ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 75 mg of omalizumab*.

After reconstitution one vial contains 125 mg/ml of omalizumab (75 mg in 0.6 ml).

*Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: white to off-white lyophilisate
Solvent: clear and colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xolair is indicated in adults, adolescents and children (6 to <12 years of age).

Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

Adults and adolescents (12 years of age and older)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Children (6 to <12 years of age)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

4.2 Posology and method of administration

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma.

Posology
The appropriate dose and frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, 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.

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that adult and adolescent patients with IgE below 76 IU/ml and children (6 to < 12 years of age) with IgE below 200 IU/ml have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting therapy.

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts in adults, adolescents and children (6 to <12 years of age).

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

The maximum recommended dose is 600 mg omalizumab every two weeks.

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

Dose (mg)	Number of vials		Number of injections	Total injection volume (ml)
	75 mg [a]	150 mg [b]		
75	1[c]	0	1	0.6
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).
[c] or use 0.6 ml from a 150 mg vial.

Table 2: ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 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
≥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					
>600-700	300		450	600						
>700-800										
>800-900										
>900-1000										
>1000-1100										

ADMINISTRATION EVERY 2 WEEKS
SEE TABLE 3

Table 3: ADMINSTRATION 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
≥30-100	ADMINISTRATION EVERY 4 WEEKS SEE TABLE 2									
>100-200										
>200-300										375
>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					
>1100-1200	300	300	450	525	600	DO NOT ADMINISTER– data is unavailable for dose recommendation				
>1200-1300	300	375	450	525						
>1300-1500	300	375	525	600						

Treatment duration, monitoring and dose adjustments
Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for Xolair treatment to show effectiveness. 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 following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician's overall assessment of treatment effectiveness).

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

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

Special populations

Elderly (65 years of age and older)

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 dose 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. 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 for these patients, Xolair should be administered with caution (see section 4.4).

Paediatric population

The safety and efficacy of Xolair in children below age 6 have not been established. No data are available.

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.

There is limited experience with self-administration of Xolair. Therefore treatment is intended to be administered by a healthcare provider only.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and also information for the healthcare professional section of the package leaflet.

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, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Xolair is not indicated for the treatment of these conditions.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). 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.

Immune system disorders

Allergic reactions type I

Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. Therefore medicinal products 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. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-Xolair antibodies is not well understood.

Serum sickness

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against 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/arthralgias, 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.

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 medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. 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.

Parasitic (helminth) infections

IgE may be involved in the immunological response to some helminth infections. In patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight increase in infection rate with omalizumab, although the course, severity, and response to treatment of infection were unaltered. The helminth infection rate in the overall clinical programme, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Since IgE may be involved in the immunological response to some helminth infections, Xolair may indirectly reduce the efficacy of medicinal products for the treatment of helminthic or other parasitic infections (see section 4.4).

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. Medicinal product or vaccine interaction studies have not been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma will interact with omalizumab.

In clinical studies Xolair was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where Xolair was co-administered with immunotherapy, the safety and efficacy of Xolair in combination with specific immunotherapy were found to be no different to that of Xolair alone.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether omalizumab is excreted in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Omalizumab should not be given during breast-feeding.

Fertility
There are no human fertility data for omalizumab. In specifically-designed non-clinical fertility studies in non-human primates, including mating studies, no impairment of male or female fertility was observed following repeated dosing with omalizumab at dose levels up to 75 mg/kg. Furthermore, no genotoxic effects were observed in separate non-clinical genotoxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Xolair has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
During clinical trials in 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 trials in children 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity.

Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Reactions reported in the post-marketing setting are listed with frequency not known (cannot be estimated from the available data).

Table 4: Adverse reactions

Infections and infestations	
Uncommon	Pharyngitis
Rare	Parasitic infection
Blood and lymphatic system disorders	
Not known	Idiopathic thrombocytopenia, including severe cases
Immune system disorders	
Rare	Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development
Not known	Serum sickness, may include fever and lymphadenopathy
Nervous system disorders	
Common	Headache*
Uncommon	Syncope, paraesthesia, somnolence, dizziness
Vascular disorders	
Uncommon	Postural hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	Allergic bronchospasm, coughing
Rare	Laryngoedema
Not known	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
Gastrointestinal disorders	
Common	Abdominal pain upper**
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
Skin and subcutaneous tissue disorders	
Uncommon	Photosensitivity, urticaria, rash, pruritus
Rare	Angioedema
Not known	Alopecia
Musculoskeletal and connective tissue disorders	
Rare	Systemic lupus erythematosus (SLE)
Not known	Arthralgia, myalgia, joint swelling
General disorders and administration site conditions	
Very common	Pyrexia**
Common	Injection site reactions such as swelling, erythema, pain, pruritus
Uncommon	Influenza-like illness, swelling arms, weight increase, fatigue

*: Very common in children 6 to <12 years of age

**: In children 6 to <12 years of age

Description of selected adverse reactions

Immune system disorders

For further information, see section 4.4.

Anaphylaxis

Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%.

Arterial thromboembolic events (ATE)
In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. The definition of the composite endpoint ATE included stroke, transient ischaemic 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 patient 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 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71).

Platelets
In clinical trials few patients had 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, as observed in non-human primates (see section 5.3), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

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

Systemic lupus erythematosus
Clinical trial and post-marketing cases of systemic lupus erythematosus (SLE) have been reported in patients with moderate to severe asthma and CSU. The pathogenesis of SLE is not well understood.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mechanism of action

Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE 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, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

Clinical efficacy and safety

Adults and adolescents ≥12 years of age

The efficacy and safety of Xolair were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12-79 years, who had reduced lung function (FEV_1 40-80% predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a 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 a long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22%, 27%, and 35% of patients, respectively).

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.

In a subgroup analysis, patients with pre-treatment total IgE ≥76 IU/ml were more likely to experience clinically meaningful benefit to Xolair. In these patients in study 1 Xolair reduced the rate of asthma exacerbations by 40% (p = 0.002). In addition more patients had clinically meaningful responses in the total IgE ≥76 IU/ml population across the Xolair severe asthma programme. Table 5 includes results in the study 1 population.

Table 5: Results of study 1

	Whole study 1 population	
	Xolair N=209	Placebo N=210
Asthma exacerbations		
Rate per 28-week period	0.74	0.92
% reduction, p-value for rate ratio	19.4%, p = 0.153	
Severe asthma exacerbations		
Rate per 28-week period	0.24	0.48
% reduction, p-value for rate ratio	50.1%, p = 0.002	
Emergency visits		
Rate per 28-week period	0.24	0.43
% reduction, p-value for rate ratio	43.9%, p = 0.038	
Physician's overall assessment		
% responders*	60.5%	42.8%
p-value**	<0.001	
AQL improvement		
% of patients ≥0.5 improvement	60.8%	47.8%
p-value	0.008	

* marked improvement or complete control
** p-value for overall distribution of assessment

Study 2 assessed the efficacy and safety of Xolair in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with Xolair in this open label study led to a 61% reduction in clinically significant asthma exacerbation rate compared to current asthma therapy alone.

Four additional large placebo-controlled supportive studies of 28 to 52 weeks duration in 1,722 adults and adolescents (studies 3, 4, 5, 6) assessed the efficacy and safety of Xolair in patients with severe persistent asthma. Most patients were inadequately controlled but were receiving less concomitant asthma therapy than patients in studies 1 or 2. Studies 3-5 used exacerbation as primary endpoint, whereas study 6 primarily evaluated inhaled corticosteroid sparing.

In studies 3, 4 and 5 patients treated with Xolair had respective reductions in asthma exacerbation rates of 37.5% (p = 0.027), 40.3% (p<0.001) and 57.6% (p<0.001) compared to placebo.

In study 6, significantly more severe allergic asthma patients on Xolair were able to reduce their fluticasone dose to ≤500 micrograms/day without deterioration of asthma control (60.3%) compared to the placebo group (45.8%, p<0.05).

Quality of life scores were measured using the Juniper Asthma-related Quality of Life Questionnaire. For all six studies there was a statistically significant improvement from baseline in quality of life scores for Xolair patients versus the placebo or control group.

Physician's overall assessment of treatment effectiveness:
Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), 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 group aged 6 to <12 years comes from one randomised, double-blind, placebo-controlled, multi-centre trial (study 7).

Study 7 was a placebo-controlled trial which included a specific subgroup (n=235) of patients as defined in the present indication, who were treated with high-dose inhaled corticosteroids (≥500 µg/day fluticasone equivalent) plus long-acting beta agonist.

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 intravenous) corticosteroids for at least 3 days.

In the specific subgroup of patients on high dose inhaled corticosteroids, the omalizumab group had a statistically significantly lower rate of clinically significant asthma exacerbations than the placebo group. At 24 weeks, the difference in rates between treatment groups represented a 34% (rate ratio 0.662, $p = 0.047$) decrease relative to placebo for omalizumab patients. In the second double-blind 28-week treatment period the difference in rates between treatment groups represented a 63% (rate ratio 0.37, $p<0.001$) decrease relative to placebo for omalizumab patients.

During the 52-week double-blind treatment period (including the 24-week fixed-dose steroid phase and the 28-week steroid adjustment phase) the difference in rates between treatment groups represented a 50% (rate ratio 0.504, $p<0.001$) relative decrease in exacerbations for omalizumab patients.

The omalizumab group showed greater decreases in beta-agonist rescue medication use than the placebo group at the end of the 52-week treatment period, although the difference between treatment groups was not statistically significant. For the global evaluation of treatment effectiveness at the end of the 52-week double-blind treatment period in the subgroup of severe patients on high-dose inhaled corticosteroids plus long-acting beta agonists, the proportion of patients rated as having 'excellent' treatment effectiveness was higher, and the proportions having 'moderate' or 'poor' treatment effectiveness lower in the omalizumab group compared to the placebo group; the difference between groups was statistically significant ($p<0.001$), while there were no differences between the omalizumab and placebo groups for patients' subjective Quality of Life ratings.

5.2 Pharmacokinetic properties

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

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

Administration of Xolair manufactured as a lyophilised 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*. The apparent volume of distribution in patients following subcutaneous administration was 78 ± 32 ml/kg.

Elimination
Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. In asthma patients the omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4 ± 1.1 ml/kg/day. In addition, doubling of body weight approximately doubled apparent clearance.

Characteristics in patient populations
Age, Race/Ethnicity, Gender, Body Mass Index
The population pharmacokinetics of Xolair were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for age (6-76 years), race/ethnicity, gender or Body Mass Index (see section 4.2).

Renal and hepatic impairment
There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

The safety of omalizumab has been studied in the cynomolgus monkey, since omalizumab binds to cynomolgus and human IgE with similar affinity. Antibodies to omalizumab were detected in some monkeys following repeated subcutaneous or intravenous administration. However, no apparent toxicity, such as immune complex-mediated disease or complement-dependent cytotoxicity, was seen. There was no evidence of an anaphylactic response due to mast-cell degranulation in cynomolgus monkeys.

Chronic administration of omalizumab at dose levels of up to 250 mg/kg (at least 14 times the highest recommended clinical dose in mg/kg according to the recommended dosing table) was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4- to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.

Formal carcinogenicity studies have not been conducted with omalizumab.

In reproduction studies in cynomolgus monkeys, subcutaneous doses up to 75 mg/kg per week (at least 8 times the highest recommended clinical dose in mg/kg over a 4-week period) 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.

Omalizumab is excreted in breast milk in cynomolgus monkeys. Milk levels of omalizumab were 0.15% of the maternal serum concentration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
L-histidine
L-histidine hydrochloride monohydrate
Polysorbate 20

Solvent
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years.

After reconstitution
The chemical and physical stability of the reconstituted medicinal product have 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 medicinal 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 or 2 hours at 25°C.

6.4 Special precautions for storage

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder vial: Clear, colourless type I glass vial with a butyl rubber stopper and grey flip-off seal.

Solvent ampoule: Clear, colourless type I glass ampoule containing 2 ml water for injections.

Pack containing one vial of powder for solution for injection and one ampoule of water for injections.

6.6 Special precautions for disposal and other handling

The lyophilised medicinal product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted medicinal product care must be taken to withdraw all of the medicinal product from the vial before expelling any air or excess solution from the syringe in order to obtain the 0.6 ml.

To prepare Xolair 75 mg vials for subcutaneous administration, please adhere to the following instructions:

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 vial containing the lyophilised powder using standard aseptic techniques, directing the water for injections directly on to the powder.

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

4. To aid in dissolution after completing step 3, gently swirl the 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 medicinal product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow. Do not use if solid particles are present.

5. Invert the vial for at least 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-ml syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Keeping the vial inverted position the needle tip at the very bottom of the solution in the vial 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, it may take 5-10 seconds to administer the solution by subcutaneous injection.

   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.

Xolair 75 mg powder for solution for injection is supplied in a single-use vial.

From a microbiological point of view, the medicinal product should be used immediately after reconstitution (see section 6.3).

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 22 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of omalizumab*.

After reconstitution one vial contains 125 mg/ml of omalizumab (150 mg in 1.2 ml).

*Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: white to off-white lyophilisate
Solvent: clear and colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergic asthma
Xolair is indicated in adults, adolescents and children (6 to <12 years of age).

Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

Adults and adolescents (12 years of age and older)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Children (6 to <12 years of age)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Chronic spontaneous urticaria (CSU)
Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

4.2 Posology and method of administration

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma or chronic spontaneous urticaria.

Allergic asthma

Posology

The appropriate dose and frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, 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.

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that adult and adolescent patients with IgE below 76 IU/ml and children (6 to < 12 years of age) with IgE below 200 IU/ml have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting therapy.

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts in adults, adolescents and children (6 to <12 years of age).

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

The maximum recommended dose is 600 mg omalizumab every two weeks.

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

Dose (mg)	Number of vials		Number of injections	Total injection volume (ml)
	75 mg [a]	150 mg [b]		
75	1[c]	0	1	0.6
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).
[c] or use 0.6 ml from a 150 mg vial.

