XOLAIR®
Omalizumab
75 mg* and 150 mg powder and solvent for solution for injection

75 mg*, 150 mg solution for injection in pre-filled syringe

* Not marketed strength or dosage form

1. PRODUCT NAME

Xolair 75 mg powder vial and solvent for solution for injection

Xolair 150 mg powder vial and solvent for solution for injection

Xolair 75 mg solution for injection in pre-filled syringe

Xolair 150 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder and solvent for solution for injection:

One vial of Xolair 75 mg powder and solvent for solution for injection contains 75 mg of omalizumab. Reconstituted Xolair contains 125 mg/mL of omalizumab (75 mg in 0.6 mL).

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

Solution for injection:

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.

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection:

Powder: white to off-white lyohilizate in a glass vial.
Solvent: clear and colorless solution in a glass ampoule

Solution for injection:

Clear to slightly opalescent, colorless to pale brownish-yellow solution in a pre-filled syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergic Asthma

Xolair (omalizumab) is indicated for the reduction of asthma exacerbations and control of asthma symptoms when given as add-on therapy for adult and adolescent patients, 6 years and older, with severe persistent allergic asthma who have IgE ≥ 30 IU/mL, a positive skin test or in

vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

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.

4.2 Dose and method of administration

Treatment is intended to be administered by a healthcare provider only (see section 4.4).

Dosage for Allergic Asthma

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

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

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

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

Dose (mg)	Number of vials 75 mg[a]	Number of vials 150 mg [b]	Number of injections	Total injection volume (mL)
150	0	1	1	1.2
225	1[c]	1	2	1.8
300	0	2	2	2.4
375	1[c]	2	3	3.0
450	0	3	3	3.6
525	1[c]	3	4	4.2
600	0	4	4	4.8

[a] *0.6 mL = maximum delivered volume per vial (Xolair 75 mg).*
[b] *1.2 ml = maximum delivered volume per vial (Xolair 150 mg) or use 0.6 mL from a 150 mg vial.*
[c] or use 0.6 mL from a 150 mg vial.

Table 2 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
450	0	3	3	3.0
525	1	3	4	3.5
600	0	4	4	4.0

Treatment duration, monitoring and dose adjustments

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

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

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

Doses should be adjusted for significant changes in body weight (see Tables 3 and 4).

Table 3 ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 weeks

Baseline IgE (IU/ml)	Body weight (kg)									
	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30–100	75	75	75	150	150	150	150	150	300	300
>100–200	150	150	150	300	300	300	300	300	450	600
>200–300	150	150	225	300	300	450	450	450	600	
>300–400	225	225	300	450	450	450	600	600		
>400–500	225	300	450	450	600	600				
>500–600	300	300	450	600	600	ADMINISTRATION EVERY 2 WEEKS				
>600–700	300		450	600	SEE TABLE 4					

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

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

In allergic asthma, safety and efficacy in paediatric patients below the age of 6 have not been established and use of Xolair in such patients is therefore not recommended.

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.

Special populations

Elderly population

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

Paediatric population

In allergic asthma, safety and efficacy in paediatric patients below the age of 6 have not been established and use of Xolair in such patients is therefore not recommended.

In chronic idiopathic urticaria, safety and efficacy in paediatric patients below the age of 12 years have not been established.

Method of administration

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

The injections are administered subcutaneously in the deltoid region of the arm. Alternatively, the injections can be administered in the thigh if there is any reason precluding administration in the deltoid region.

Treatment is intended to be administered by a healthcare provider only.

For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

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

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

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

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

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

Anaphylaxis

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

Xolair should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Patients should be closely observed for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports (see section 4.8). Patients should be informed of the signs and symptoms of anaphylaxis, and instructed to seek immediate medical care should signs or symptoms occur.

Xolair should be discontinued in patients who experience a severe hypersensitivity reaction (see Contraindications in section 4.3).

Allergic reactions

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

Parasitic infections

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

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.

4.5 Interaction with other medicines and other forms of interaction

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

Allergic Asthma

In clinical studies Xolair was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta2-agonists, leukotriene modifiers, theophyllines and

oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used asthma medications. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy).

