individuals has not been studied.

**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 MEDICINES

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.

**Chronic Idiopathic Urticaria (CIU)**

In clinical studies in CIU Xolair was used in conjunction with antihistamines (anti-H1, anti-H2) and leukotriene receptor antagonists (LTRAs). In the phase III studies Q4881g and Q4882g all patients received H1 antihistamines in addition to Xolair or placebo. In the phase III study Q4883g, all patients received one or more H1 antihistamine(s), and/or H2 antihistamines and/or LTRAs in addition to Xolair or placebo. There was no evidence that the safety of omalizumab was altered when used with these medicinal products relative to its known safety profile in allergic asthma. In addition, a population pharmacokinetic analysis showed no relevant effect of H2 antihistamines and LTRAs on omalizumab pharmacokinetics (see PHARMACOLOGY).

# ADVERSE EFFECTS

## Clinical trial experience in allergic asthma

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 6 were recorded in clinical studies in the total allergic asthma 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 6: Adverse reactions listed in Table 6 recorded in clinical studies in the total allergic asthma safety population treated with Xolair**

| |
|---|
| ***Body as a whole disorders***<br>Common: injection site reactions<br>Uncommon: weight increase, fatigue, swelling arms, post-injection phenomena |
| ***Cardiovascular disorders***<br>Uncommon: syncope and vasovagal syncope |
| ***Vascular disorders***<br>Uncommon: postural hypotension, flushing |
| ***Gastrointestinal disorders***<br>Uncommon: nausea, diarrhoea, dyspeptic signs and symptoms |
| ***Infections and infestations***<br>Uncommon: moniliasis |
| ***Immune system disorders***<br>Rare: anaphylactic reactions, anti-therapeutic antibody development |
| ***Nervous system disorders***<br>Common: headache<br>Uncommon: dizziness, somnolence, paresthesia |
| ***Respiratory system***<br>Uncommon: pharyngitis, coughing, allergic bronchospasm<br>Rare: laryngoedema |
| ***Skin and subcutaneous tissue disorders***<br>Uncommon: urticaria, rash, pruritus, photosensitivity<br>Rare: angioedema |
| ***Adverse event special categories (causality not established)***<br>Uncommon: asymptomatic platelet decreases, parasitic infections |

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 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 7.

**Table 7: Most frequently reported adverse events regardless of causality in adult/adolescent asthma population (≥ 5% in either treatment group)**

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

**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

**Clinical trial experience in Chronic Idiopathic Urticaria (CIU)**

**Chronic Idiopathic Urticaria (CIU)**

**Summary of the safety profile**

The safety and tolerability of omalizumab were investigated with the doses of 75 mg, 150 mg and 300 mg every four weeks in 975 CIU patients, 242 of whom received placebo. 733 patients were treated with omalizumab for up to 12 weeks and 490 patients for up to 24 weeks. 175 and 412 patients were treated for up to 12 weeks and 87 and 333 patients were treated for up to 24 weeks at the recommended doses of 150 mg and 300 mg respectively.

During clinical studies with adult and adolescent patients (12 years of age and older) the most commonly reported adverse reactions observed were headache and nasopharyngitis.

**Tabulated summary of adverse reactions from the clinical studies at the recommended doses (150 mg and 300 mg)**

Adverse reactions (events occurring in ≥1% of patients in any treatment group and ≥2% more frequently in any omalizumab treatment group than in the placebo group after medical review) reported at the recommended doses (150mg and 300mg) in the three pooled Phase III studies are listed by MedDRA system organ class (Table 8). Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions listed first. The corresponding frequency category for each adverse reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data).