Table 2: ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 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
≥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					
>600-700	300		450	600						
>700-800										
>800-900										
>900-1000										
>1000-1100										

ADMINISTRATION EVERY 2 WEEKS
SEE TABLE 3

Table 3: ADMINSTRATION 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
≥30-100	ADMINISTRATION EVERY 4 WEEKS SEE TABLE 2									
>100-200										
>200-300										375
>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					
>1100-1200	300	300	450	525	600	DO NOT ADMINISTER– data is unavailable for dose recommendation				
>1200-1300	300	375	450	525						
>1300-1500	300	375	525	600						

Treatment duration, monitoring and dose adjustments
Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for Xolair treatment to show effectiveness. 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 following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician's overall assessment of treatment effectiveness).

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

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

Chronic spontaneous urticaria (CSU)
Posology
The recommended dose is 300 mg by subcutaneous injection 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.

Special populations
Elderly (65 years of age and older)
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 dose 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 for these patients, Xolair should be administered with caution (see section 4.4).

Paediatric population
In allergic asthma, the safety and efficacy of Xolair in paediatric patients below the age of 6 years have not been established. No data are available.

In CSU, the safety and efficacy of Xolair 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.

There is limited experience with self-administration of Xolair. Therefore treatment is intended to be administered by a healthcare provider only.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and also information for the healthcare professional section of the package leaflet.

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, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Xolair is not indicated for the treatment of these conditions.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). 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.

Immune system disorders
Allergic reactions type I
Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. Therefore medicinal products 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. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-Xolair antibodies is not well understood.

Serum sickness
Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against 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/arthralgias, 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.

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 medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. 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.

Parasitic (helminth) infections
IgE may be involved in the immunological response to some helminth 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 programme, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Since IgE may be involved in the immunological response to some helmith infections, Xolair may indirectly reduce the efficacy of medicinal products for the treatment of helminthic or other parasitic infections (see section 4.4).

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. Medicinal product or vaccine interaction studies have not been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma or CSU 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 beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where Xolair was co-administered with immunotherapy, the safety and efficacy of Xolair in combination with specific immunotherapy were found to be no different to that of Xolair alone.

Chronic spontaneous urticaria (CSU)
In clinical studies in CSU, Xolair was used in conjunction with antihistamines (anti-H1, anti-H2) and leukotriene receptor antagonists (LTRAs). 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 5.2).

Paediatric population
Clinical studies in CSU included some patients aged 12 to 17 years taking Xolair in conjunction with antihistamines (anti-H1, anti-H2) and LTRAs. No studies have been performed in children under 12 years.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether omalizumab is excreted in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Omalizumab should not be given during breast-feeding.

Fertility
There are no human fertility data for omalizumab. In specifically-designed non-clinical fertility studies, in non-human primates including mating studies, no impairment of male or female fertility was observed following repeated dosing with omalizumab at dose levels up to 75 mg/kg. Furthermore, no genotoxic effects were observed in separate non-clinical genotoxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Xolair has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Allergic asthma
Summary of safety profile
During clinical trials in 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 trials in children 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity.

Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Reactions reported in the post-marketing setting are listed with frequency not known (cannot be estimated from the available data).

Table 4: Adverse reactions in allergic asthma

Infections and infestations	
Uncommon	Pharyngitis
Rare	Parasitic infection
Blood and lymphatic system disorders	
Not known	Idiopathic thrombocytopenia, including severe cases
Immune system disorders	
Rare	Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development
Not known	Serum sickness, may include fever and lymphadenopathy
Nervous system disorders	
Common	Headache*
Uncommon	Syncope, paraesthesia, somnolence, dizziness
Vascular disorders	
Uncommon	Postural hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	Allergic bronchospasm, coughing
Rare	Laryngoedema
Not known	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
Gastrointestinal disorders	
Common	Abdominal pain upper**
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
Skin and subcutaneous tissue disorders	
Uncommon	Photosensitivity, urticaria, rash, pruritus
Rare	Angioedema
Not known	Alopecia
Musculoskeletal and connective tissue disorders	
Rare	Systemic lupus erythematosus (SLE)
Not known	Arthralgia, myalgia, joint swelling
General disorders and administration site conditions	
Very common	Pyrexia**
Common	Injection site reactions such as swelling, erythema, pain, pruritus
Uncommon	Influenza-like illness, swelling arms, weight increase, fatigue

*: Very common in children 6 to <12 years of age

**: In children 6 to <12 years of age

Chronic spontaneous urticaria (CSU)

Summary of safety profile

The safety and tolerability of omalizumab were investigated with doses of 75 mg, 150 mg and 300 mg every four weeks in 975 CSU patients, 242 of whom received placebo. Overall, 733 patients were treated with omalizumab for up to 12 weeks and 490 patients for up to 24 weeks. Of those, 412 patients were treated for up to 12 weeks and 333 patients were treated for up to 24 weeks at the 300 mg dose.

Tabulated list of adverse reactions
A separate table (Table 5) shows the adverse reactions for the CSU indication resulting from differences in dosages and treatment populations (with significantly different risk factors, comorbidities, co-medications and ages [e.g. asthma trials included children from 6-12 years of age]).

Table 5 lists the adverse reactions (events occurring in ≥1% of patients in any treatment group and ≥2% more frequently in any omalizumab treatment group than with placebo (after medical review)) reported with 300 mg in the three pooled phase III studies. The adverse reactions presented are divided into two groups: those identified in the 12-week and the 24-week treatment periods.

The adverse reactions are listed by MedDRA system organ class. 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: 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) and not known (cannot be estimated from the available data).

Table 5: Adverse reactions from the pooled CSU safety database (day 1 to week 24) at 300 mg omalizumab

12-Week	**Omalizumab studies 1, 2 and 3 Pooled**		**Frequency category**
	Placebo N=242	300 mg N=412	
Infections and infestations			
Sinusitis	5 (2.1%)	20 (4.9%)	Common
Nervous system disorders			
Headache	7 (2.9%)	25 (6.1%)	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (0.4%)	12 (2.9%)	Common
General disorder and administration site conditions			
Injection site reaction*	2 (0.8%)	11 (2.7%)	Common
24-Week	**Omalizumab studies 1 and 3 Pooled**		**Frequency category**
	Placebo N=163	300 mg N=333	
Infections and infestations			
Upper respiratory tract infection	5 (3.1%)	19 (5.7%)	Common

***** Despite not showing a 2% difference to placebo, injection site reactions were included as all cases were assessed causally related to study treatment.

Description of selected adverse reactions pertinent to allergic asthma and CSU indications
No relevant data was obtained in clinical studies in CSU that would require a modification of the sections below.

Immune system disorders
For further information, see section 4.4.

Anaphylaxis
Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%.

Arterial thromboembolic events (ATE)
In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. The definition of the composite endpoint ATE included stroke, transient ischaemic 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 patient 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 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71).

Platelets
In clinical trials few patients had 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, as observed in non-human primates (see section 5.3), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

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 were unaltered (see section 4.4).

Systemic lupus erythematosus
Clinical trial and post-marketing cases of systemic lupus erythematosus (SLE) have been reported in patients with moderate to severe asthma and CSU. The pathogenesis of SLE is not well understood.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Allergic asthma

Mechanism of action

Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE receptor) on basophils and mast cells, 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 allergic asthma patients, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

Chronic spontaneous urticaria (CSU)

Mechanism of action

Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate. It is not entirely understood how this results in an improvement of CSU symptoms.

Pharmacodynamic effect

In clinical studies in CSU 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. After discontinuation of Xolair, free IgE levels increased 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 efficacy and safety of Xolair were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12-79 years, who had reduced lung function (FEV_1 40-80% predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a 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 a long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22%, 27%, and 35% of patients, respectively).

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.

In a subgroup analysis, patients with pre-treatment total IgE ≥76 IU/ml were more likely to experience clinically meaningful benefit to Xolair. In these patients in study 1 Xolair reduced the rate of asthma exacerbations by 40% (p = 0.002). In addition more patients had clinically meaningful responses in the total IgE ≥76 IU/ml population across the Xolair severe asthma programme. Table 6 includes results in the study 1 population.

Table 6: Results of study 1

	Whole study 1 population	
	Xolair N=209	Placebo N=210
Asthma exacerbations		
Rate per 28-week period	0.74	0.92
% reduction, p-value for rate ratio	19.4%, p = 0.153	
Severe asthma exacerbations		
Rate per 28-week period	0.24	0.48
% reduction, p-value for rate ratio	50.1%, p = 0.002	
Emergency visits		
Rate per 28-week period	0.24	0.43
% reduction, p-value for rate ratio	43.9%, p = 0.038	
Physician's overall assessment		
% responders*	60.5%	42.8%
p-value**	<0.001	
AQL improvement		
% of patients ≥0.5 improvement	60.8%	47.8%
p-value	0.008	

* marked improvement or complete control
** p-value for overall distribution of assessment

Study 2 assessed the efficacy and safety of Xolair in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with Xolair in this open label study led to a 61% reduction in clinically significant asthma exacerbation rate compared to current asthma therapy alone.

Four additional large placebo-controlled supportive studies of 28 to 52 weeks duration in 1,722 adults and adolescents (studies 3, 4, 5, 6) assessed the efficacy and safety of Xolair in patients with severe persistent asthma. Most patients were inadequately controlled but were receiving less concomitant asthma therapy than patients in studies 1 or 2. Studies 3-5 used exacerbation as primary endpoint, whereas study 6 primarily evaluated inhaled corticosteroid sparing.

In studies 3, 4 and 5 patients treated with Xolair had respective reductions in asthma exacerbation rates of 37.5% (p = 0.027), 40.3% (p<0.001) and 57.6% (p<0.001) compared to placebo.

In study 6, significantly more severe allergic asthma patients on Xolair were able to reduce their fluticasone dose to ≤500 micrograms/day without deterioration of asthma control (60.3%) compared to the placebo group (45.8%, p<0.05).

Quality of life scores were measured using the Juniper Asthma-related Quality of Life Questionnaire. For all six studies there was a statistically significant improvement from baseline in quality of life scores for Xolair patients versus the placebo or control group.

Physician's overall assessment of treatment effectiveness:
Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), 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 group aged 6 to <12 years comes from one randomised, double-blind, placebo-controlled, multi-centre trial (study 7).

Study 7 was a placebo-controlled trial which included a specific subgroup (n=235) of patients as defined in the present indication, who were treated with high-dose inhaled corticosteroids (≥500 µg/day fluticasone equivalent) plus long-acting beta agonist.

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 intravenous) corticosteroids for at least 3 days.

In the specific subgroup of patients on high dose inhaled corticosteroids, the omalizumab group had a statistically significantly lower rate of clinically significant asthma exacerbations than the placebo group. At 24 weeks, the difference in rates between treatment groups represented a 34% (rate ratio 0.662, p = 0.047) decrease relative to placebo for omalizumab patients. In the second double-blind 28-week treatment period the difference in rates between treatment groups represented a 63% (rate ratio 0.37, p<0.001) decrease relative to placebo for omalizumab patients.

During the 52-week double-blind treatment period (including the 24-week fixed-dose steroid phase and the 28-week steroid adjustment phase) the difference in rates between treatment groups represented a 50% (rate ratio 0.504, p<0.001) relative decrease in exacerbations for omalizumab patients.

The omalizumab group showed greater decreases in beta-agonist rescue medication use than the placebo group at the end of the 52-week treatment period, although the difference between treatment groups was not statistically significant. For the global evaluation of treatment effectiveness at the end of the 52-week double-blind treatment period in the subgroup of severe patients on high-dose inhaled corticosteroids plus long-acting beta agonists, the proportion of patients rated as having 'excellent' treatment effectiveness was higher, and the proportions having 'moderate' or 'poor' treatment effectiveness lower in the omalizumab group compared to the placebo group; the difference between groups was statistically significant (p<0.001), while there were no differences between the omalizumab and placebo groups for patients' subjective Quality of Life ratings.

Clinical efficacy and safety in chronic spontaneous urticaria (CSU)
The efficacy and safety of Xolair were demonstrated in two randomised, placebo-controlled phase III studies (study 1 and 2) in patients with CSU who remained symptomatic despite H1 antihistamine therapy at the approved dose. A third study (study 3) primarily evaluated the safety of Xolair in patients with CSU who remained symptomatic despite treatment with H1 antihistamines at up to four times the approved dose and H2 antihistamine and/or LTRA treatment. 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 1 and 2, 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 3 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 CSU symptoms prior to study enrollment. 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.

The primary endpoint was the change from baseline to week 12 in weekly itch severity score. Omalizumab at 300 mg reduced the weekly itch severity score by 8.55 to 9.77 ($p < 0.0001$) compared to a reduction of 3.63 to 5.14 for placebo (see Table 7). Statistically significant results were further observed in the responder rates for UAS7≤6 (at week 12) which were higher for the 300 mg treatment groups, ranging from 52-66% ($p<0.0001$) compared to 11-19% for the placebo groups, and complete response (UAS7=0) was achieved by 34-44% ($p<0.0001$) of patients treated with 300 mg compared to 5-9% of patients in the placebo groups. Patients in the 300 mg treatment groups achieved the highest mean proportion of angioedema-free days from week 4 to week 12, (91.0-96.1%; $p<0.001$) compared to the placebo groups (88.1-89.2%). Mean change from baseline to week 12 in the overall DLQI for the 300 mg treatment groups was greater ($p<0.001$) than for placebo showing an improvement ranging from 9.7-10.3 points compared to 5.1-6.1 points for the corresponding placebo groups.