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 section 5).

4.6 Fertility, pregnancy and lactation

Women of Child-bearing potential

There are no special recommendations for women of child-bearing potential.

Pregnancy

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

Reproduction studies in cynomolgus monkeys have been conducted with omalizumab. Subcutaneous doses up to 75 mg/kg per week (at least 8-fold the highest recommended clinical dose in mg/kg over a 4-week period) of omalizumab did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on foetal or neonatal growth when administered throughout late gestation, delivery and nursing.

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

Breastfeeding

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

The excretion of omalizumab in milk was evaluated in female cynomolgus monkeys receiving subcutaneous doses of 75 mg/kg/week. Neonatal serum levels of omalizumab after *in utero* exposure and 28 days of nursing were between 11% and 94% of the maternal serum level. Milk levels of omalizumab were 0.15% of the maternal serum concentration.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Allergic Asthma

Clinical trials experience

The most serious adverse reactions occurring in clinical trials with Xolair were anaphylaxis and malignancies (see section 4.4). Anaphylaxis was reported in 3 of 3507 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

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

Table 5 lists the adverse reactions recorded in clinical studies in the total allergic asthma safety population treated with Xolair by system organ class and by frequency. Frequencies are defined as: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) very rare (<1/10,000).

Table 5 Adverse reactions from the clinical studies

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

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

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

Post-marketing observations

The following reactions have been identified through spontaneous reporting.

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

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

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

Immune system disorders (see section 4.4): Serum sickness.

Skin and subcutaneous disorders: Alopecia.

Blood and lymphatic system disorders: Idiopathic severe thrombocytopenia.

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

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

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 6). 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 6 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.

Anaphylaxis

In post-marketing reports, the frequency of anaphylaxis in patients exposed to Xolair use was estimated to be 0.2% based on a total number of anaphylactic reactions observed from an estimated exposure of over 500,000 patient years.
A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

Malignancies

During initial clinical trials in adults and adolescents 12 years of age and older, there was a numerical imbalance in cancers arising in the active treatment group, compared with the control group. The number of observed cases was uncommon (<1/100) in both the active and the control group. In a subsequent observational study comparing 5,007 Xolair-treated and 2,829 non-Xolair-treated patients followed for up to 5 years, the incidence rates of primary malignancies per 1,000 patient years were 16.01 (295/18,426 patient years) and 19.07 (190/9,963 patients years), respectively, which does not indicate an increased malignancy risk (rate ratio 0.84, 95% confidence interval, 0.62 to 1.13). In a further analysis of randomized, double-blind, placebo-controlled clinical trials including 4,254 patients on Xolair and 3,178 patients on placebo, Xolair treatment was not associated with an increased malignancy risk based on incidence rates per 1,000 patient years of 4.14 (14/3,382 patient years) for Xolair treated patients and 4.45 (11/2,474 patient years) for placebo patients (rate ratio 0.93, 95% confidence interval 0.39 to 2.27). The overall observed incidence rate of malignancy in the Xolair clinical trial programme was comparable to that reported in the general population.

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

Arterial Thromboembolic Events (ATE)

In controlled clinical trials and 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, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patients years) for Xolair-treated patients and 5.12 (51/9,963 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 to 1.91). In a separate 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 1,000 patient years was 2.69 (5/1,856 patients years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24 to 5.71).

Platelets

In clinical trials few patients experienced platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in haemoglobin. No pattern of persistent decrease in platelet counts has been reported in humans (patients greater than 6 years of age), as was observed in non-human primates (see section 5.3).

Parasitic infections

In allergic patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight numerical increase in infection rate with omalizumab that was not statistically significant. The course, severity, and response to treatment of infections was unaltered (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

General characteristics

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 murine parent 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 cross-linked by allergen. This results in the degranulation of these effector cells and the release of histamines, leukotrienes, cytokines and other mediators. These mediators are causally linked to the pathophysiology of allergic asthma including airway oedema, smooth muscle contraction and altered cellular activity associated with the inflammatory process. They also contribute to the signs and symptoms of allergic disease such as bronchoconstriction, mucus production, wheezing, dyspnoea, chest tightness, nasal congestion, sneezing, itchy, runny nose and itchy, watery eyes.

