

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Xolair 75 mg solution for injection in pre-filled syringe  
Xolair 75 mg solution for injection in pre-filled pen

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Xolair 75 mg solution for injection in pre-filled syringe

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

Xolair 75 mg solution for injection in pre-filled pen

Each pre-filled pen contains 75 mg of omalizumab\* in 0.5 ml solution.

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

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Solution for injection (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 rhinosinusitis with nasal polyps (CRSwNP)

Xolair is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control.

### **4.2 Posology and method of administration**

Treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma or chronic rhinosinusitis with nasal polyps (CRSwNP).

#### Posology

Dosing for allergic asthma and CRSwNP follows the same dosing principles. The appropriate dose and frequency of omalizumab for these conditions 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 omalizumab in 1 to 4 injections may be needed for each administration.

Allergic asthma patients with baseline 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.

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

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

**Table 1 Conversion from dose to number of pre-filled syringes/pens\*, number of injections\*\* and total injection volume for each administration**

Dose (mg)	Number of syringes/pens*			Number of injections	Total injection volume (ml)
	75 mg	150 mg	300 mg*		
75	1	0	0	1	0.5
150	0	1	0	1	1.0
225	1	1	0	2	1.5
300	0	0	1	1	2.0
375	1	0	1	2	2.5
450	0	1	1	2	3.0
525	1	1	1	3	3.5
600	0	0	2	2	4.0

\*Xolair 300 mg pre-filled syringe and all dose strengths of Xolair pre-filled pen are not intended for use in patients <12 years of age.

\*\*This table represents the least number of injections for the patients, however there are other syringe/pen dosing combinations possible to achieve the desired dose.

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

<b>Baseline IgE (IU/ml)</b>	<b>Body weight (kg)</b>									
	≥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	ADMINISTRATION EVERY 2 WEEKS SEE TABLE 3
>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- 1 000										
>1 000- 1 100										

\*Body weights below 30 kg were not studied in the pivotal trials for CRSwNP.

**Table 3 ADMINISTRATION EVERY 2 WEEKS. Omalizumab 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									
>100-200	SEE TABLE 2									
>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			
>900-1 000	225	300	375	450	525	600				
>1 000-1 100	225	300	375	450	600					
>1 100-1 200	300	300	450	525	600	Insufficient data to recommend a dose				
>1 200-1 300	300	375	450	525						
>1 300-1 500	300	375	525	600						

\*Body weights below 30 kg were not studied in the pivotal trials for CRSwNP.

#### Treatment duration, monitoring and dose adjustments

##### *Allergic asthma*

Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for the 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 treatment 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).

##### *Chronic rhinosinusitis with nasal polyps (CRSwNP)*

In clinical trials for CRSwNP, changes in nasal polyps score (NPS) and nasal congestion score (NCS) were observed at 4 weeks. The need for continued therapy should be periodically reassessed based upon the patient's disease severity and level of symptom control.

##### *Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)*

Discontinuation of 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 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 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 omalizumab 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, omalizumab should be administered with caution (see section 4.4).

##### *Paediatric population*

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

In CRSwNP, the safety and efficacy of omalizumab in patients below the age of 18 years have not been established. No data are available.

#### Method of administration

For subcutaneous administration only. Omalizumab must not be administered by the intravenous or intramuscular route.

Xolair 300 mg pre-filled syringe and all dose strengths of Xolair pre-filled pen are not intended for use in children <12 years of age. Xolair 75 mg pre-filled syringe and Xolair 150 mg pre-filled syringe may be used in children 6 to 11 years of age with allergic asthma.

If more than one injection is needed to achieve the required dose, injections should be divided across two or more injection sites (Table 1).

Patients with no known history of anaphylaxis may self-inject Xolair or be injected by a caregiver from the 4th dose onwards if a physician determines that this is appropriate (see section 4.4). The patient or the caregiver must have been trained in the correct injection technique and the recognition of the early signs and symptoms of serious allergic reactions.

Patients or caregivers should be instructed to inject the full amount of Xolair according to the instructions for use provided in 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**

#### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

#### General

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

Omalizumab 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. Omalizumab is not indicated for the treatment of these conditions.