Table 7: Change from baseline to week 12 in weekly itch severity score, studies 1, 2 and 3 (mITT population*)

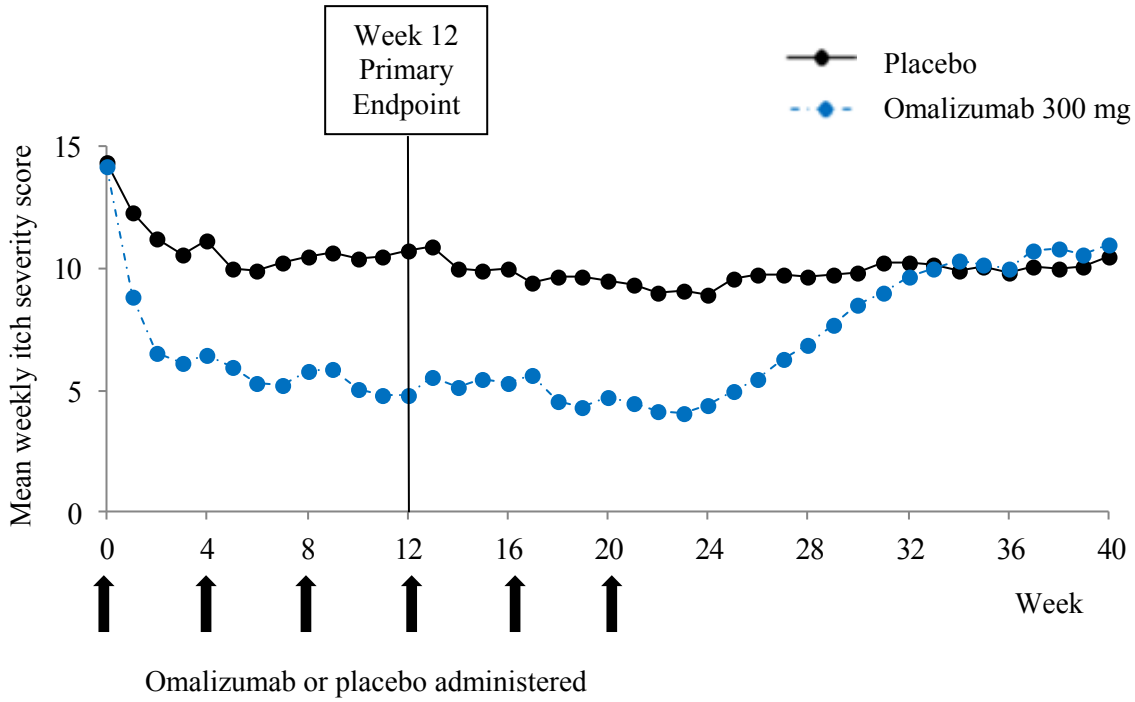
	Placebo	**Omalizumab 300 mg**
Study 1		
N	80	81
Mean (SD)	−3.63 (5.22)	−9.40 (5.73)
Difference in LS means vs. placebo[1]	-	−5.80
95% CI for difference	-	−7.49,−4.10
P-value vs. placebo[2]	-	<0.0001
Study 2		
N	79	79
Mean (SD)	−5.14 (5.58)	−9.77 (5.95)
Difference in LS means vs. placebo[1]	-	−4.81
95% CI for difference	-	−6.49,−3.13
P-value vs. placebo[2]	-	<0.0001
Study 3		
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 randomised 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 1. The mean weekly itch severity scores significantly decreased with a maximum effect around week 12 that was sustained over the 24-week treatment period. The results were similar in study 3.

In all three studies the mean weekly itch severity score 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 1 (mITT population)



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

Efficacy after 24 weeks of treatment

The magnitude of the efficacy outcomes observed at week 24 of treatment was comparable to that observed at week 12:

For 300 mg, in studies 1 and 3, the mean decrease from baseline in weekly itch severity score was 9.8 and 8.6, the proportion of patients with UAS7≤6 was 61.7% and 55.6%, and the proportion of patients with complete response (UAS7=0) was 48.1% and 42.5%, respectively, (all $p<0.0001$, when compared to placebo).

There is limited clinical experience in re-treatment of patients with omalizumab.

Clinical trial data on adolescents (12 to 17 years) included a total of 39 patients, of whom 11 received the 300 mg dose. Results for the 300 mg are available for 9 patients at week 12 and 6 patients at week 24, and show a similar magnitude of response to omalizumab treatment compared to the adult population. Mean change from baseline in weekly itch severity score showed a reduction of 8.25 at week 12 and of 8.95 at week 24. The responder rates were: 33% at week 12 and 67% at week 24 for UAS7=0, and 56% at week 12 and 67% at week 24 for UAS7≤6.

5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma as well as in adult and adolescent patients with CSU. The general pharmacokinetic characteristics of omalizumab are similar in these populations.

Absorption
After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single subcutaneous dose in adult and adolescent patients with asthma or CSU, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 6-8 days. In patients with asthma, 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.

The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg. Following doses of 75 mg, 150 mg or 300 mg every 4 weeks in patients with CSU, trough serum concentrations of omalizumab increased proportionally with the dose level.

Administration of Xolair manufactured as a lyophilised 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*. Based on population pharmacokinetics, distribution of omalizumab was similar in patients with allergic asthma and patients with CSU. The apparent volume of distribution in patients with asthma following subcutaneous administration was 78 ± 32 ml/kg.

Elimination
Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. In asthma patients the 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. In CSU patients, based on population pharmacokinetic simulations, omalizumab serum elimination half-life at steady state averaged 24 days and apparent clearance at steady state for a patient of 80 kg weight was 3.0 ml/kg/day.

Characteristics in patient populations
Patients with asthma: The population pharmacokinetics of omalizumab were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary in patients with asthma for age (6-76 years), race/ethnicity, gender or body mass index (see section 4.2).

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

Renal and hepatic impairment
There are no pharmacokinetic or pharmacodynamic data in allergic asthma or CSU patients with renal or hepatic impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

The safety of omalizumab has been studied in the cynomolgus monkey, since omalizumab binds to cynomolgus and human IgE with similar affinity. Antibodies to omalizumab were detected in some monkeys following repeated subcutaneous or intravenous administration. However, no apparent toxicity, such as immune complex-mediated disease or complement-dependent cytotoxicity, was seen. There was no evidence of an anaphylactic response due to mast-cell degranulation in cynomolgus monkeys.

Chronic administration of omalizumab at dose levels of up to 250 mg/kg (at least 14 times the highest recommended clinical dose in mg/kg according to the recommended dosing table) was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4- to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.

Formal carcinogenicity studies have not been conducted with omalizumab.

In reproduction studies in cynomolgus monkeys, subcutaneous doses up to 75 mg/kg per week (at least 8 times the highest recommended clinical dose in mg/kg over a 4-week period) 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.

Omalizumab is excreted in breast milk in cynomolgus monkeys. Milk levels of omalizumab were 0.15% of the maternal serum concentration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
L-histidine
L-histidine hydrochloride monohydrate
Polysorbate 20

Solvent
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years.

After reconstitution
The chemical and physical stability of the reconstituted medicinal product have 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 medicinal 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 or 2 hours at 25°C.

6.4 Special precautions for storage

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Solvent ampoule: Clear, colourless type I glass ampoule containing 2 ml water for injections.

Pack containing 1 vial of powder and 1 ampoule of water for injections, and multipacks containing 4 (4 packs of 1+1) or 10 (10 packs of 1+1) vials of powder and ampoules of water for injections.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The lyophilised medicinal product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted medicinal product care must be taken to withdraw all of the medicinal product from the vial before expelling any air or excess solution from the syringe in order to obtain the 1.2 ml.

To prepare Xolair 150 mg vials for subcutaneous administration, please adhere to the following instructions:

1. Draw 1.4 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 vial containing the lyophilised powder using standard aseptic techniques, directing the water for injections directly on to the powder.

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

4. To aid in dissolution after completing step 3, gently swirl the 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 medicinal product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow. Do not use if solid particles are present.

5. Invert the vial for at least 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-ml syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Keeping the vial inverted position the needle tip at the very bottom of the solution in the vial 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, it may take 5-10 seconds to administer the solution by subcutaneous injection.

   The vial delivers 1.2 ml (150 mg) of Xolair. For a 75 mg dose, draw up 0.6 ml into the syringe and discard the remaining solution.

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

Xolair 150 mg powder for solution for injection is supplied in a single-use vial.

From a microbiological point of view, the medicinal product should be used immediately after reconstitution (see section 6.3).

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/002
EU/1/05/319/003
EU/1/05/319/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 22 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 0.5 ml solution contains 75 mg of omalizumab*.

*Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opalescent, colourless to pale brownish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xolair is indicated in adults, adolescents and children (6 to <12 years of age).

Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

Adults and adolescents (12 years of age and older)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Children (6 to <12 years of age)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

4.2 Posology and method of administration

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma.

Posology

The appropriate dose and frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, 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.

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that adult and adolescent patients with IgE below 76 IU/ml and children (6 to < 12 years of age) with IgE below 200 IU/ml have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting therapy.

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts in adults, adolescents and children (6 to <12 years of age).

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

The maximum recommended dose is 600 mg omalizumab every two weeks.

Table 1: 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

Table 2: ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 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
≥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					
>600-700	300		450	600						
>700-800										
>800-900					ADMINISTRATION EVERY 2 WEEKS SEE TABLE 3					
>900-1000										
>1000-1100										

Table 3: ADMINSTRATION 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
≥30-100	ADMINISTRATION EVERY 4 WEEKS SEE TABLE 2									
>100-200										
>200-300										375
>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					
>1100-1200	300	300	450	525	600	DO NOT ADMINISTER– data is unavailable for dose recommendation				
>1200-1300	300	375	450	525						
>1300-1500	300	375	525	600						

Treatment duration, monitoring and dose adjustments
Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for Xolair treatment to show effectiveness. 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 following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician's overall assessment of treatment effectiveness).

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

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

Special populations

Elderly (65 years of age and older)

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 dose 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. 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 for these patients, Xolair should be administered with caution (see section 4.4).

Paediatric population

The safety and efficacy of Xolair in children below age 6 have not been established. No data are available.

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.

There is limited experience with self-administration of Xolair. Therefore treatment is intended to be administered by a healthcare provider only (see section 6.6 and also information for the healthcare professional section of the package leaflet).

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, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Xolair is not indicated for the treatment of these conditions.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). 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.

Immune system disorders

Allergic reactions type I

Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. Therefore medicinal products 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. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-Xolair antibodies is not well understood.

Serum sickness

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against 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/arthralgias, 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.

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 medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. 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.

Parasitic (helminth) infections

IgE may be involved in the immunological response to some helminth infections. In patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight increase in infection rate with omalizumab, although the course, severity, and response to treatment of infection were unaltered. The helminth infection rate in the overall clinical programme, 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.

Latex-sensitive individuals

The removable needle cap of this pre-filled syringe contains a derivative of natural rubber latex. No natural rubber latex has to date been detected in the removable needle cap. Nevertheless, the use of Xolair solution for injection in pre-filled syringe in latex-sensitive individuals has not been studied and thus there is a potential risk for hypersensitivity reactions which cannot be completely ruled out.

4.5 Interaction with other medicinal products and other forms of interaction

Since IgE may be involved in the immunological response to some helminth infections, Xolair may indirectly reduce the efficacy of medicinal products for the treatment of helminthic or other parasitic infections (see section 4.4).

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. Medicinal product or vaccine interaction studies have not been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma will interact with omalizumab.

In clinical studies Xolair was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where Xolair was co-administered with immunotherapy, the safety and efficacy of Xolair in combination with specific immunotherapy were found to be no different to that of Xolair alone.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether omalizumab is excreted in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Omalizumab should not be given during breast-feeding.

Fertility
There are no human fertility data for omalizumab. In specifically-designed non-clinical fertility studies in non-human primates, including mating studies, no impairment of male or female fertility was observed following repeated dosing with omalizumab at dose levels up to 75 mg/kg. Furthermore, no genotoxic effects were observed in separate non-clinical genotoxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Xolair has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
During clinical trials in 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 trials in children 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity.

Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Reactions reported in the post-marketing setting are listed with frequency not known (cannot be estimated from the available data).

Table 4: Adverse reactions

Infections and infestations	
Uncommon	Pharyngitis
Rare	Parasitic infection
Blood and lymphatic system disorders	
Not known	Idiopathic thrombocytopenia, including severe cases
Immune system disorders	
Rare	Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development
Not known	Serum sickness, may include fever and lymphadenopathy
Nervous system disorders	
Common	Headache*
Uncommon	Syncope, paraesthesia, somnolence, dizziness
Vascular disorders	
Uncommon	Postural hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	Allergic bronchospasm, coughing
Rare	Laryngoedema
Not known	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
Gastrointestinal disorders	
Common	Abdominal pain upper**
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
Skin and subcutaneous tissue disorders	
Uncommon	Photosensitivity, urticaria, rash, pruritus
Rare	Angioedema
Not known	Alopecia
Musculoskeletal and connective tissue disorders	
Rare	Systemic lupus erythematosus (SLE)
Not known	Arthralgia, myalgia, joint swelling
General disorders and administration site conditions	
Very common	Pyrexia**
Common	Injection site reactions such as swelling, erythema, pain, pruritus
Uncommon	Influenza-like illness, swelling arms, weight increase, fatigue

*: Very common in children 6 to <12 years of age

**: In children 6 to <12 years of age

Description of selected adverse reactions

Immune system disorders

For further information, see section 4.4.

Anaphylaxis

Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%.

Arterial thromboembolic events (ATE)
In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. The definition of the composite endpoint ATE included stroke, transient ischaemic 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 patient 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 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71).

Platelets
In clinical trials few patients had 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, as observed in non-human primates (see section 5.3), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

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

Systemic lupus erythematosus
Clinical trial and post-marketing cases of systemic lupus erythematosus (SLE) have been reported in patients with moderate to severe asthma and CSU. The pathogenesis of SLE is not well understood.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mechanism of action
Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE 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, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

Clinical efficacy and safety
Adults and adolescents ≥12 years of age
The efficacy and safety of Xolair were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12-79 years, who had reduced lung function (FEV_1 40-80% predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a 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 a long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22%, 27%, and 35% of patients, respectively).

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.

In a subgroup analysis, patients with pre-treatment total IgE ≥76 IU/ml were more likely to experience clinically meaningful benefit to Xolair. In these patients in study 1 Xolair reduced the rate of asthma exacerbations by 40% (p = 0.002). In addition more patients had clinically meaningful responses in the total IgE ≥76 IU/ml population across the Xolair severe asthma programme. Table 5 includes results in the study 1 population.