Mechanism of action

Omalizumab binds to IgE and prevents binding of IgE to the high-affinity FcεRI receptor, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils.

Pharmacodynamic effects

The *in vitro* histamine release from basophils isolated from Xolair treated subjects was reduced by approximately 90% following stimulation with an allergen compared to pre-treatment values.

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

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.

Mechanism of action

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.

Pharmacodynamic effect

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

Clinical efficacy and safety in Allergic Asthma

Adults and adolescents > 12 years of age

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

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

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

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

In studies 1 and 2, clinically meaningful improvement in asthma-related quality of life, measured by the validated Juniper's Asthma Quality of Life Questionnaire, was demonstrated in the Xolair

group at the end of the 28-week core trial compared to that observed in the placebo treated group (difference from placebo p ≤0.001 in studies 1 and 2).

In study 3 the safety and corticosteroid-sparing effect of omalizumab was demonstrated in 246 patients with severe allergic asthma requiring daily treatment with high-dose inhaled corticosteroids (fluticasone ≥1,000 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.

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

The co-primary endpoints for study 4 were the incidence of asthma exacerbations (worsening of asthma requiring systemic corticosteroids or a doubling of the patient's baseline budesonide dose) and the proportion of patients in each treatment group with a ≥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 study 5 the efficacy and safety of Xolair were demonstrated in a 28-week study involving 419 severe allergic asthmatics, ages 12 to 79 years, who had reduced lung function (Forced Expiratory Volume/1 second: FEV_1 40 to 80% predicted) and poor asthma symptom control despite receiving >1,000 micrograms of beclomethasone dipropionate (or equivalent) plus long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone diproprionate (or equivalent) plus long-acting beta2-agonist. Oral corticosteroid (22%), theophylline (27%) and anti-leukotriene (35%) maintenance therapies were allowed. In the treatment phase concomitant asthma therapy was not changed.

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

judged to have achieved either a marked improvement or complete control of their asthma compared to placebo patients.

Children 6 to <12 years of age

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

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

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

Exacerbation rates during the 52-week double-blind treatment period in Xolair patients with FEV_1 >80% at baseline had relative decreases of 43% in asthma exacerbations compared with placebo ($p<0.001$). Xolair patients had statistically significant reduction in the rate of asthma exacerbations irrespective of concomitant long-acting beta2-agonist use at baseline compared with placebo patients, representing a 45% decrease for long-acting beta2-agonist users and a 42% decrease for long-acting beta2-agonist non-users ($p<0.001$ and $p=0.011$, respectively).

Study 7 was a 28 week randomized, double blind, placebo-controlled study primarily evaluating safety in 334 children, aged 6-12 years of age, with asthma who were well controlled with inhaled corticosteroids. During the first 16 weeks of treatment, patients' steroid doses remained constant from baseline and this was followed by a 12 week steroid dose reduction period. The study assessed percent reduction in the dose of beclomethasone dipropionate (BDP) and the proportion of patients with a reduction in the dose of BDP at 28 weeks. The percent reduction in the dose of BDP at 28 weeks was higher in the Xolair group than in the placebo group (median reduction 100% vs. 66.7%, $p=0.001$) as well as the proportion of patients with a reduction in the dose of BDP ($p=0.002$). Frequency and incidence of asthma exacerbation episodes during the steroid dose-reduction phase were also lower in the omalizumab group (mean rate 0.42 vs. 0.72, $p<0.001$; percent patients with exacerbations 18% vs. 39%, $p<0.001$). A trend for superiority of omalizumab with respect to reduction of exacerbation frequency and incidence was evident during the first 16 weeks of the 24 week treatment period. 55.7% omalizumab patients had a complete (100%) reduction in corticosteroid dose at the end of the 28 week treatment period compared with a 43.2% of placebo patients. In addition, more omalizumab patients had a ≥50% reduction in corticosteroid dose compared with placebo (80.4% vs. 69.5%. $p=0.017$).