**Table 8 Adverse reactions from the pooled CIU safety database (day 1 to week 12) at the recommended doses**

| Adverse reactions (by MedDRA preferred term) | Omalizumab Studies Q4881g, Q4882g and Q4883g Pooled | | | Frequency category |
|---|---|---|---|---|
| | Placebo N=242 | 150 mg N=175 | 300 mg N=412 | |
| **Infections and infestations** | | | | |
| Nasopharyngitis | 17 (7.0%) | 16 (9.1%) | 27 (6.6%) | Common |
| Sinusitis | 5 (2.1%) | 2 (1.1%) | 20 (4.9%) | Common |
| Viral upper respiratory tract infection | 0 | 4 (2.3%) | 2 (0.5%) | Common |
| **Nervous system disorders** | | | | |
| Headache | 7 (2.9%) | 21 (12.0%) | 25 (6.1%) | Very common |
| **Musculo skeletal and connective tissue disorders** | | | | |
| Arthralgia | 1 (0.4%) | 5 (2.9%) | 12 (2.9%) | Common |

Additional events reported anytime during the day 1 to week 24 treatment period (studies Q4881g and Q4883g) that met the criteria of adverse reactions:Infections and infestations: upper respiratory tract infections (placebo 3.1%, 150 mg 3.4%, 300 mg 5.7%), urinary tract infection (placebo 1.8%, 150 mg 4.6%, 300 mg 2.4%).

Nervous system disorders: sinus headache (placebo 0%, 150 mg 2.3%, 300 mg 0.3%).

Musculoskeletal and connective tissue disorders: myalgia (placebo 0%, 150 mg 2.3%, 300 mg 0.9%), pain in extremity (placebo 0%, 150 mg 3.4%, 300 mg 0.9%), musculoskeletal pain (placebo 0%, 150 mg 2.3%, 300 mg 0.9%).

General disorders and administration site conditions: pyrexia (placebo 1.2%, 150 mg 3.4%, 300 mg 0.9%).

Injection site reactions: Injection site reactions occurred during the studies in more omalizumab-treated patients than placebo patients (2.7% at 300 mg, 0.6% at 150 mg, 0.8% with placebo). They included: swelling, erythema, pain, bruising, itching, bleeding and urticaria.

**Description of safety aspects of special interest pertinent to allergic asthma and CIU indications**

No relevant data was obtained in CIU studies that alter the safety profile of Xolair. The following information was obtained from the allergic asthma trials.

**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 initial clinical trials for adults and adolescents 12 years of age and older, 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 (0.5%) and the control group, (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 initial Xolair clinical trial programme was comparable to that reported in the general population (0.4%).

In a subsequent observational study comparing 5007 Xolair-treated and 2829 non-Xolair-treated patients followed for up to 5 years, the incidence rates of primary malignancies per 1000 patient years were 16.01 (295/18426 patient years) and 19.07 (190/9963 patient years), respectively, which does not indicate an increased malignancy risk (rate ratio 0.84, 95% confidence interval, 0.62-1.13). In a further analysis of randomized, double-blind, placebo-controlled clinical trials including 4254 patients on Xolair and 3178 patients on placebo, Xolair treatment was not associated with an increased malignancy risk based on incidence rates per 1000 patient years of 4.14 (14/3382 patient years) for Xolair treated patients and 4.45 (11/2474 patient years) for placebo patients (rate ratio 0.93, 95% confidence interval 0.39-2.27).

**Arterial Thromboembolic Events (ATE):** In controlled clinical trials and during interim analyses of an 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). In the final analysis of the observational study, a numerical imbalance of ATEs was observed for: transient ischemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause) while no notable numerical imbalance was observed for stroke. The rate of ATE per 1000 patient years was 7.52 (115/15286 patients years) for Xolair-treated patients and 5.12 (51/9963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% confidence interval 0.91-1.91). In a new analysis of pooled clinical trials including all randomized double-blind, placebo-controlled clinical trials of 8 or more weeks duration, the rate of ATE per 1000 patient years was 2.69 (5/1856 patients years) for Xolair-treated patients and 2.38 (4/1680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71).

**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.

# DOSAGE AND ADMINISTRATION

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

Treatment is intended to be administered by a healthcare provider only (see PRECAUTIONS – Allergic Reactions).