Table 5: Results of study 1

	Whole study 1 population	
	Xolair N=209	Placebo N=210
Asthma exacerbations		
Rate per 28-week period	0.74	0.92
% reduction, p-value for rate ratio	19.4%, p = 0.153	
Severe asthma exacerbations		
Rate per 28-week period	0.24	0.48
% reduction, p-value for rate ratio	50.1%, p = 0.002	
Emergency visits		
Rate per 28-week period	0.24	0.43
% reduction, p-value for rate ratio	43.9%, p = 0.038	
Physician's overall assessment		
% responders*	60.5%	42.8%
p-value**	<0.001	
AQL improvement		
% of patients ≥0.5 improvement	60.8%	47.8%
p-value	0.008	

* marked improvement or complete control

** p-value for overall distribution of assessment

Study 2 assessed the efficacy and safety of Xolair in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with Xolair in this open label study led to a 61% reduction in clinically significant asthma exacerbation rate compared to current asthma therapy alone.

Four additional large placebo-controlled supportive studies of 28 to 52 weeks duration in 1,722 adults and adolescents (studies 3, 4, 5, 6) assessed the efficacy and safety of Xolair in patients with severe persistent asthma. Most patients were inadequately controlled but were receiving less concomitant asthma therapy than patients in studies 1 or 2. Studies 3-5 used exacerbation as primary endpoint, whereas study 6 primarily evaluated inhaled corticosteroid sparing.

In studies 3, 4 and 5 patients treated with Xolair had respective reductions in asthma exacerbation rates of 37.5% (p = 0.027), 40.3% (p<0.001) and 57.6% (p<0.001) compared to placebo.

In study 6, significantly more severe allergic asthma patients on Xolair were able to reduce their fluticasone dose to ≤500 micrograms/day without deterioration of asthma control (60.3%) compared to the placebo group (45.8%, p<0.05).

Quality of life scores were measured using the Juniper Asthma-related Quality of Life Questionnaire. For all six studies there was a statistically significant improvement from baseline in quality of life scores for Xolair patients versus the placebo or control group.

Physician's overall assessment of treatment effectiveness:
Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), 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 group aged 6 to <12 years comes from one randomised, double-blind, placebo-controlled, multi-centre trial (study 7).

Study 7 was a placebo-controlled trial which included a specific subgroup (n=235) of patients as defined in the present indication, who were treated with high-dose inhaled corticosteroids (≥500 µg/day fluticasone equivalent) plus long-acting beta agonist.

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 intravenous) corticosteroids for at least 3 days.

In the specific subgroup of patients on high dose inhaled corticosteroids, the omalizumab group had a statistically significantly lower rate of clinically significant asthma exacerbations than the placebo group. At 24 weeks, the difference in rates between treatment groups represented a 34% (rate ratio 0.662, p = 0.047) decrease relative to placebo for omalizumab patients. In the second double-blind 28-week treatment period the difference in rates between treatment groups represented a 63% (rate ratio 0.37, p<0.001) decrease relative to placebo for omalizumab patients.

During the 52-week double-blind treatment period (including the 24-week fixed-dose steroid phase and the 28-week steroid adjustment phase) the difference in rates between treatment groups represented a 50% (rate ratio 0.504, p<0.001) relative decrease in exacerbations for omalizumab patients.

The omalizumab group showed greater decreases in beta-agonist rescue medication use than the placebo group at the end of the 52-week treatment period, although the difference between treatment groups was not statistically significant. For the global evaluation of treatment effectiveness at the end of the 52-week double-blind treatment period in the subgroup of severe patients on high-dose inhaled corticosteroids plus long-acting beta agonists, the proportion of patients rated as having 'excellent' treatment effectiveness was higher, and the proportions having 'moderate' or 'poor' treatment effectiveness lower in the omalizumab group compared to the placebo group; the difference between groups was statistically significant (p<0.001), while there were no differences between the omalizumab and placebo groups for patients' subjective Quality of Life ratings.

5.2 Pharmacokinetic properties

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

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

Administration of Xolair manufactured as a lyophilised 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*. The apparent volume of distribution in patients following subcutaneous administration was 78 ± 32 ml/kg.

Elimination
Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. In asthma patients the omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4 ± 1.1 ml/kg/day. In addition, doubling of body weight approximately doubled apparent clearance.

Characteristics in patient populations
Age, Race/Ethnicity, Gender, Body Mass Index
The population pharmacokinetics of Xolair were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for age (6-76 years), race/ethnicity, gender or Body Mass Index (see section 4.2).

Renal and hepatic impairment
There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

The safety of omalizumab has been studied in the cynomolgus monkey, since omalizumab binds to cynomolgus and human IgE with similar affinity. Antibodies to omalizumab were detected in some monkeys following repeated subcutaneous or intravenous administration. However, no apparent toxicity, such as immune complex-mediated disease or complement-dependent cytotoxicity, was seen. There was no evidence of an anaphylactic response due to mast-cell degranulation in cynomolgus monkeys.

Chronic administration of omalizumab at dose levels of up to 250 mg/kg (at least 14 times the highest recommended clinical dose in mg/kg according to the recommended dosing table) was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4- to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.

Formal carcinogenicity studies have not been conducted with omalizumab.

In reproduction studies in cynomolgus monkeys, subcutaneous doses up to 75 mg/kg per week (at least 8 times the highest recommended clinical dose in mg/kg over a 4-week period) 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.

Omalizumab is excreted in breast milk in cynomolgus monkeys. Milk levels of omalizumab were 0.15% of the maternal serum concentration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine hydrochloride
L-histidine hydrochloride
L-histidine
Polysorbate 20
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

15 months.

The shelf life includes potential temperature excursions. 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.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml solution in a pre-filled syringe barrel (type I glass) with staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack containing 1 pre-filled syringe, and multipacks containing 4 (4 packs of 1) or 10 (10 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Prior to completion of the injection, avoid contact with the device activation clips to keep from prematurely covering the needle with the needle guard.

<u>Using the syringe</u>

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.
2. Gently pinch the skin at the injection site and insert the needle.
3. Holding onto the finger flange, slowly depress the plunger as far as it will go. If any solution leaks from the injection site, insert the needle further.
4. Keeping the plunger fully depressed, carefully lift the needle straight out from the injection site.
5. Slowly release the plunger and allow the needle guard to automatically cover the exposed needle.

Disposal instructions
Dispose of the used syringe immediately in a sharps container.

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/005
EU/1/05/319/006
EU/1/05/319/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 22 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 1 ml solution contains 150 mg of omalizumab*.

*Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opalescent, colourless to pale brownish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergic asthma
Xolair is indicated in adults, adolescents and children (6 to <12 years of age).

Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

Adults and adolescents (12 years of age and older)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Children (6 to <12 years of age)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Chronic spontaneous urticaria (CSU)
Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

4.2 Posology and method of administration

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma or chronic spontaneous urticaria.

Allergic asthma

Posology

The appropriate dose and frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, 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.

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that adult and adolescent patients with IgE below 76 IU/ml and children (6 to < 12 years of age) with IgE below 200 IU/ml have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting therapy.

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts in adults, adolescents and children (6 to <12 years of age).

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

The maximum recommended dose is 600 mg omalizumab every two weeks.

Table 1: 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

Table 2: ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 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
≥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					
>600-700	300		450	600						
>700-800										
>800-900					ADMINISTRATION EVERY 2 WEEKS SEE TABLE 3					
>900-1000										
>1000-1100										

Table 3: ADMINSTRATION 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
≥30-100	ADMINISTRATION EVERY 4 WEEKS SEE TABLE 2									
>100-200										
>200-300										375
>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					
>1100-1200	300	300	450	525	600	DO NOT ADMINISTER– data is unavailable for dose recommendation				
>1200-1300	300	375	450	525						
>1300-1500	300	375	525	600						

Treatment duration, monitoring and dose adjustments
Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for Xolair treatment to show effectiveness. 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 following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician's overall assessment of treatment effectiveness).

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

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

Chronic spontaneous urticaria (CSU)
Posology
The recommended dose is 300 mg by subcutaneous injection 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.

Special populations
Elderly (65 years of age and older)
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 dose 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 for these patients, Xolair should be administered with caution (see section 4.4).

Paediatric population
In allergic asthma, the safety and efficacy of Xolair in paediatric patients below the age of 6 years have not been established. No data are available.

In CSU, the safety and efficacy of Xolair 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.

There is limited experience with self-administration of Xolair. Therefore treatment is intended to be administered by a healthcare provider only (see section 6.6 and also information for the healthcare professional section of the package leaflet).

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, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Xolair is not indicated for the treatment of these conditions.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). 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.

Immune system disorders

Allergic reactions type I

Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. Therefore medicinal products 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. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-Xolair antibodies is not well understood.

Serum sickness

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against 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/arthralgias, 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.

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 medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. 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.

Parasitic (helminth) infections
IgE may be involved in the immunological response to some helminth 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 programme, 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.

Latex-sensitive individuals
The removable needle cap of this pre-filled syringe contains a derivative of natural rubber latex. No natural rubber latex has to date been detected in the removable needle cap. Nevertheless, the use of Xolair solution for injection in pre-filled syringe in latex-sensitive individuals has not been studied and thus there is a potential risk for hypersensitivity reactions which cannot be completely ruled out.

4.5 Interaction with other medicinal products and other forms of interaction

Since IgE may be involved in the immunological response to some helminth infections, Xolair may indirectly reduce the efficacy of medicinal products for the treatment of helminthic or other parasitic infections (see section 4.4).

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. Medicinal product or vaccine interaction studies have not been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma or CSU 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 beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where Xolair was co-administered with immunotherapy, the safety and efficacy of Xolair in combination with specific immunotherapy were found to be no different to that of Xolair alone.

Chronic spontaneous urticaria (CSU)
In clinical studies in CSU, Xolair was used in conjunction with antihistamines (anti-H1, anti-H2) and leukotriene receptor antagonists (LTRAs). 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 5.2).

Paediatric population
Clinical studies in CSU included some patients aged 12 to 17 years taking Xolair in conjunction with antihistamines (anti-H1, anti-H2) and LTRAs. No studies have been performed in children under 12 years.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether omalizumab is excreted in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Omalizumab should not be given during breast-feeding.

Fertility
There are no human fertility data for omalizumab. In specifically-designed non-clinical fertility studies in non-human primates, including mating studies, no impairment of male or female fertility was observed following repeated dosing with omalizumab at dose levels up to 75 mg/kg. Furthermore, no genotoxic effects were observed in separate non-clinical genotoxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Xolair has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Allergic asthma
Summary of the safety profile
During clinical trials in 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 trials in children 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity.

Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Reactions reported in the post-marketing setting are listed with frequency not known (cannot be estimated from the available data).

Table 4: Adverse reactions in allergic asthma

Infections and infestations	
Uncommon	Pharyngitis
Rare	Parasitic infection
Blood and lymphatic system disorders	
Not known	Idiopathic thrombocytopenia, including severe cases
Immune system disorders	
Rare	Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development
Not known	Serum sickness, may include fever and lymphadenopathy
Nervous system disorders	
Common	Headache*
Uncommon	Syncope, paraesthesia, somnolence, dizziness
Vascular disorders	
Uncommon	Postural hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	Allergic bronchospasm, coughing
Rare	Laryngoedema
Not known	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
Gastrointestinal disorders	
Common	Abdominal pain upper**
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
Skin and subcutaneous tissue disorders	
Uncommon	Photosensitivity, urticaria, rash, pruritus
Rare	Angioedema
Not known	Alopecia
Musculoskeletal and connective tissue disorders	
Rare	Systemic lupus erythematosus (SLE)
Not known	Arthralgia, myalgia, joint swelling
General disorders and administration site conditions	
Very common	Pyrexia**
Common	Injection site reactions such as swelling, erythema, pain, pruritus
Uncommon	Influenza-like illness, swelling arms, weight increase, fatigue

*: Very common in children 6 to <12 years of age

**: In children 6 to <12 years of age

Chronic spontaneous urticaria (CSU)

Summary of the safety profile

The safety and tolerability of omalizumab were investigated with doses of 75 mg, 150 mg and 300 mg every four weeks in 975 CSU patients, 242 of whom received placebo. Overall, 733 patients were treated with omalizumab for up to 12 weeks and 490 patients for up to 24 weeks. Of those, 412 patients were treated for up to 12 weeks and 333 patients were treated for up to 24 weeks at the 300 mg dose.

Tabulated list of adverse reactions
A separate table (Table 5) shows the adverse reactions for the CSU indication resulting from differences in dosages and treatment populations (with significantly different risk factors, comorbidities, co-medications and ages [e.g. asthma trials included children from 6-12 years of age]).

Table 5 lists the adverse reactions (events occurring in ≥1% of patients in any treatment group and ≥2% more frequently in any omalizumab treatment group than with placebo (after medical review)) reported with 300 mg in the three pooled phase III studies. The adverse reactions presented are divided into two groups: those identified in the 12-week and the 24-week treatment periods.

The adverse reactions are listed by MedDRA system organ class. 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: 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) and not known (cannot be estimated from the available data).

Table 5: Adverse reactions from the pooled CSU safety database (day 1 to week 24) at 300 mg omalizumab

12-Week	**Omalizumab studies 1, 2 and 3 Pooled**		**Frequency category**
	Placebo N=242	300 mg N=412	
Infections and infestations			
Sinusitis	5 (2.1%)	20 (4.9%)	Common
Nervous system disorders			
Headache	7 (2.9%)	25 (6.1%)	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (0.4%)	12 (2.9%)	Common
General disorder and administration site conditions			
Injection site reaction*	2 (0.8%)	11 (2.7%)	Common
24-Week	**Omalizumab studies 1 and 3 Pooled**		**Frequency category**
	Placebo N=163	300 mg N=333	
Infections and infestations			
Upper respiratory tract infection	5 (3.1%)	19 (5.7%)	Common

***** Despite not showing a 2% difference to placebo, injection site reactions were included as all cases were assessed causally related to study treatment.

Description of selected adverse reactions pertinent to allergic asthma and CSU indications
No relevant data was obtained in clinical studies in CSU that would require a modification of the sections below.

Immune system disorders
For further information, see section 4.4.

Anaphylaxis
Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%.

Arterial thromboembolic events (ATE)
In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. The definition of the composite endpoint ATE included stroke, transient ischaemic 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 patient 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 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71).

Platelets
In clinical trials few patients had 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, as observed in non-human primates (see section 5.3), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

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 were unaltered (see section 4.4).