Omalizumab 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 omalizumab in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of omalizumab therapy in allergic asthma or CRSwNP 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, even after a long duration of treatment. However, most of these reactions occurred within 2 hours after the first and subsequent injections of omalizumab but some started beyond 2 hours and even beyond 24 hours after the injection. The majority of anaphylactic reactions occurred within the first 3 doses of omalizumab. Therefore, the first 3 doses must be administered either by or under the supervision of a healthcare professional. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following omalizumab administration. Therefore for patients with a known history of anaphylaxis, omalizumab must be administered by a health care professional, who should always have medicinal products for the treatment of anaphylactic reactions available for immediate use following administration of omalizumab. If an anaphylactic or other serious allergic reaction occurs, administration of omalizumab must be discontinued immediately, and appropriate therapy initiated. Patients should be informed that such reactions are possible, and prompt medical attention should be sought if allergic reactions occur.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-omalizumab 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 omalizumab should be considered.

#### Latex-sensitive individuals (pre-filled syringe)

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

#### Allergic asthma

In clinical studies omalizumab 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 omalizumab was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of omalizumab in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where omalizumab was co-administered with immunotherapy, the safety and efficacy of omalizumab in combination with specific immunotherapy were found to be no different to that of omalizumab alone.

#### Chronic rhinosinusitis with nasal polyps (CRSwNP)

In clinical studies omalizumab was used in conjunction with intranasal mometasone spray as per protocol. Other commonly used concomitant medicinal products included other intranasal corticosteroids, bronchodilators, antihistamines, leukotriene receptor antagonists, adrenergics/sympathomimetics and local nasal anaesthetics. There was no indication that the safety of omalizumab was altered by the concomitant use of these other commonly used medicinal products.



## 4.6 Fertility, pregnancy and lactation

### Pregnancy

A moderate amount of data on pregnant women (between 300-1 000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foeto/neonatal toxicity. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to omalizumab showed the prevalence of major congenital anomalies was similar (8.1% vs. 8.9%) between EXPECT and disease-matched (moderate and severe asthma) patients. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Omalizumab crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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).

If clinically needed, the use of omalizumab may be considered during pregnancy.

### Breast-feeding

Immunoglobulins G (IgGs) are present in human milk and therefore it is expected that omalizumab will be present in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3).

The EXPECT study, with 154 infants who had been exposed to omalizumab during pregnancy and through breast-feeding did not indicate adverse effects on the breast-fed infant. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breast-fed newborns/infants are anticipated. Consequently, if clinically needed, the use of omalizumab may be considered 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 a separate non-clinical genotoxicity study.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

### Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

#### Summary of the safety profile

During allergic asthma 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. In clinical trials in patients  $\geq 18$  years of age

in CRSwNP, the most commonly reported adverse reactions were headache, dizziness, arthralgia, abdominal pain upper and injection site reactions.

#### Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total allergic asthma and CRSwNP 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1\,000$  to  $< 1/100$ ), rare ( $\geq 1/10\,000$  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 and CRSwNP**

<b>Infections and infestations</b>	
Uncommon	Pharyngitis
Rare	Parasitic infection
<b>Blood and lymphatic system disorders</b>	
Not known	Idiopathic thrombocytopenia, including severe cases
<b>Immune system disorders</b>	
Rare	Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development
Not known	Serum sickness, may include fever and lymphadenopathy
<b>Nervous system disorders</b>	
Common	Headache*
Uncommon	Syncope, paraesthesia, somnolence, dizziness#
<b>Vascular disorders</b>	
Uncommon	Postural hypotension, flushing
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon	Allergic bronchospasm, coughing
Rare	Laryngoedema
Not known	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
<b>Gastrointestinal disorders</b>	
Common	Abdominal pain upper**.#
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon	Photosensitivity, urticaria, rash, pruritus
Rare	Angioedema
Not known	Alopecia
<b>Musculoskeletal and connective tissue disorders</b>	
Common	Athralgia†
Rare	Systemic lupus erythematosus (SLE)
Not known	Myalgia, joint swelling
<b>General disorders and administration site conditions</b>	
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

#: Common in nasal polyp trials

†: Unknown in allergic asthma trials

#### 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. 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

#### Mechanism of action

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (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. 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.

Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils. Omalizumab inhibits IgE-mediated inflammation, as evidenced by reduced blood and tissue eosinophils and reduced inflammatory mediators, including IL-4, IL-5, and IL-13 by innate, adaptive and non-immune cells.

#### Pharmacodynamic effects

##### Allergic asthma

The *in vitro* histamine release from basophils isolated from omalizumab-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 omalizumab dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

##### Chronic rhinosinusitis with nasal polyps (CRSwNP)

In clinical studies in patients with CRSwNP, omalizumab treatment led to a reduction in serum free IgE (approx. 95%) and an increase in serum total IgE levels, to a similar extent as observed in patients with allergic asthma. Total IgE levels in serum increased due to the formation of omalizumab-IgE complexes that have a slower elimination rate compared with free IgE.