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

Clinical efficacy and safety in 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 to 42) of ≥16, and a weekly itch severity score (which is a component of the UAS7; range 0 to 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 7 Efficacy endpoints

Change from baseline to week 12 in weekly Itch Severity Score (ISS, range 0-21)	Primary endpoint in studies Q4881g and Q4882g 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 (secondary endpoint; see Table 8).

Table 8 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.

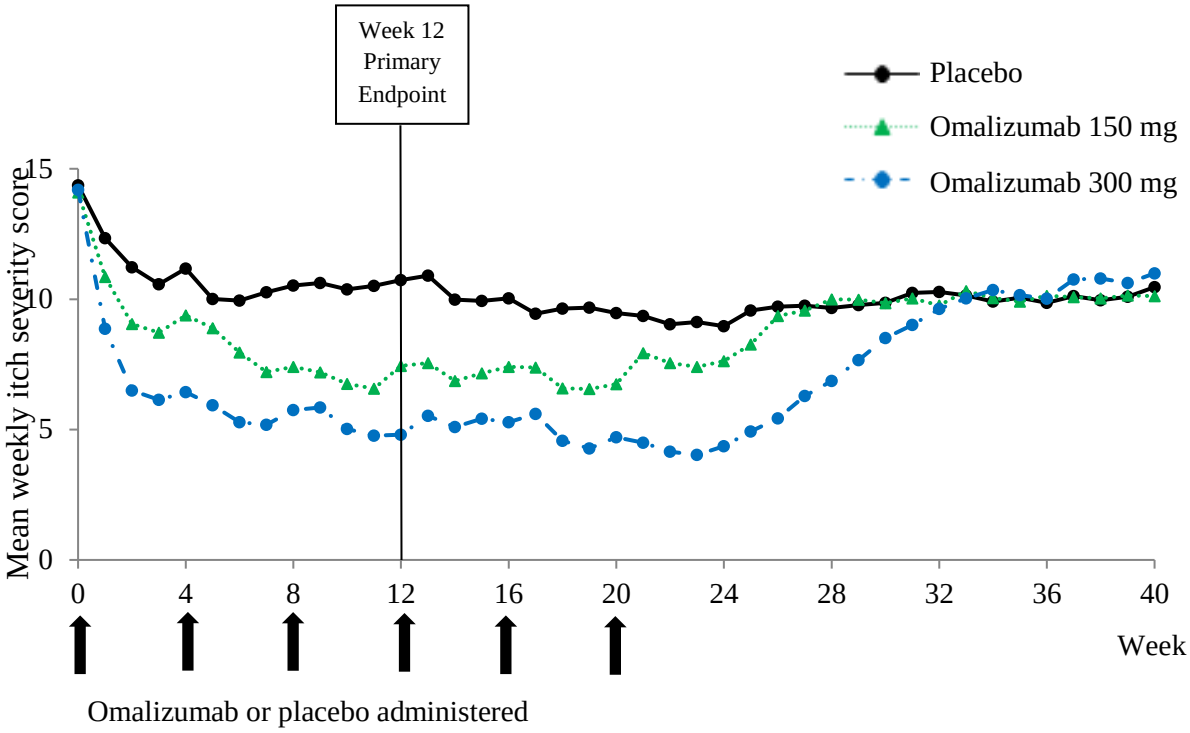
[1] The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (< 13 vs. ≥13) and baseline weight (< 80 kg vs. ≥ 80 kg).

[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 9.