Systemic lupus erythematosus
Clinical trial and post-marketing cases of systemic lupus erythematosus (SLE) have been reported in patients with moderate to severe asthma and CSU. The pathogenesis of SLE is not well understood.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Allergic asthma

Mechanism of action

Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE receptor) on basophils and mast cells, 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 allergic asthma patients, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

Chronic spontaneous urticaria (CSU)

Mechanism of action

Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate. It is not entirely understood how this results in an improvement of CSU symptoms.

Pharmacodynamic effects

In clinical studies in CSU 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. After discontinuation of Xolair, free IgE levels increased 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 efficacy and safety of Xolair were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12-79 years, who had reduced lung function (FEV_1 40-80% predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a 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 a long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22%, 27%, and 35% of patients, respectively).

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.

In a subgroup analysis, patients with pre-treatment total IgE ≥76 IU/ml were more likely to experience clinically meaningful benefit to Xolair. In these patients in study 1 Xolair reduced the rate of asthma exacerbations by 40% (p = 0.002). In addition more patients had clinically meaningful responses in the total IgE ≥76 IU/ml population across the Xolair severe asthma programme. Table 6 includes results in the study 1 population.

Table 6: Results of study 1

	Whole study 1 population	
	Xolair N=209	Placebo N=210
Asthma exacerbations		
Rate per 28-week period	0.74	0.92
% reduction, p-value for rate ratio	19.4%, p = 0.153	
Severe asthma exacerbations		
Rate per 28-week period	0.24	0.48
% reduction, p-value for rate ratio	50.1%, p = 0.002	
Emergency visits		
Rate per 28-week period	0.24	0.43
% reduction, p-value for rate ratio	43.9%, p = 0.038	
Physician's overall assessment		
% responders*	60.5%	42.8%
p-value**	<0.001	
AQL improvement		
% of patients ≥0.5 improvement	60.8%	47.8%
p-value	0.008	

* marked improvement or complete control

** p-value for overall distribution of assessment

Study 2 assessed the efficacy and safety of Xolair in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with Xolair in this open label study led to a 61% reduction in clinically significant asthma exacerbation rate compared to current asthma therapy alone.

Four additional large placebo-controlled supportive studies of 28 to 52 weeks duration in 1,722 adults and adolescents (studies 3, 4, 5, 6) assessed the efficacy and safety of Xolair in patients with severe persistent asthma. Most patients were inadequately controlled but were receiving less concomitant asthma therapy than patients in studies 1 or 2. Studies 3-5 used exacerbation as primary endpoint, whereas study 6 primarily evaluated inhaled corticosteroid sparing.

In studies 3, 4 and 5 patients treated with Xolair had respective reductions in asthma exacerbation rates of 37.5% (p = 0.027), 40.3% (p<0.001) and 57.6% (p<0.001) compared to placebo.

In study 6, significantly more severe allergic asthma patients on Xolair were able to reduce their fluticasone dose to ≤500 micrograms/day without deterioration of asthma control (60.3%) compared to the placebo group (45.8%, p<0.05).

Quality of life scores were measured using the Juniper Asthma-related Quality of Life Questionnaire. For all six studies there was a statistically significant improvement from baseline in quality of life scores for Xolair patients versus the placebo or control group.

Physician's overall assessment of treatment effectiveness:
Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), 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 group aged 6 to <12 years comes from one randomised, double-blind, placebo-controlled, multi-centre trial (study 7).

Study 7 was a placebo-controlled trial which included a specific subgroup (n=235) of patients as defined in the present indication, who were treated with high-dose inhaled corticosteroids (≥500 µg/day fluticasone equivalent) plus long-acting beta agonist.

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 intravenous) corticosteroids for at least 3 days.

In the specific subgroup of patients on high dose inhaled corticosteroids, the omalizumab group had a statistically significantly lower rate of clinically significant asthma exacerbations than the placebo group. At 24 weeks, the difference in rates between treatment groups represented a 34% (rate ratio 0.662, p = 0.047) decrease relative to placebo for omalizumab patients. In the second double-blind 28-week treatment period the difference in rates between treatment groups represented a 63% (rate ratio 0.37, p<0.001) decrease relative to placebo for omalizumab patients.

During the 52-week double-blind treatment period (including the 24-week fixed-dose steroid phase and the 28-week steroid adjustment phase) the difference in rates between treatment groups represented a 50% (rate ratio 0.504, p<0.001) relative decrease in exacerbations for omalizumab patients.

The omalizumab group showed greater decreases in beta-agonist rescue medication use than the placebo group at the end of the 52-week treatment period, although the difference between treatment groups was not statistically significant. For the global evaluation of treatment effectiveness at the end of the 52-week double-blind treatment period in the subgroup of severe patients on high-dose inhaled corticosteroids plus long-acting beta agonists, the proportion of patients rated as having ‘excellent’ treatment effectiveness was higher, and the proportions having ‘moderate’ or ‘poor’ treatment effectiveness lower in the omalizumab group compared to the placebo group; the difference between groups was statistically significant (p<0.001), while there were no differences between the omalizumab and placebo groups for patients’ subjective Quality of Life ratings.

Clinical efficacy and safety in chronic spontaneous urticaria (CSU)
The efficacy and safety of Xolair were demonstrated in two randomised, placebo-controlled phase III studies (study 1 and 2) in patients with CSU who remained symptomatic despite H1 antihistamine therapy at the approved dose. A third study (study 3) primarily evaluated the safety of Xolair in patients with CSU who remained symptomatic despite treatment with H1 antihistamines at up to four times the approved dose and H2 antihistamine and/or LTRA treatment. 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 1 and 2, 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 3 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 CSU symptoms prior to study enrollment. 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.

The primary endpoint was the change from baseline to week 12 in weekly itch severity score. Omalizumab at 300 mg reduced the weekly itch severity score by 8.55 to 9.77 ($p < 0.0001$) compared to a reduction of 3.63 to 5.14 for placebo (see Table 7). Statistically significant results were further observed in the responder rates for UAS7≤6 (at week 12) which were higher for the 300 mg treatment groups, ranging from 52-66% ($p<0.0001$) compared to 11-19% for the placebo groups, and complete response (UAS7=0) was achieved by 34-44% ($p<0.0001$) of patients treated with 300 mg compared to 5-9% of patients in the placebo groups. Patients in the 300 mg treatment groups achieved the highest mean proportion of angioedema-free days from week 4 to week 12, (91.0-96.1%; $p<0.001$) compared to the placebo groups (88.1-89.2%). Mean change from baseline to week 12 in the overall DLQI for the 300 mg treatment groups was greater ($p<0.001$) than for placebo showing an improvement ranging from 9.7-10.3 points compared to 5.1-6.1 points for the corresponding placebo groups.

Table 7: Change from baseline to week 12 in weekly itch severity score, studies 1, 2 and 3 (mITT population*)

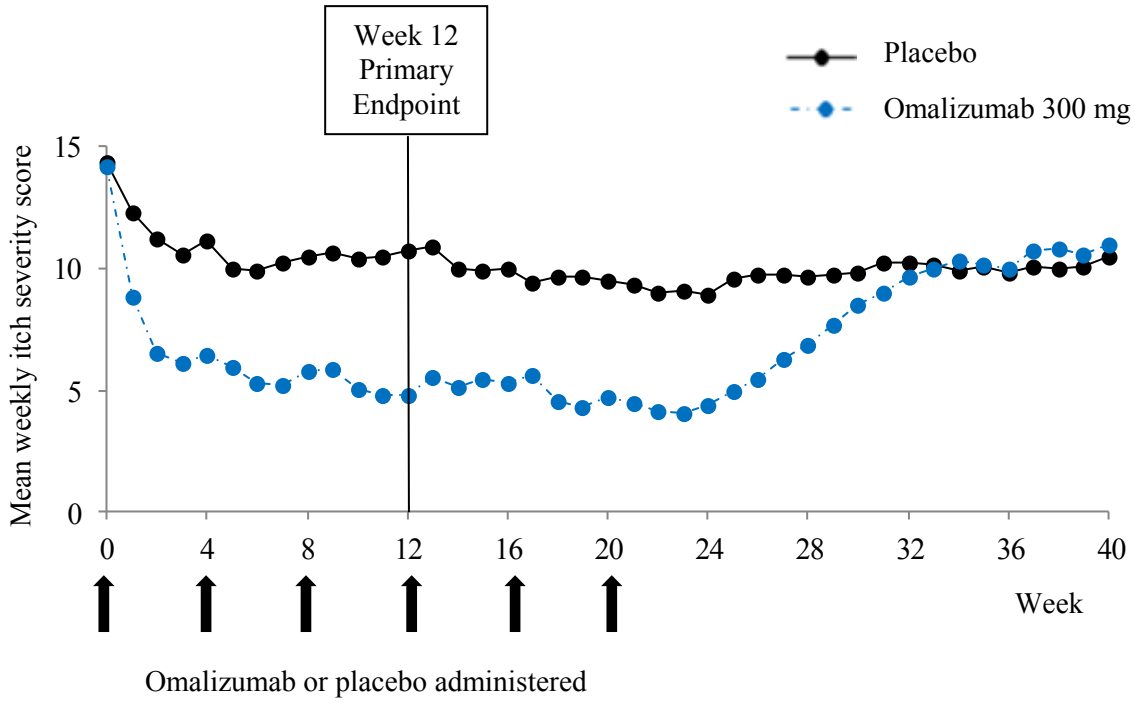
	Placebo	Omalizumab 300 mg
Study 1		
N	80	81
Mean (SD)	−3.63 (5.22)	−9.40 (5.73)
Difference in LS means vs. placebo[1]	-	−5.80
95% CI for difference	-	−7.49,−4.10
P-value vs. placebo[2]	-	<0.0001
Study 2		
N	79	79
Mean (SD)	−5.14 (5.58)	−9.77 (5.95)
Difference in LS means vs. placebo[1]	-	−4.81
95% CI for difference	-	−6.49,−3.13
P-value vs. placebo[2]	-	<0.0001
Study 3		
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 randomised 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 1. The mean weekly itch severity scores significantly decreased with a maximum effect around week 12 that was sustained over the 24-week treatment period. The results were similar in study 3.

In all three studies the mean weekly itch severity score 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 1 (mITT population)



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

Efficacy after 24 weeks of treatment

The magnitude of the efficacy outcomes observed at week 24 of treatment was comparable to that observed at week 12:

For 300 mg, in studies 1 and 3, the mean decrease from baseline in weekly itch severity score was 9.8 and 8.6, the proportion of patients with UAS7≤6 was 61.7% and 55.6%, and the proportion of patients with complete response (UAS7=0) was 48.1% and 42.5%, respectively, (all $p<0.0001$, when compared to placebo).

There is limited clinical experience in re-treatment of patients with omalizumab.

Clinical trial data on adolescents (12 to 17 years) included a total of 39 patients, of whom 11 received the 300 mg dose. Results for the 300 mg are available for 9 patients at week 12 and 6 patients at week 24, and show a similar magnitude of response to omalizumab treatment compared to the adult population. Mean change from baseline in weekly itch severity score showed a reduction of 8.25 at week 12 and of 8.95 at week 24. The responder rates were: 33% at week 12 and 67% at week 24 for UAS7=0, and 56% at week 12 and 67% at week 24 for UAS7≤6.

5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma as well as in adult and adolescent patients with CSU. The general pharmacokinetic characteristics of omalizumab are similar in these populations.

Absorption
After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single subcutaneous dose in adult and adolescent patients with asthma or CSU, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 6-8 days. In patients with asthma, 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.

The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg. Following doses of 75 mg, 150 mg or 300 mg every 4 weeks in patients with CSU, trough serum concentrations of omalizumab increased proportionally with the dose level.

Administration of Xolair manufactured as a lyophilised 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*. Based on population pharmacokinetics, distribution of omalizumab was similar in patients with allergic asthma and patients with CSU. The apparent volume of distribution in patients with asthma following subcutaneous administration was 78 ± 32 ml/kg.

Elimination
Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. In asthma patients the 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. In CSU patients, based on population pharmacokinetic simulations, omalizumab serum elimination half-life at steady state averaged 24 days and apparent clearance at steady state for a patient of 80 kg weight was 3.0 ml/kg/day.

Characteristics in patient populations
Patients with asthma: The population pharmacokinetics of omalizumab were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary in patients with asthma for age (6-76 years), race/ethnicity, gender or body mass index (see section 4.2).

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

Renal and hepatic impairment
There are no pharmacokinetic or pharmacodynamic data in allergic asthma or CSU patients with renal or hepatic impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

The safety of omalizumab has been studied in the cynomolgus monkey, since omalizumab binds to cynomolgus and human IgE with similar affinity. Antibodies to omalizumab were detected in some monkeys following repeated subcutaneous or intravenous administration. However, no apparent toxicity, such as immune complex-mediated disease or complement-dependent cytotoxicity, was seen. There was no evidence of an anaphylactic response due to mast-cell degranulation in cynomolgus monkeys.

Chronic administration of omalizumab at dose levels of up to 250 mg/kg (at least 14 times the highest recommended clinical dose in mg/kg according to the recommended dosing table) was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4- to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.

Formal carcinogenicity studies have not been conducted with omalizumab.

In reproduction studies in cynomolgus monkeys, subcutaneous doses up to 75 mg/kg per week (at least 8 times the highest recommended clinical dose in mg/kg over a 4-week period) 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.

Omalizumab is excreted in breast milk in cynomolgus monkeys. Milk levels of omalizumab were 0.15% of the maternal serum concentration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine hydrochloride
L-histidine hydrochloride
L-histidine
Polysorbate 20
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

15 months.

The shelf life includes potential temperature excursions. 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.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

1 ml solution in a pre-filled syringe barrel (type I glass) with staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack containing 1 pre-filled syringe, and multipacks containing 4 (4 packs of 1) or 10 (10 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Prior to completion of the injection, avoid contact with the device activation clips to keep from prematurely covering the needle with the needle guard.

Using the syringe

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.
2. Gently pinch the skin at the injection site and insert the needle.
3. Holding onto the finger flange, slowly depress the plunger as far as it will go. If any solution leaks from the injection site, insert the needle further.
4. Keeping the plunger fully depressed, carefully lift the needle straight out from the injection site.
5. Slowly release the plunger and allow the needle guard to automatically cover the exposed needle.

Disposal instructions
Dispose of the used syringe immediately in a sharps container.