## Dosage for allergic asthma

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 9).

**Table 9: Xolair doses for adults and adolescents (12 years of age and older) with allergic asthma, subcutaneous administration.**

| **Baseline IgE (IU/mL)** | Total milligrams of Xolair required per 4-week interval Body Weight (kg) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **>30–40** | **>40–50** | **>50–60** | **>60–70** | **>70–80** | **>80–90** | **>90–150** |
| **>30–100** | 150 | 150 | 150 | 150 | 150 | 150 | 300 |
| **>100–200** | 150 | 300 | 300 | 300 | 300 | 300 | 450 |
| **>200–300** | 300 | 300 | 300 | 450 | 450 | 450 | 600 |
| **>300–400** | 300 | 450 | 450 | 450 | 600 | 600 | |
| **>400–500** | 450 | 450 | 600 | 600 | 750 | 750 | |
| **>500–600** | 450 | 600 | 600 | 750 | | | |
| **>600–700** | 450 | 600 | 750 | | | | |
| **>700–800** | 600 | 750 | Note: | | | | |
| **>800–900** | 600 | 750 | Doses £300 mg per 4-week interval are administered | | | | |
| **>900–1000** | 750 | | once per 4 weeks. | | | | |
| **>1000–1100** | 750 | | Doses >300 mg per 4-week interval are split into | | | | |
| **>1100–1200** | | | 2 equal doses administered every 2 weeks (i.e. 600 mg | | | | |
| **>1200–1300** | | | 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:

BW (kg) x baseline IgE (IU/mL) x 0.008 mg/kg/(IU/mL) = 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.

**Table 10: Number of injections and total injection volumes.**

| Dose (mg) | Number of vials | | Number of injections | Total volume injected (mL)[a] |
|---|---|---|---|---|
| | 75 mg | 150 mg | | |
| 75 | 1 | 0 | 1 | 0.6 |
| 150 | 0 | 1 | 1 | 1.2 |
| 225 | 1 | 1 | 2 | 1.8 |
| 300 | 0 | 2 | 2 | 2.4 |
| 375 | 1 | 2 | 3 | 3.0 |

1.2 mL = maximum volume delivered per vial.

**Table 11 Conversion from dose to number of syringes, number of injections and total injection volume for each administration**

| Dose (mg) | Number of syringes | | Number of injections | Total injection volume (mL) |
|---|---|---|---|---|
| | 75 mg | 150 mg | | |
| 75 | 1 | 0 | 1 | 0.5 |
| 150 | 0 | 1 | 1 | 1.0 |
| 225 | 1 | 1 | 2 | 1.5 |
| 300 | 0 | 2 | 2 | 2.0 |
| 375 | 1 | 2 | 3 | 2.5 |

For doses of 225 or 375 mg. Xolair 150 mg should be used in combination with Xolair 75 mg.

**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 one year 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.

**Dosage for Chronic Idiopathic Urticaria (CIU)**

The recommended dose is 300 mg by subcutaneous injection every four weeks. Some patients may achieve control of their symptoms with a dose of 150 mg every four weeks.

Prescribers are advised to periodically reassess the need for continued therapy.

Clinical trial experience of long-term treatment beyond 6 months in this indication is limited.

Xolair should be used as add-on therapy to H1 antihistamine treatment.

**Administration of Xolair**

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

**Xolair powder vial and solvent for solution for injection**

Xolair is for single use in one patient only and contains no antimicrobial agent.

For Xolair 75 mg vials:

1. Draw 0.9 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 to 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 0.6 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 0.6 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.
8. The injections are administered subcutaneously in the deltoid region of the arm or the thigh, avoiding urticarial lesions.

The vial delivers 0.6 mL (75 mg) of omalizumab.

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.
8. The injections are administered subcutaneously in the deltoid region of the arm or the thigh, avoiding urticarial lesions.

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.