Table 9 ***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)

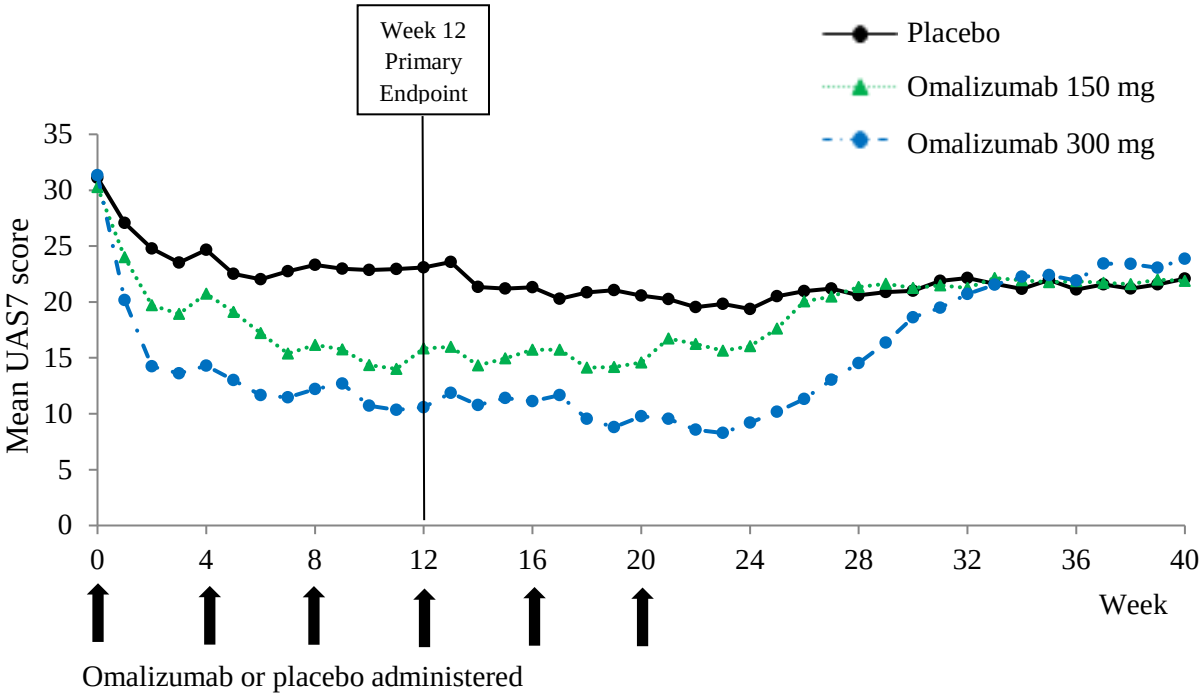
	Placebo	Omalizumab 150mg	Omalizumab 300mg
Q4882g	-10.36	-17.89 (p = 0.0001)	-21.74 (p<0.0001)
Q4883g	-8.50	NA	-19.01 (p<0.0001)
Changes from baseline in the weekly number of hives score at week 12 (mean)			
Q4881g	-4.37	-7.78 (p=0.0017)	-11.35 (p<0.0001)
Q4882g	-5.22	-9.75 (p<0.0001)	-11.97 (p<0.0001)
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 10 shows the results after 24 weeks of treatment. Similar magnitudes of response are seen as at 12 weeks.

Table 10 ***Efficacy results after 24 weeks of treatment, Studies Q4881g and Q4883g (mITT population*)***

Parameter 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.

5.2 Pharmacokinetic properties

General characteristics

Absorption

After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg.

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. Precipitating complexes and complexes larger than one million Daltons in molecular weight are not observed *in vitro* or *in vivo*.

Tissue distribution studies in cynomolgus monkeys showed no specific uptake of ^{125}I-omalizumab by any organ or tissue.

Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the liver reticuloendothelial system (RES) and endothelial cells. Intact IgG is also excreted in bile. In studies with mice and monkeys, omalizumab: IgE complexes were eliminated by interactions with Fcγ receptors within the RES at rates that were generally faster than IgG clearance.

Patients with Allergic Asthma

Absorption

Following a single subcutaneous dose in adult and adolescent patients with asthma, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7 to 8 days. Following multiple doses of omalizumab, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose.

Distribution

The apparent volume of distribution of omalizumab in patients with asthma following subcutaneous administration was 78 ± 32 mL/kg.

Elimination

In asthma patients omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4 ± 1.1 mL/kg/day. Doubling of body weight approximately doubled apparent clearance.