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/008
EU/1/05/319/009
EU/1/05/319/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 22 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novartis Pharma S.A.S.
Centre de Biotechnologie
8, rue de l'Industrie
F-68330 Huningue
France

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg powder and solvent for solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 75 mg omalizumab.

3. LIST OF EXCIPIENTS

Powder: sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.
Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 x 75 mg vial
1 x 2 ml solvent ampoule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Use immediately after reconstitution (may be stored at 2°C - 8°C for up to 8 hours or at 25°C for 2 hours).
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 75 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xolair 75 mg powder for solution for injection
omalizumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

75 mg

6. OTHER

Store in a refrigerator (2°C - 8°C).

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Xolair
Water for injections

2. METHOD OF ADMINISTRATION

Use 0.9 ml and discard the rest.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING 1 VIAL AND 1 AMPOULE AS UNIT PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg powder and solvent for solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg omalizumab.

3. LIST OF EXCIPIENTS

Powder: sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.
Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 x 150 mg vial
1 x 2 ml solvent ampoule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Use immediately after reconstitution (may be stored at 2°C - 8°C for up to 8 hours or at 25°C for 2 hours).
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR INTERMEDIATE PACK (WITHOUT BLUE BOX) OF MULTIPACKS

1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg powder and solvent for solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg omalizumab.

3. LIST OF EXCIPIENTS

Powder: sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.
Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 x 150 mg vial
1 x 2 ml solvent ampoule
1 vial and 1 ampoule. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Use immediately after reconstitution (may be stored at 2°C - 8°C for up to 8 hours or at 25°C for 2 hours).
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/003	Multipack comprising 4 packs
EU/1/05/319/004	Multipack comprising 10 packs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg powder and solvent for solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg omalizumab.

3. LIST OF EXCIPIENTS

Powder: sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.
Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Multipack: 4 packs, each containing 1 vial (150 mg) and 1 solvent ampoule (2 ml).
Multipack: 10 packs, each containing 1 vial (150 mg) and 1 solvent ampoule (2 ml).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Use immediately after reconstitution (may be stored at 2°C - 8°C for up to 8 hours or at 25°C for 2 hours).
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/003	Multipack comprising 4 packs
EU/1/05/319/004	Multipack comprising 10 packs

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 150 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xolair 150 mg powder for solution for injection
omalizumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg

6. OTHER

Store in a refrigerator (2°C - 8°C).

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Xolair
Water for injections

2. METHOD OF ADMINISTRATION

Use 1.4 ml and discard the rest.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose the used syringe immediately in a sharps container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/005 75 mg solution for injection

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 75 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 4 packs, each containing 1 x 0.5 ml.
Multipack: 10 packs, each containing 1 x 0.5 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose the used syringe immediately in a sharps container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/006	75 mg solution for injection (4)
EU/1/05/319/007	75 mg solution for injection (10)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 75 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 0.5 ml. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose the used syringe immediately in a sharps container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/006	75 mg solution for injection (4)
EU/1/05/319/007	75 mg solution for injection (10)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 75 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg solution for injection
omalizumab
Subcutaneous use.

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xolair 75 mg solution for injection
omalizumab
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose the used syringe immediately in a sharps container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/008 150 mg solution for injection

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 4 packs, each containing 1 x 1 ml.
Multipack: 10 packs, each containing 1 x 1 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose the used syringe immediately in a sharps container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/009	150 mg solution for injection (4)
EU/1/05/319/010	150 mg solution for injection (10)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg solution for injection
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 1 ml. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose the used syringe immediately in a sharps container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/009	150 mg solution for injection (4)
EU/1/05/319/010	150 mg solution for injection (10)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg solution for injection
omalizumab
Subcutaneous use.

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xolair 150 mg solution for injection
omalizumab
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Xolair 75 mg powder and solvent for solution for injection
omalizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xolair is and what it is used for

The active substance of Xolair is omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body; it belongs to a class of medicines called monoclonal antibodies. It is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults and adolescents (12 years of age and older) and children (6 to less than 12 years of age) who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high-dose steroid inhalers or beta-agonist inhalers.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE plays a key role in causing allergic asthma.

2. What you need to know before you are given Xolair

You should not be given Xolair
- if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic to any of the ingredients, tell your doctor as you should not be given Xolair.

Warnings and precautions
Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.

A certain type of allergic reaction called serum sickness has been observed in patients treated with Xolair. The symptoms of serum sickness can be one or more of the following symptoms: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Churg-Strauss and Hypereosinophilic syndrome have been observed in patients treated with Xolair. The symptoms may include one or more of the following: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arm and legs. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Talk to your doctor before you are given Xolair:
- if you have kidney or liver problems.
- if you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
- if you live in a region where infections caused by parasites are common or if you are travelling to such a region as Xolair may weaken your resistance to such infections.

Xolair does not treat acute asthma symptoms, such as a sudden asthma attack. Therefore Xolair should not be used to treat such symptoms.

Xolair is not meant to prevent or treat other allergy-type conditions, such as sudden allergic reactions, hyperimmunoglobulin E syndrome (an inherited immune disorder), aspergillosis (a fungus-related lung disease), food allergy, eczema or hay fever because Xolair has not been studied in these conditions.

Children (under 6 years of age)
Xolair should not be given to children under 6 years of age. There are not enough data in this group.

Other medicines and Xolair
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

This is especially important if you are taking:
- medicines to treat an infection caused by a parasite, as Xolair may reduce the effect of your medicines,
- inhaled corticosteroids and other medicines for allergic asthma.

Pregnancy and breast-feeding
You should not be given Xolair when you are pregnant, unless this is considered necessary by your doctor.

If you plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor immediately.

You should not be given Xolair when you are breast-feeding.

Driving and using machines
It is unlikely that Xolair will affect your ability to drive and use machines.

3. How Xolair is given

Instructions on how to use Xolair are given in the section "Information for the healthcare professional".

Your doctor will work out how much Xolair you need and how often you will be given it. This depends on your body weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in your blood.

Xolair is given to you by a doctor or nurse as an injection just under the skin (subcutaneously).

Follow carefully all instructions given by your doctor or nurse.

How much you will be given
You will be given 1 to 4 injections at a time, either every two weeks, or every four weeks.

Carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medicines without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes between 12 and 16 weeks to have the full effect.

Use in children and adolescents
Xolair can be given to children and adolescents aged 6 years or older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers or beta-agonist inhalers. Your doctor will work out how much Xolair your child needs and how often it needs to be given. This will depend on your child's weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in his/her blood.

If a dose of Xolair is missed
Contact your doctor or hospital as soon as possible to re-schedule your appointment.

If you stop treatment with Xolair
Do not stop treatment with Xolair unless your doctor tells you to. Interrupting or stopping the treatment with Xolair may cause your asthma symptoms to come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by Xolair are usually mild to moderate but can occasionally be serious.

<u>Serious side effects include</u>:
Rare side effects (may affect up to 1 in 1,000 people)
- Sudden severe allergic reactions: if you notice any serious sudden signs of allergy or combination of signs such as rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Xolair you may be more at risk of developing a severe allergic reaction following use of Xolair.
- Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)
- Development of one or more of the following symptoms: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems**,** pain, numbness, tingling in the arms and legs (signs of so-called "Churg-Strauss syndrome or hypereosinophilic syndrome").
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Development of any of the following symptoms, especially if in combination: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain (signs of serum sickness).

If you experience any of these, tell your doctor or nurse straight away.

Other side effects include:
Very common side effects (may affect more than 1 in 10 people)
- fever (in children)

Common side effects (may affect up to 1 in 10 people)
- reactions at the injection site including pain, swelling, itching and redness
- pain in the upper part of the tummy (in children)
- headache (very common in children)

Uncommon side effects (may affect up to 1 in 100 people)
- feeling dizzy, sleepy or tired
- tingling or numbness of the hands or feet
- fainting, low blood pressure while sitting or standing (postural hypotension), flushing
- sore throat, coughing, acute breathing problems
- feeling sick (nausea), diarrhoea, indigestion
- itching, hives, rash, increased sensitivity of the skin to sun
- weight increase
- flu-like symptoms
- swelling arms

Rare side effects (may affect up to 1 in 1,000 people)
- parasitic infection

Not known (frequency cannot be estimated from the available data)
- joint pain, muscle pain and joint swelling
- hair loss

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xolair

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.

6. Contents of the pack and other information

What Xolair contains
- The active substance is omalizumab. One vial contains 75 mg of omalizumab. After reconstitution one vial contains 125 mg/ml of omalizumab (75 mg in 0.6 ml).
- The other ingredients are sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.

What Xolair looks like and contents of the pack
Xolair 75 mg powder and solvent for solution for injection is supplied as a white to off-white powder in a small glass vial together with an ampoule containing 2 ml of water for injections. The powder is reconstituted in the water before it is injected by a doctor or nurse.

Xolair is available in packs containing one vial of powder for solution for injection and one ampoule of 2 ml water for injections.

Xolair is also available in vials with 150 mg omalizumab.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for healthcare professionals only:

The lyophilised medicinal product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted medicinal product care must be taken to withdraw all of the medicinal product from the vial before expelling any air or excess solution from the syringe in order to obtain the 0.6 ml.

To prepare Xolair 75 mg vials for subcutaneous administration, please adhere to the following instructions:

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 vial containing the lyophilised powder using standard aseptic techniques, directing the water for injections directly onto the powder.

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

4. To aid in dissolution after completing step 3, gently swirl the 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 medicinal product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow. Do not use if solid particles are present.

5. Invert the vial for at least 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-ml syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Keeping the vial inverted position the needle tip at the very bottom of the solution in the vial 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, it may take 5-10 seconds to administer the solution by subcutaneous injection.

   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.

Package leaflet: Information for the user

Xolair 150 mg powder and solvent for solution for injection
omalizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xolair is and what it is used for

Xolair is used for the treatment of allergic asthma and chronic spontaneous urticaria (CSU). The active substance of Xolair is omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body; it belongs to a class of medicines called monoclonal antibodies. Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE plays a key role in causing allergic asthma or CSU.

Allergic asthma
This medicine is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults and adolescents (12 years of age and older) and children (6 to less than 12 years of age) who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high-dose steroid inhalers or beta-agonist inhalers.

Chronic spontaneous urticaria (CSU)
This medicine is used to treat chronic spontaneous urticaria in adults and adolescents (12 years of age or older) who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

2. What you need to know before you are given Xolair

You should not be given Xolair
- if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic to any of the ingredients, tell your doctor as you should not be given Xolair.

Warnings and precautions
Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.

A certain type of allergic reaction called serum sickness has been observed in patients treated with Xolair. The symptoms of serum sickness can be one or more of the following symptoms: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Churg-Strauss and Hypereosinophilic syndrome have been observed in allergic asthma patients treated with Xolair. The symptoms may include one or more of the following: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arm and legs. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Talk to your doctor before you are given Xolair:
- if you have kidney or liver problems.
- if you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
- if you live in a region where infections caused by parasites are common or if you are travelling to such a region as Xolair may weaken your resistance to such infections.

Xolair does not treat acute asthma symptoms, such as a sudden asthma attack. Therefore Xolair should not be used to treat such symptoms.

Xolair is not meant to prevent or treat other allergy-type conditions, such as sudden allergic reactions, hyperimmunoglobulin E syndrome (an inherited immune disorder), aspergillosis (a fungus-related lung disease), food allergy, eczema or hay fever because Xolair has not been studied in these conditions.

Children and adolescents
Allergic asthma
Xolair is not recommended for children under 6 years of age.

Chronic spontaneous urticaria (CSU)
Do not give Xolair to children under 12 years of age. Its use in children under 12 has not been studied.

Other medicines and Xolair
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

This is especially important if you are taking:
- medicines to treat an infection caused by a parasite, as Xolair may reduce the effect of your medicines,
- inhaled corticosteroids and other medicines for allergic asthma.

Pregnancy and breast-feeding
You should not be given Xolair when you are pregnant, unless this is considered necessary by your doctor.

If you plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor immediately.

You should not be given Xolair when you are breast-feeding.

Driving and using machines
It is unlikely that Xolair will affect your ability to drive and use machines.

3. How Xolair is given

Instructions on how to use Xolair are given in the section "Information for the healthcare professional".

Xolair is given to you by a doctor or nurse as an injection just under the skin (subcutaneously).

Follow carefully all instructions given by your doctor or nurse.

How much you will be given
Allergic asthma
Your doctor will work out how much Xolair you need and how often you will be given it. This depends on your body weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in your blood.

You will be given 1 to 4 injections at a time, either every two weeks, or every four weeks.

Carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medicines without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes between 12 and 16 weeks to have the full effect.

Chronic spontaneous urticaria (CSU)
You will be given two 150 mg injections at a time every four weeks.

Continue taking your current medicine for CSU during Xolair treatment. Do not stop taking any medicine without talking to your doctor first.

Use in children and adolescents
Allergic asthma
Xolair can be given to children and adolescents aged 6 years or older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers or beta-agonist inhalers. Your doctor will work out how much Xolair your child needs and how often it needs to be given. This will depend on your child's weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in his/her blood.

Chronic spontaneous urticaria (CSU)
Xolair can be given to adolescents aged 12 years or older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

If a dose of Xolair is missed
Contact your doctor or hospital as soon as possible to re-schedule your appointment.

If you stop treatment with Xolair
Do not stop treatment with Xolair unless your doctor tells you to. Interrupting or stopping the treatment with Xolair may cause your asthma or CSU symptoms to come back.

However, if you are being treated for CSU, your doctor may stop Xolair treatment from time to time so that your symptoms can be assessed. Follow your doctor's instructions.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by Xolair are usually mild to moderate but can occasionally be serious.

Serious side effects include:
Rare side effects (may affect up to 1 in 1,000 people)
- Sudden severe allergic reactions: if you notice any serious sudden signs of allergy or combination of signs such as rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Xolair you may be more at risk of developing a severe allergic reaction following use of Xolair.
- Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)
- Development of one or more of the following symptoms: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arms and legs (signs of so-called "Churg-Strauss syndrome or hypereosinophilic syndrome").
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Development of any of the following symptoms, especially if in combination: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain (signs of serum sickness).