**Xolair pre-filled syringe**

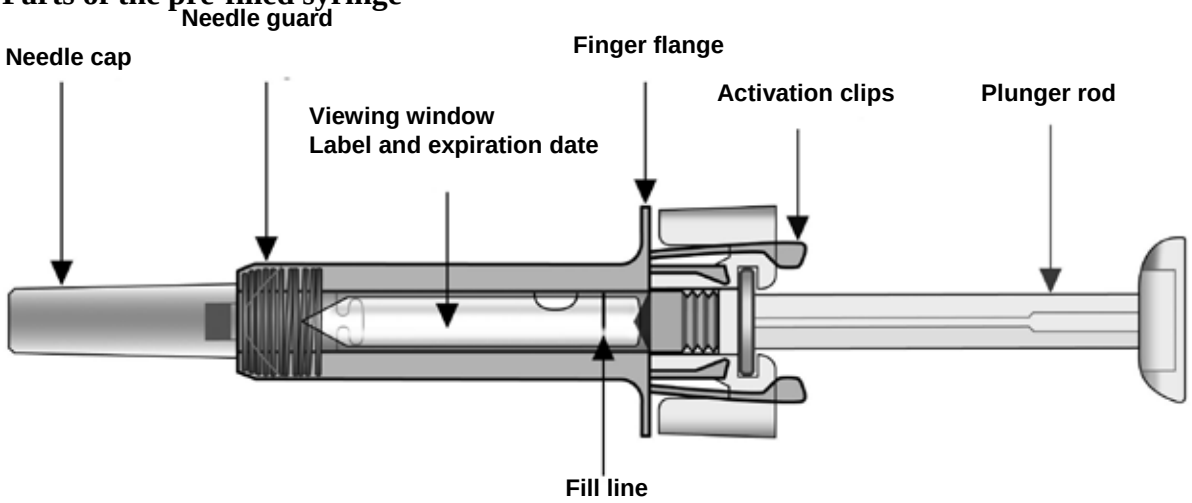
The following information is intended for medical or healthcare professionals only.

Before using the syringe, please read the following information carefully.

Each Xolair pack contains a pre-filled syringe individually sealed in a plastic wrapper.

Xolair is for single use in one patient only and contains no antimicrobial agent.

**Parts of the pre-filled syringe**




**Important Safety Information**

**Caution: Keep the syringe out of the reach of children.**

1. The needle cap of the syringe may contain dry rubber (latex), which should not be handled by persons sensitive to this substance.
2. Do not open the sealed outer box until you are ready to use the syringe.

3. Do not use the syringe if either the seal on the outer box or the plastic wrapper is broken, as it may be not safe for you to use.
4. Never leave the syringe where others might tamper with it.
5. Be careful not to touch the device activation clips (see first illustration) at any time. By touching them, the safety device may self-activate.
6. Do not remove the needle cap until just before you give the injection.
7. The syringe cannot be re-used. Dispose of the used syringe immediately after use.

**Storage of the pre-filled syringe**

1. Store the syringe sealed in its outer box in the refrigerator between 2°C and 8°C (36°F and 46°F). DO NOT FREEZE.
2. Take the syringe out of the refrigerator and allow it to reach room temperature before preparing it for injection (about 20 minutes).
3. Do not use the syringe after the expiration date shown on the outer box or syringe label. If it has expired, return the entire pack to the pharmacy.

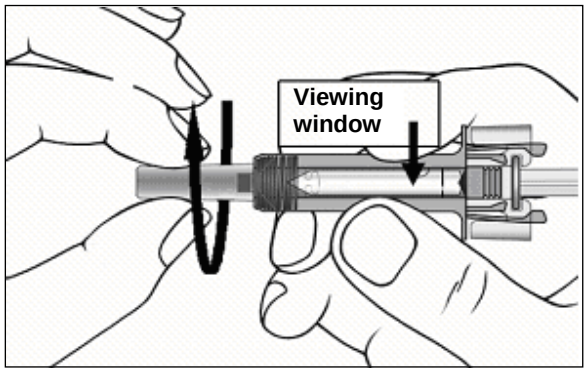
**The Injection Site**

The injection site is the place on the body where you are going to use the syringe. Xolair can be injected in either the upper outer thigh or the upper outer arm. If you need more than one injection at a time, repeat the injection in another location (e.g. the opposite thigh or arm).