Age, Race/Ethnicity, Gender, Body Mass Index

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

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 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 section 4.4).

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder and solvent for solution for injection:

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

Solvent: Water for injection

Solution for injection in pre-filled syringe:

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

6.2 Incompatibilities

Powder and solvent for solution for injection: Xolair should not be mixed with any medication or diluents other than sterile water for injection.

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

6.3 Shelf life

Powder and solvent for solution for injection:

4 years

After reconstitution:

Reconstituted solution should be used within 8 hours when stored at 2-8°C or 2 hours when stored below 25°C.

Solution for injection in pre-filled syringe:

18 months

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze.

Store in original package In order to protect from light.

6.5 Nature and contents of container

Powder and solvent for solution for injection:

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

Powder vial:	Clear, colourless type I glass vial with stopper and grey (75 mg) or blue (150 mg) flip-off seal.
Solvent ampoule:	Clear, colourless type I glass ampoule containing 2 mL water for injection.

Solution for injection in pre-filled syringe:

Pre-filled syringe comprising a type I glass syringe barrel with staked needle (stainless steel), latex-free rubber plunger stopper, and rigid needle shield composed of a latex-free 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.

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 may be marketed.

6.6 Special precautions for disposal and other handling

Xolair 75 mg and 150 mg powder for solution for injection is supplied in a single-use vial and contains no antibacterial preservatives. Chemical and physical stability of the reconstituted product has been demonstrated for 8 hours at 2°C to 8°C and for 4 hours at 30°C. From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 8 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

The lyophilized product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted product will appear clear or slightly opaque and may have a few small bubbles or foam around the edge of the vial. Because the reconstituted product is somewhat viscous, care must be taken to WITHDRAW ALL OF THE PRODUCT from the vial before expelling any air or excess solution from the syringe in order to obtain the full 0.6 mL or 1.2 mL dose.

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

Xolair 150 mg vials

1. Draw 1.4 mL of water for injection from the ampoule into a syringe equipped with a large-bore 18-gauge needle.

2. With the vial placed upright on a flat surface, insert the needle and transfer the water for injections into the omalizumab vial using standard aseptic techniques, directing the water for injections directly onto the powder.

3. Keeping the vial in an upright position, vigorously swirl the upright vial (do not shake) for approximately 1 minute to evenly wet the powder.

4. To aid in dissolution after completing step 3, gently swirl the upright vial for 5 to10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

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

  When the product is fully dissolved, there should be no visible gel-like particles in the solution. It is acceptable to have small bubbles or foam around the edge of the vial. The reconstituted product will appear clear or slightly opaque. Do not use if foreign particles are present.

5. Invert the vial for 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-cc syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.

6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

7. Expel air, large bubbles, and any excess solution in order to obtain the required 1.2 mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, the injection may take 5 to10 seconds to administer. The vial delivers 1.2 mL (150 mg) of Xolair.

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

For Xolair 75 mg vials.

1. Draw 0.9 mL of water for injections from the ampoule into a syringe equipped with a large-bore 18-gauge needle.

2. With the vial placed upright on a flat surface, insert the needle and transfer the water for injections into the omalizumab vial using standard aseptic techniques, directing the water for injections directly onto the powder.

3. Keeping the vial in an upright position, vigorously swirl the upright vial (do not shake) for approximately 1 minute to evenly wet the powder.

4. To aid in dissolution after completing step 3, gently swirl the upright vial for 5-10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

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

     When the product is fully dissolved, there should be no visible gel-like particles in the solution. It is acceptable to have small bubbles or foam around the edge of the vial. The reconstituted product will appear clear or slightly opaque. Do not use if foreign particles are present.

5. Invert the vial for 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-cc syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to **remove all of the solution** from the inverted vial.

6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

7. Expel air, large bubbles, and any excess solution in order to obtain the required 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. The vial delivers 0.6 mL (75 mg) of Xolair.

8. The injections are administered subcutaneously in the deltoid region of the arm or the thigh.

Disposal instructions

Dispose of the used syringe immediately in a sharps container.