If you experience any of these, tell your doctor or nurse straight away.

Other side effects include:
Very common side effects (may affect more than 1 in 10 people)
- fever (in children)

Common side effects (may affect up to 1 in 10 people)
- reactions at the injection site including pain, swelling, itching and redness
- pain in the upper part of the tummy (in children)
- headache (very common in children)
- upper respiratory tract infection, such as inflammation of the pharynx and common cold
- feeling of pressure or pain in the cheeks and forehead (sinusitis, sinus headache)
- pain in joints (arthralgia)

Uncommon side effects (may affect up to 1 in 100 people)
- feeling dizzy, sleepy or tired
- tingling or numbness of the hands or feet
- fainting, low blood pressure while sitting or standing (postural hypotension), flushing
- sore throat, coughing, acute breathing problems
- feeling sick (nausea), diarrhoea, indigestion
- itching, hives, rash, increased sensitivity of the skin to sun
- weight increase
- flu-like symptoms
- swelling arms

Rare side effects (may affect up to 1 in 1,000 people)
- parasitic infection

Not known (frequency cannot be estimated from the available data)
- muscle pain and joint swelling
- hair loss

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xolair

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.

6. Contents of the pack and other information

What Xolair contains
- The active substance is omalizumab. One vial contains 150 mg of omalizumab. After reconstitution one vial contains 125 mg/ml of omalizumab (150 mg in 1.2 ml).
- The other ingredients are sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.

What Xolair looks like and contents of the pack
Xolair 150 mg powder and solvent for solution for injection is supplied as a white to off-white powder in a small glass vial together with an ampoule containing 2 ml of water for injections. The powder is reconstituted in the water before it is injected by a doctor or nurse.

Xolair 150 mg powder and solvent for solution for injection is available in packs containing one vial of powder for solution for injection and one ampoule of 2 ml water for injections, and in multipacks containing four or ten intermediate packs, each with one vial of powder for solution for injection and one ampoule of 2 ml water for injections. Not all pack sizes may be marketed.

Xolair is also available in vials with 75 mg omalizumab.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for healthcare professionals only:

The lyophilised medicinal product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted medicinal product care must be taken to withdraw all of the medicinal product from the vial before expelling any air or excess solution from the syringe in order to obtain the 1.2 ml.

To prepare Xolair 150 mg vials for subcutaneous administration, please adhere to the following instructions:

1. Draw 1.4 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 vial containing the lyophilised powder using standard aseptic techniques, directing the water for injections directly onto the powder.

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

4. To aid in dissolution after completing step 3, gently swirl the 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 medicinal product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow. Do not use if solid particles are present.

5. Invert the vial for at least 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-ml syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Keeping the vial inverted position the needle tip at the very bottom of the solution in the vial 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, it may take 5-10 seconds to administer the solution by subcutaneous injection.

   The vial delivers 1.2 ml (150 mg) of Xolair. For a 75 mg dose, draw up 0.6 ml into the syringe and discard the remaining solution.

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

Package leaflet: Information for the user

Xolair 75 mg solution for injection
omalizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xolair is and what it is used for

The active substance of Xolair is omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body; it belongs to a class of medicines called monoclonal antibodies. It is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults and adolescents (12 years of age and older) and children (6 to less than 12 years of age) who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high-dose steroid inhalers or beta-agonist inhalers.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE plays a key role in causing allergic asthma.

2. What you need to know before you are given Xolair

You should not be given Xolair
- if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic to any of the ingredients, tell your doctor as you should not be given Xolair.

Warnings and precautions
Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.

A certain type of allergic reaction called serum sickness has been observed in patients treated with Xolair. The symptoms of serum sickness can be one or more of the following symptoms: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Take special care with Xolair if you have ever had an allergic reaction to latex (the needle cap of the syringe may contain dry rubber (latex)).

Churg-Strauss and Hypereosinophilic syndrome have been observed in patients treated with Xolair. The symptoms may include one or more of the following: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arm and legs. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Talk to your doctor before you are given Xolair:
- If you have kidney or liver problems.
- If you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
- If you live in a region where infections caused by parasites are common or if you are travelling to such a region as Xolair may weaken your resistance to such infections.

Xolair does not treat acute asthma symptoms, such as a sudden asthma attack. Therefore Xolair should not be used to treat such symptoms.

Xolair is not meant to prevent or treat other allergy-type conditions, such as sudden allergic reactions, hyperimmunoglobulin E syndrome (an inherited immune disorder), aspergillosis (a fungus-related lung disease), food allergy, eczema or hay fever because Xolair has not been studied in these conditions.

Children (under 6 years of age)
Xolair should not be given to children under 6 years of age. There are not enough data in this group.

Other medicines and Xolair
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

This is especially important if you are taking:
- medicines to treat an infection caused by a parasite, as Xolair may reduce the effect of your medicines,
- inhaled corticosteroids and other medicines for allergic asthma.

Pregnancy and breast-feeding
You should not be given Xolair when you are pregnant, unless this is considered necessary by your doctor.

If you plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor immediately.

You should not be given Xolair when you are breast-feeding.

Driving and using machines
It is unlikely that Xolair will affect your ability to drive and use machines.

3. How Xolair is given

Instructions on how to use Xolair are given in the section "Information for the healthcare professional".

Your doctor will work out how much Xolair you need, and how often you will be given it. This depends on your body weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in your blood.

Xolair is given to you by a doctor or nurse as an injection just under the skin (subcutaneously).

Follow carefully all instructions given by your doctor or nurse.

How much you will be given
You will be given 1 to 4 injections at a time, either every two weeks, or every four weeks.

Carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medicines without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes between 12 and 16 weeks to have the full effect.

Use in children and adolescents
Xolair can be given to children and adolescents aged 6 years or older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers or beta-agonist inhalers. Your doctor will work out how much Xolair your child needs and how often it needs to be given. This will depend on your child's weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in his/her blood.

If a dose of Xolair is missed
Contact your doctor or hospital as soon as possible to re-schedule your appointment.

If you stop treatment with Xolair
Do not stop treatment with Xolair unless your doctor tells you to. Interrupting or stopping the treatment with Xolair may cause your asthma symptoms to come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by Xolair are usually mild to moderate but can occasionally be serious.

<u>Serious side effects include</u>:
Rare side effects (may affect up to 1 in 1,000 people)
- Sudden severe allergic reactions: if you notice any serious sudden signs of allergy or combination of signs such as rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Xolair you may be more at risk of developing a severe allergic reaction following use of Xolair.
- Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)
- Development of one or more of the following symptoms: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arms and legs (signs of so-called "Churg-Strauss syndrome or hypereosinophilic syndrome").
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Development of any of the following symptoms, especially if in combination: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain (signs of serum sickness).

If you experience any of these, tell your doctor or nurse straight away.

Other side effects include:
Very common side effects (may affect more than 1 in 10 people)
- fever (in children)

Common side effects (may affect up to 1 in 10 people)
- reactions at the injection site including pain, swelling, itching and redness
- pain in the upper part of the tummy (in children)
- headache (very common in children)

Uncommon side effects (may affect up to 1 in 100 people)
- feeling dizzy, sleepy or tired
- tingling or numbness of the hands or feet
- fainting, low blood pressure while sitting or standing (postural hypotension), flushing
- sore throat, coughing, acute breathing problems
- feeling sick (nausea), diarrhoea, indigestion
- itching, hives, rash, increased sensitivity of the skin to sun
- weight increase
- flu-like symptoms
- swelling arms

Rare side effects (may affect up to 1 in 1,000 people)
- parasitic infection

Not known (frequency cannot be estimated from the available data)
- joint pain, muscle pain and joint swelling
- hair loss

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xolair

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from light.
- Store in a refrigerator (2°C – 8°C). Do not freeze.
- Do not use any pack that is damaged or shows signs of tampering.

6. Contents of the pack and other information

What Xolair contains
- The active substance is omalizumab. One syringe of 0.5 ml solution contains 75 mg omalizumab.
- The other ingredients are L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, Polysorbate 20 and water for injections.
- The needle cap of the syringe may contain dry rubber (latex).

What Xolair looks like and contents of the pack
Xolair solution for injection is supplied as a clear to slightly opalescent, colourless to pale brownish-yellow solution in a pre-filled syringe.

Xolair 75 mg solution for injection is available in packs containing 1 pre-filled syringe and in multipacks comprising 4 or 10 intermediate packs, each containing 1 pre-filled syringe.

Not all pack sizes may be marketed in your country.

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Manufacturer
Novartis Pharma GmbH
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Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

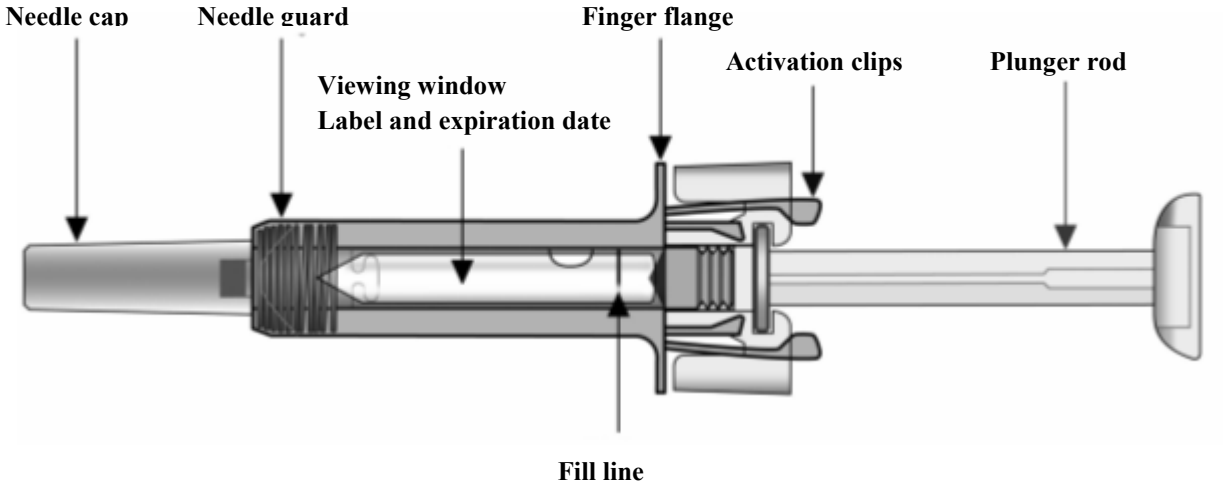
INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for 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



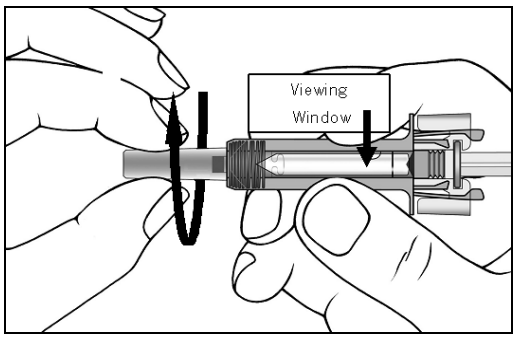
Xolair syringes are intended to be used by a healthcare professional only.

The needle cap of the syringe may contain dry rubber (latex), which should not be handled by persons sensitive to this substance.

Preparing the syringe for use

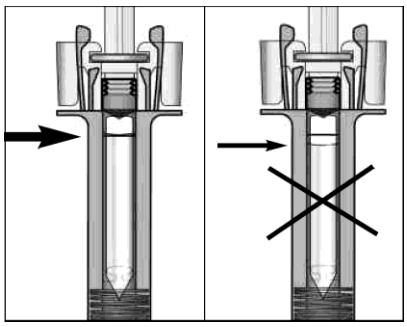
Prior to completion of the injection, avoid contact with the device activation clips (see first illustration) to keep from prematurely covering the needle with the needle guard.

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 pack to the pharmacy.
7. Holding the syringe horizontally (as shown below), look into the viewing window to check the dose (75 mg) of medicine and the expiry date printed on the label. Note: Rotate the inner part of the syringe assembly as shown below so that the label can be read in the viewing window.

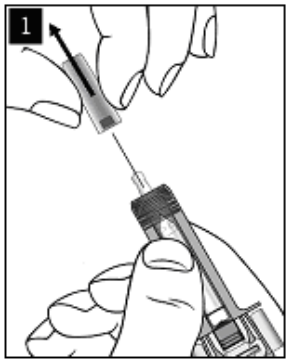
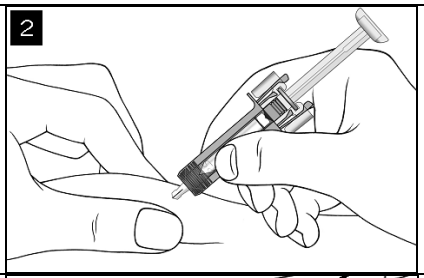
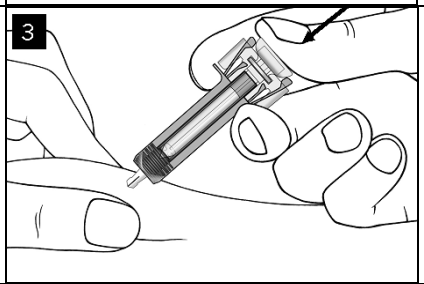
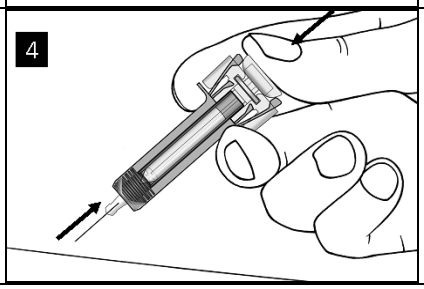


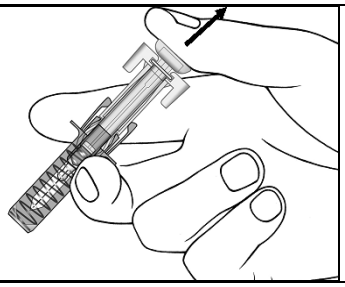
DO NOT USE if the product has expired or if the dose is incorrect. In both these cases, return the entire pack to the pharmacy.

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.