#### Clinical efficacy and safety

##### Allergic asthma

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

The efficacy and safety of omalizumab 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<sub>1</sub> 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 omalizumab 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 omalizumab 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  $\geq 76$  IU/ml were more likely to experience clinically meaningful benefit to omalizumab. In these patients in study 1 omalizumab reduced the rate of asthma exacerbations by 40% ( $p = 0.002$ ). In addition more patients had clinically meaningful responses in the total IgE  $\geq 76$  IU/ml population across the omalizumab severe asthma programme. Table 5 includes results in the study 1 population.

**Table 5 Results of study 1**

	Whole study 1 population	
	Omalizumab N=209	Placebo N=210
<b>Asthma exacerbations</b>		
Rate per 28-week period	0.74	0.92
% reduction, p-value for rate ratio	19.4%, p = 0.153	
<b>Severe asthma exacerbations</b>		
Rate per 28-week period	0.24	0.48
% reduction, p-value for rate ratio	50.1%, p = 0.002	
<b>Emergency visits</b>		
Rate per 28-week period	0.24	0.43
% reduction, p-value for rate ratio	43.9%, p = 0.038	
<b>Physician's overall assessment</b>		
% responders*	60.5%	42.8%
p-value**	<0.001	
<b>AQL improvement</b>		
% 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 omalizumab in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with omalizumab 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 omalizumab 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 omalizumab 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 omalizumab were able to reduce their fluticasone dose to  $\leq 500$  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 omalizumab 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 medicinal product use, spirometry and exacerbations. In all five studies a significantly greater proportion of omalizumab-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 omalizumab 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 ( $\geq 500$  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 medicinal product 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.

#### *Chronic rhinosinusitis with nasal polyps (CRSwNP)*

The safety and efficacy of omalizumab were evaluated in two randomised, double-blind, placebo-controlled trials in patients with CRSwNP (Table 7). Patients received omalizumab or placebo subcutaneously every 2 or 4 weeks (see section 4.2). All patients received background intranasal mometasone therapy throughout the study. Prior sino-nasal surgery or prior systemic corticosteroid usage were not required for inclusion in the studies. Patients received omalizumab or placebo for 24 weeks followed by a 4-week follow-up period. Demographics and baseline characteristics, including allergic comorbidities, are described in Table 6.

**Table 6 Demographics and baseline characteristics of nasal polyp studies**

<b>Parameter</b>	<b>Nasal polyp study 1 N=138</b>	<b>Nasal polyp study 2 N=127</b>
Mean age (years) (SD)	51.0 (13.2)	50.1 (11.9)
% Male	63.8	65.4
Patients with systemic corticosteroid use in the previous year (%)	18.8	26.0
Bilateral endoscopic nasal polyp score (NPS): mean (SD), range 0-8	6.2 (1.0)	6.3 (0.9)
Nasal congestion score (NCS): mean (SD), range 0-3	2.4 (0.6)	2.3 (0.7)
Sense of smell score: mean (SD), range 0-3	2.7 (0.7)	2.7 (0.7)
SNOT-22 total score: mean (SD) range 0-110	60.1 (17.7)	59.5 (19.3)
Blood eosinophils (cells/ $\mu$ l): mean (SD)	346.1 (284.1)	334.6 (187.6)
Total IgE IU/ml: mean (SD)	160.9 (139.6)	190.2 (200.5)
Asthma (%)	53.6	60.6
Mild (%)	37.8	32.5
Moderate (%)	58.1	58.4
Severe (%)	4.1	9.1
Aspirin exacerbated respiratory disease (%)	19.6	35.4
Allergic rhinitis	43.5	42.5

SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; IgE = Immunoglobulin E; IU = international units. For NPS, NCS, and SNOT-22 higher scores indicate greater disease severity.

The co-primary endpoints were bilateral nasal polyps score (NPS) and average daily nasal congestion score (NCS) at Week 24. In both nasal polyp studies 1 and 2, patients who received omalizumab had statistically significant greater improvements from baseline at Week 24 in NPS and weekly average NCS than patients who received placebo. Results from nasal polyp studies 1 and 2 are shown in Table 7.