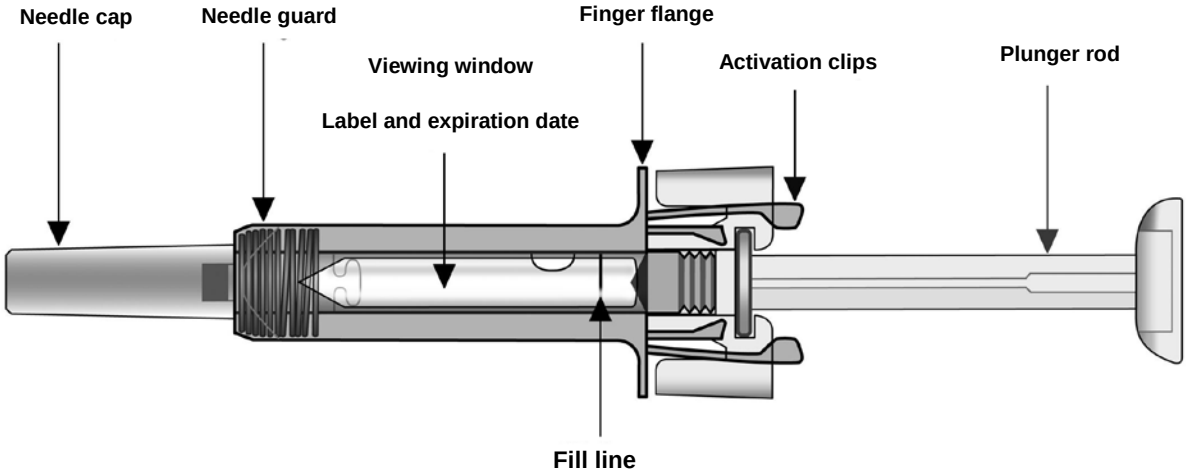
Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling - *Xolair solution for injection in 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.

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. 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.

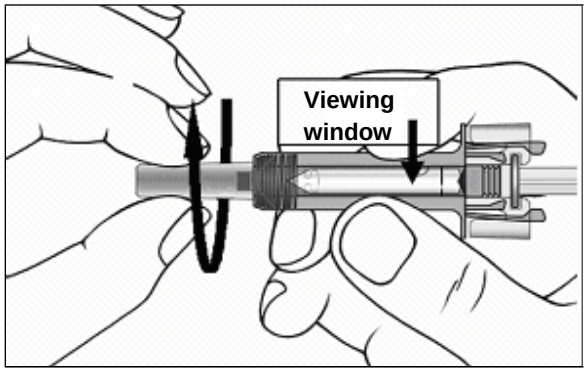
The Injection Site

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 the opposite thigh or arm, avoiding urticarial lesions.

Preparing the syringe for use

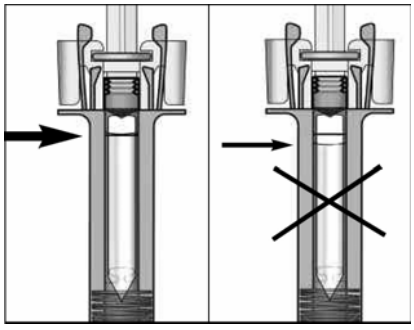
Warning: Prior to completion of the injection, avoid contact with the device activation clips (see first illustration) to keep from prematurely covering the needle with the needle guard.

1. Take the box containing the syringe out of the refrigerator and leave it for about 20 minutes so that it reaches room temperature (leave the syringe in the box to protect it from light).
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 (25°C) 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.



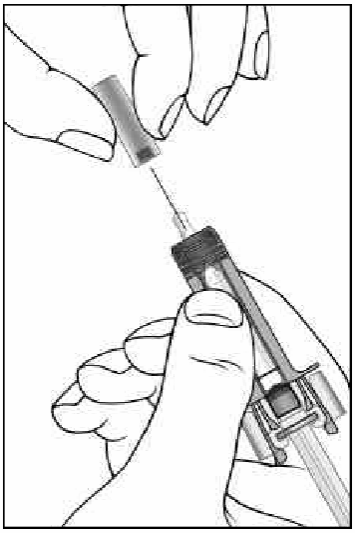
DO NOT USE if the product has expired or if the dose is incorrect. In either case, return the entire product pack to the pharmacy.