Using the syringe

	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.
	Gently pinch the skin at the injection site and insert the needle.
	Holding onto the finger flange, slowly depress the plunger as far as it will go. If any solution leaks from the injection site, insert the needle further.
	Keeping the plunger fully depressed, carefully lift the needle straight out from the injection site.

	5 	Slowly release the plunger and allow the needle guard to automatically cover the exposed needle. Hold gauze on the injection site for approximately 30 seconds.

Disposal instructions
Dispose of the used syringe immediately in a sharps container. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Xolair 150 mg solution for injection
omalizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xolair is and what it is used for

Xolair is used for the treatment of allergic asthma and chronic spontaneous urticaria (CSU). The active substance of Xolair is omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body; it belongs to a class of medicines called monoclonal antibodies. Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE plays a key role in causing allergic asthma or CSU.

Allergic asthma
This medicine is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults and adolescents (12 years of age and older) and children (6 to less than 12 years of age) who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high-dose steroid inhalers or beta-agonist inhalers.

Chronic spontaneous urticaria (CSU)
This medicine is used to treat chronic spontaneous urticaria in adults and adolescents (12 years of age or older) who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

2. What you need to know before you are given Xolair

You should not be given Xolair
- if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic to any of the ingredients, tell your doctor as you should not be given Xolair.

Warnings and precautions
Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.

A certain type of allergic reaction called serum sickness has been observed in patients treated with Xolair. The symptoms of serum sickness can be one or more of the following symptoms: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Take special care with Xolair if you have ever had an allergic reaction to latex (the needle cap of the syringe may contain dry rubber (latex)).

Churg-Strauss and Hypereosinophilic syndrome have been observed in allergic asthma patients treated with Xolair. The symptoms may include one or more of the following: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arm and legs. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Talk to your doctor before you are given Xolair:
- If you have kidney or liver problems.
- If you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
- If you live in a region where infections caused by parasites are common or if you are travelling to such a region as Xolair may weaken your resistance to such infections.

Xolair does not treat acute asthma symptoms, such as a sudden asthma attack. Therefore Xolair should not be used to treat such symptoms.

Xolair is not meant to prevent or treat other allergy-type conditions, such as sudden allergic reactions, hyperimmunoglobulin E syndrome (an inherited immune disorder), aspergillosis (a fungus-related lung disease), food allergy, eczema or hay fever because Xolair has not been studied in these conditions.

Children and adolescents
Allergic asthma
Xolair is not recommended for children under 6 years of age.

Chronic spontaneous urticaria (CSU)
Do not give Xolair to children under 12 years of age. Its use in children under 12 has not been studied.

Other medicines and Xolair
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

This is especially important if you are taking:
- medicines to treat an infection caused by a parasite, as Xolair may reduce the effect of your medicines,
- inhaled corticosteroids and other medicines for allergic asthma.

Pregnancy and breast-feeding
You should not be given Xolair when you are pregnant, unless this is considered necessary by your doctor.

If you plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor immediately.

You should not be given Xolair when you are breast-feeding.

Driving and using machines
It is unlikely that Xolair will affect your ability to drive and use machines.

3. How Xolair is given

Instructions on how to use Xolair are given in the section "Information for the healthcare professional".

Xolair is given to you by a doctor or nurse as an injection just under the skin (subcutaneously).

Follow carefully all instructions given by your doctor or nurse.

How much you will be given
Allergic asthma
Your doctor will work out how much Xolair you need and how often you will be given it. This depends on your body weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in your blood.

You will be given 1 to 4 injections at a time, either every two weeks, or every four weeks.

Carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medicines without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes between 12 and 16 weeks to have the full effect.

Chronic spontaneous urticaria (CSU)
You will be given two 150 mg injections at a time every four weeks.

Continue taking your current medicine for CSU during Xolair treatment. Do not stop taking any medicine without talking to your doctor first.

Use in children and adolescents
Allergic asthma
Xolair can be given to children and adolescents aged 6 years or older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers or beta-agonist inhalers. Your doctor will work out how much Xolair your child needs and how often it needs to be given. This will depend on your child's weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in his/her blood.

Chronic spontaneous urticaria (CSU)
Xolair can be given to adolescents aged 12 years or older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

If a dose of Xolair is missed
Contact your doctor or hospital as soon as possible to re-schedule your appointment.

If you stop treatment with Xolair
Do not stop treatment with Xolair unless your doctor tells you to. Interrupting or stopping the treatment with Xolair may cause your asthma or CSU symptoms to come back.

However, if you are being treated for CSU, your doctor may stop Xolair treatment from time to time so that your symptoms can be assessed. Follow your doctor's instructions.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by Xolair are usually mild to moderate but can occasionally be serious.

Serious side effects include:
Rare side effects (may affect up to 1 in 1,000 people)
- Sudden severe allergic reactions: if you notice any serious sudden signs of allergy or combination of signs such as rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Xolair you may be more at risk of developing a severe allergic reaction following use of Xolair.
- Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)
- Development of one or more of the following symptoms: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arms and legs (signs of so-called "Churg-Strauss syndrome or hypereosinophilic syndrome").
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Development of any of the following symptoms, especially if in combination: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain (signs of serum sickness).

If you experience any of these, tell your doctor or nurse straight away.

Other side effects include:
Very common side effects (may affect more than 1 in 10 people)
- fever (in children)

Common side effects (may affect up to 1 in 10 people)
- reactions at the injection site including pain, swelling, itching and redness
- pain in the upper part of the tummy (in children)
- headache (very common in children)
- upper respiratory tract infection, such as inflammation of the pharynx and common cold
- feeling of pressure or pain in the cheeks and forehead (sinusitis, sinus headache)
- pain in joints (arthralgia)

Uncommon side effects (may affect up to 1 in 100 people)
- feeling dizzy, sleepy or tired
- tingling or numbness of the hands or feet
- fainting, low blood pressure while sitting or standing (postural hypotension), flushing
- sore throat, coughing, acute breathing problems
- feeling sick (nausea), diarrhoea, indigestion
- itching, hives, rash, increased sensitivity of the skin to sun
- weight increase
- flu-like symptoms
- swelling arms

Rare side effects (may affect up to 1 in 1,000 people)
- parasitic infection

Not known (frequency cannot be estimated from the available data)
- muscle pain and joint swelling
- hair loss

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xolair

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from light.
- Store in a refrigerator (2°C – 8°C). Do not freeze.
- Do not use any pack that is damaged or shows signs of tampering.

6. Contents of the pack and other information

What Xolair contains
- The active substance is omalizumab. One syringe of 1 ml solution contains 150 mg omalizumab.
- The other ingredients are L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, Polysorbate 20 and water for injections.
- The needle cap of the syringe may contain dry rubber (latex).

What Xolair looks like and contents of the pack
Xolair solution for injection is supplied as a clear to slightly opalescent, colourless to pale brownish-yellow solution in a pre-filled syringe.

Xolair 150 mg solution for injection is available in packs containing 1 pre-filled syringe and in multipacks comprising 4 or 10 intermediate packs, each containing 1 pre-filled syringe.

Not all pack sizes may be marketed in your country.

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Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

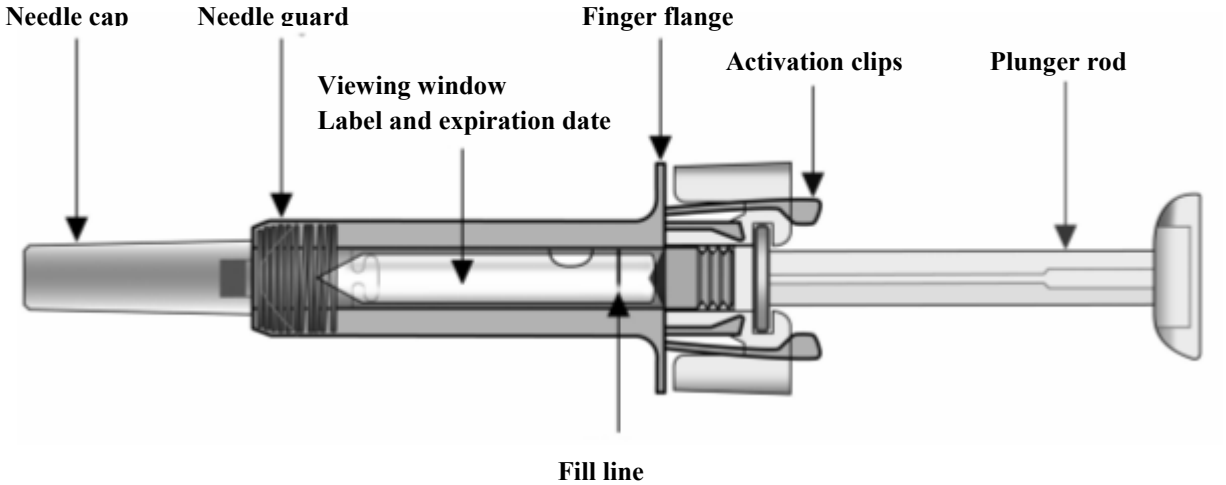
INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for 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



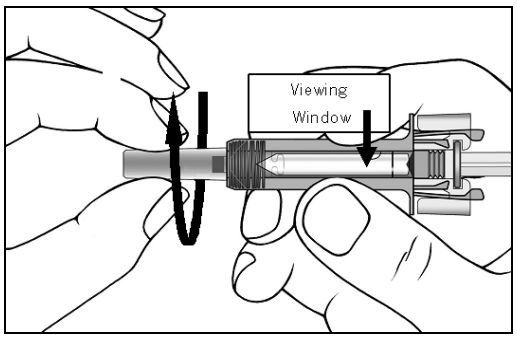
Xolair syringes are intended to be used by a healthcare professional only.

The needle cap of the syringe may contain dry rubber (latex), which should not be handled by persons sensitive to this substance.

Preparing the syringe for use

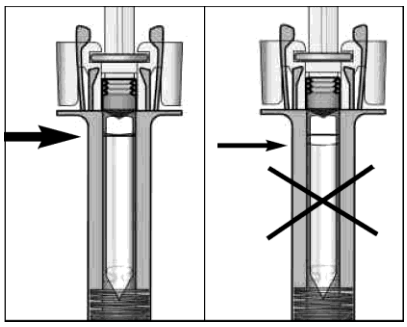
Prior to completion of the injection, avoid contact with the device activation clips (see first illustration) to keep from prematurely covering the needle with the needle guard.

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 pack to the pharmacy.
7. Holding the syringe horizontally (as shown below), look into the viewing window to check the dose (150 mg) of medicine and the expiry date printed on the label. Note: Rotate the inner part of the syringe assembly as shown below so that the label can be read in the viewing window.

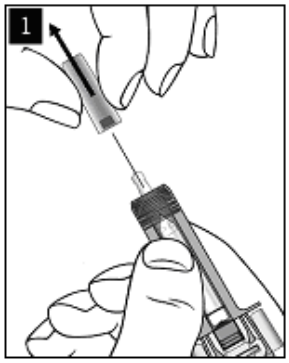
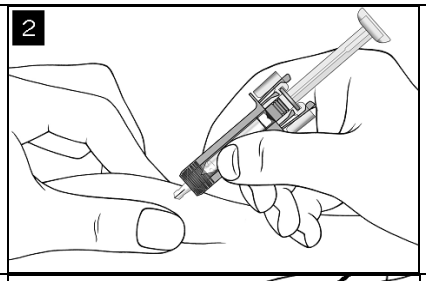
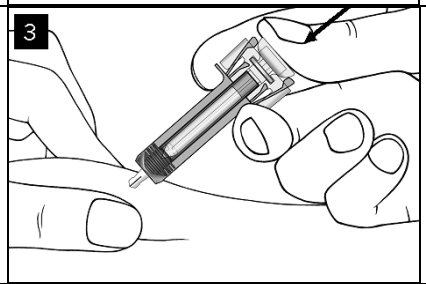
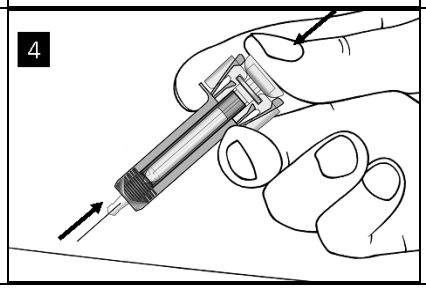


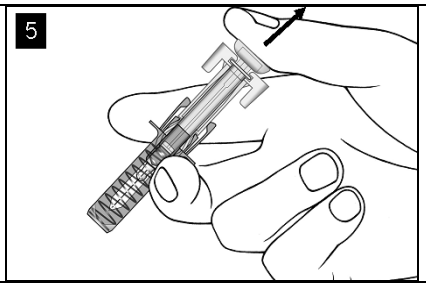
DO NOT USE if the product has expired or if the dose is incorrect. In both these cases, return the entire pack to the pharmacy.

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.



Using the syringe

	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.
	Gently pinch the skin at the injection site and insert the needle.
	Holding onto the finger flange, slowly depress the plunger as far as it will go. If any solution leaks from the injection site, insert the needle further.
	Keeping the plunger fully depressed, carefully lift the needle straight out from the injection site.

	5 	Slowly release the plunger and allow the needle guard to automatically cover the exposed needle. Hold gauze on the injection site for approximately 30 seconds.

Disposal instructions
Dispose of the used syringe immediately in a sharps container. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for omalizumab, the scientific conclusions of CHMP are as follows:

Cases of systemic lupus erythematosus (SLE) in relation to Xolair treatment, including two cases with positive dechallenge and one case with positive dechallenge /rechallenged, were reported. Although in the majority of cases the information was too limited to allow a causality assessment, confounding factors such as pre-existing lupus, including potential incipient SLE, were present in many of the remaining cases and the pathogenesis of SLE/drug-induced lupus is still poorly understood and probably multifactorial, it does not appear unreasonable that Xolair, a drug that forms immune complexes with IgE with the potential to induce immune complex injury and for which events such as serum sickness have been rarely reported, could play a role in the pathogenesis of SLE/drug-induced lupus. After a thorough assessment of the available data, there appears to be reasonable support for the possibility of a causal relationship between Xolair and systemic lupus erythematosus.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing omalizumab were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for omalizumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing omalizumab is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.