**Preparing the syringe for use**

**Warning: Prior to completion of the injection, avoid contact with the device activation clips (see first illustration) to keep from prematurely covering the needle with the needle guard.**

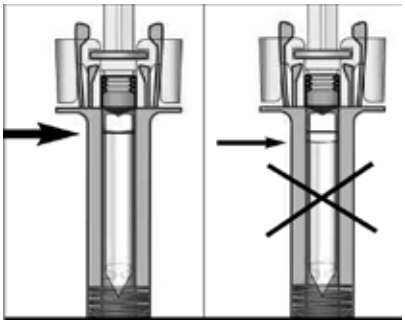
1. Take the box containing the syringe out of the refrigerator and leave it unopened for about 20 minutes so that it reaches room temperature.
2. If necessary, the syringe can be returned to the refrigerator for use at a later time, but this must not be done more than once. The cumulative time during which the syringe is kept at room temperature must not exceed 4 hours.
3. When you are ready to use the syringe, wash your hands thoroughly with soap and water.
4. Clean the injection site.
5. Remove the plastic tray from the box, peel back the paper cover, and remove the syringe.
6. Inspect the syringe. DO NOT USE if it is broken or if the liquid looks cloudy or contains particles. In all these cases, return the entire product pack to the pharmacy.
7. Hold the syringe horizontally as shown below, look into the viewing window to check the dose (75 mg or 150 mg) of medicine and the expiration date printed on the label. Note: Rotate the internal syringe as shown below so the label can be read in the viewing window.




DO NOT USE if the product has expired or if the dose is incorrect. In either case, return the entire product pack to the pharmacy.

8. Hold the syringe vertically with the plunger uppermost and tap the side of the syringe against your finger to allow the air bubble to rise.

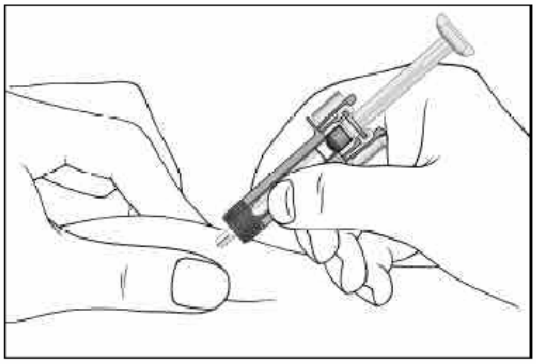
9. Check to see if the liquid level is at or above the minimum fill line. If the liquid is below the fill line, return the entire pack to the pharmacy.



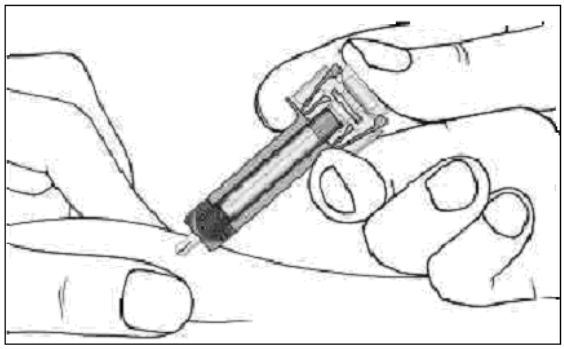
**How to use the syringe**

Step 1: Holding the syringe with the needle pointing up, carefully pull off the needle cap from the syringe and discard it. Do not touch the exposed needle. Then, gently tap the syringe with your finger until the air bubble rises to the top of the syringe. Slowly push the plunger up to force the air bubble out of the syringe without inadvertently expelling solution.