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.

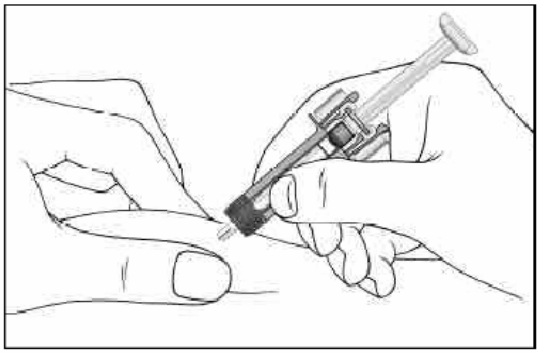


How to use the syringe

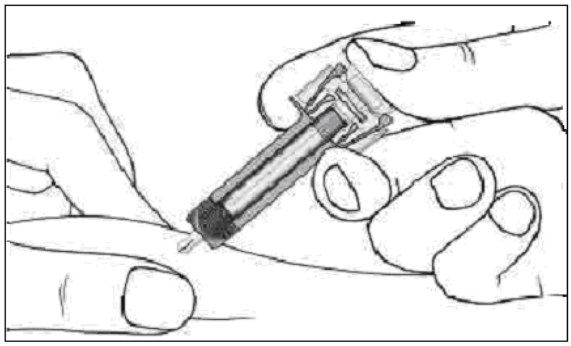
Step 1: Holding the syringe with the needle pointing upwards, carefully pull off the needle cap from the syringe and discard it. Do not touch the exposed needle. Then, gently tap the syringe with your finger until the air bubble rises to the top of the syringe. Slowly push the plunger up to force the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



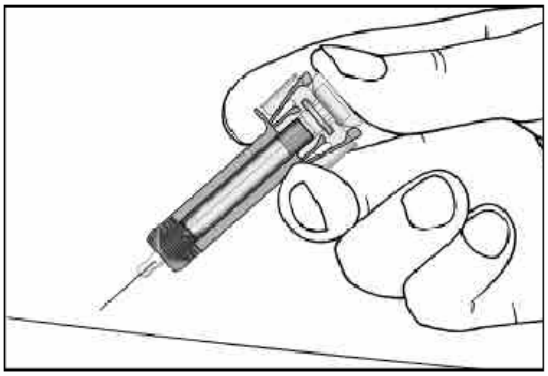
Step 2: Gently pinch the skin at the injection site. Insert the needle into the skin fold.



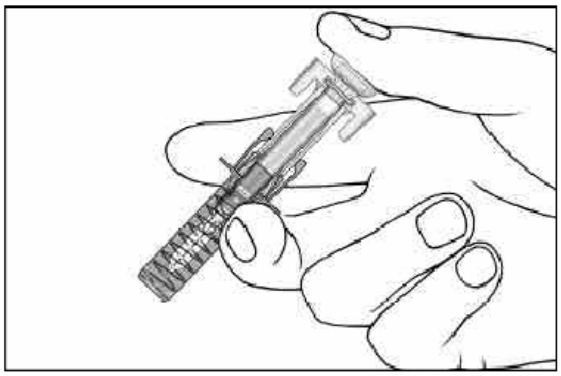
Step 3: Holding onto the finger flange, slowly press the plunger all the way down until all the solution is injected.



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.

Disposal instructions

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket

Auckland 1149

Telephone: 0800 354 335

9. DATE OF FIRST APPROVAL

Xolair injection with diluent: 24 September 2004

Xolair solution for injection, pre-filled syringe: 10 August 2017

10. DATE OF REVISION OF THE TEXT

11 August 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 8 Sponsor	Removed Sponsor's old address

Internal document code: xol280820iNZ based on CDS 22-July-2015