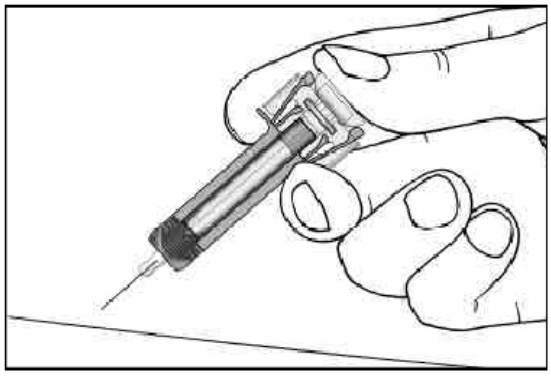
Step 2: Gently pinch the skin at the injection site. Insert the needle into the skin fold.



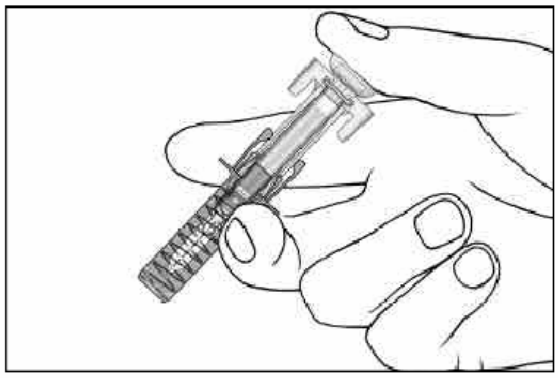
Step 3: Holding onto the finger flange, slowly press the plunger all the way down until all the solution is injected.



Step 4: After the complete dose is given, remove the needle from the skin while holding the plunger down.



Step 5: Slowly release the plunger and allow the needle guard to automatically cover the exposed needle.



NOTE: If the needle guard does not extend automatically, firmly push on the plunger. Then release the plunger and allow the guard to cover the needle.

Step 6: Dispose the used syringe immediately in a sharps container.

**Incompatibilities:**

**Powder vial and solvent for solution for injection:** Xolair should not be mixed with any other medicinal product or diluent other than water for injections.

**Solution for injection in pre-filled syringe:** This medicinal product must not be mixed with other medicinal products.

## 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

## PRESENTATION AND STORAGE CONDITIONS

**Powder vial and solvent for solution for injection:** Xolair is supplied as a pack containing 1 single-use vial of either 75 mg or 150 mg sterile, lyophilised powder and 1 ampoule of water for injections for use as diluent. Upon reconstitution, both Xolair 75 mg and 150 mg contain 150 mg omalizumab per 1.2 mL (125 mg/mL of omalizumab).

**Solution for injection in pre-filled syringe:** Pre-filled syringe comprising a type I glass syringe barrel with staked needle (stainless steel), rubber plunger stopper, and rigid needle shield composed of a rubber needle shield covered by a rigid shell. Each pre-filled syringe is mounted with a plastic safety device (needle guard) to prevent from needle stick injury. Each pre-filled syringe of 0.5 mL contains 75 mg of omalizumab. Each pre-filled syringe of 1 mL contains 150 mg of omalizumab. Available as a single packaged pre-filled syringe and in multipacks containing either 4 or 10 individually packaged pre-filled syringes.

Not all pack sizes and presentations may be marketed.

Storage:

**Powder vial and solvent for solution for injection:** Store at 2° to 8°C. Do not freeze. Store in the original package. Medicines should be kept out of the reach of children.

**Solution for injection in pre-filled syringe:** Store at 2° to 8°C. Do not freeze. Store in the original package. The product may be kept for a total of 4 hours at 25°C. If necessary, the product may be returned to the refrigerator for later use, but this must not be done more than once. Medicines should be kept out of the reach of children.

## NAME AND ADDRESS OF THE SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
NORTH RYDE NSW 2113
Ò= Registered Trademark

## POISON SCHEDULE OF THE MEDICINE

Poison schedule: 4

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS: 13 June 2003

## DATE OF MOST RECENT AMENDMENT: 11 November 2014

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