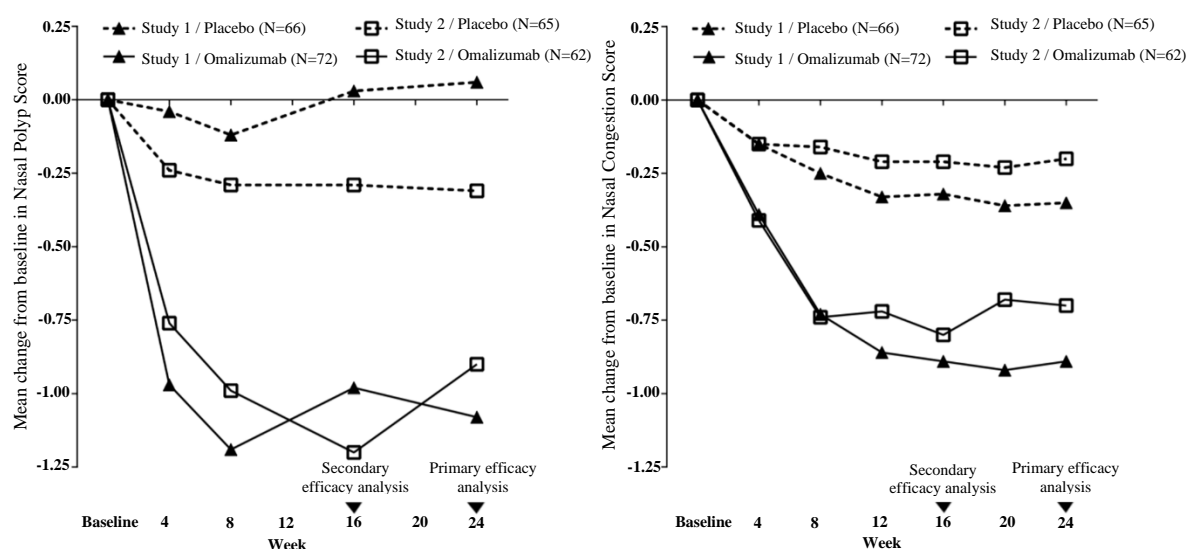
**Table 7** Change from baseline at Week 24 in clinical scores from nasal polyp study 1, nasal polyp study 2, and pooled data

	Nasal polyp study 1		Nasal polyp study 2		Nasal polyp pooled results	
	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab
N	66	72	65	62	131	134
Nasal polyp score						
Baseline mean	6.32	6.19	6.09	6.44	6.21	6.31
LS mean change at Week 24	0.06	-1.08	-0.31	-0.90	-0.13	-0.99
Difference (95% CI)	-1.14 (-1.59, -0.69)		-0.59 (-1.05, -0.12)		-0.86 (-1.18, -0.54)	
p-value	<0.0001		0.0140		<0.0001	
7-day average of daily nasal congestion score						
Baseline mean	2.46	2.40	2.29	2.26	2.38	2.34
LS mean change at Week 24	-0.35	-0.89	-0.20	-0.70	-0.28	-0.80
Difference (95% CI)	-0.55 (-0.84, -0.25)		-0.50 (-0.80, -0.19)		-0.52 (-0.73, -0.31)	
p-value	0.0004		0.0017		<0.0001	
TNSS						
Baseline mean	9.33	8.56	8.73	8.37	9.03	8.47
LS mean change at Week 24	-1.06	-2.97	-0.44	-2.53	-0.77	-2.75
Difference (95% CI)	-1.91 (-2.85, -0.96)		-2.09 (-3.00, -1.18)		-1.98 (-2.63, -1.33)	
p-value	0.0001		<0.0001		<0.0001	
SNOT-22						
Baseline mean	60.26	59.82	59.80	59.21	60.03	59.54
LS mean change at Week 24	-8.58	-24.70	-6.55	-21.59	-7.73	-23.10
Difference (95% CI)	-16.12 (-21.86, -10.38)		-15.04 (-21.26, -8.82)		-15.36 (-19.57, -11.16)	
p-value (MID = 8.9)	<0.0001		<0.0001		<0.0001	
UPSIT						
Baseline mean	13.56	12.78	13.27	12.87	13.41	12.82
LS mean change at Week 24	0.63	4.44	0.44	4.31	0.54	4.38
Difference (95% CI)	3.81 (1.38, 6.24)		3.86 (1.57, 6.15)		3.84 (2.17, 5.51)	
p-value	0.0024		0.0011		<0.0001	

LS=least-square; CI = confidence interval; TNSS = Total nasal symptom score; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; UPSIT = University of Pennsylvania Smell Identification Test; MID = minimal important difference.



**Figure 1 Mean change from baseline in nasal congestion score and mean change from baseline in nasal polyp score by treatment group in nasal polyp study 1 and study 2**



In a pre-specified pooled analysis of rescue treatment (systemic corticosteroids for  $\geq 3$  consecutive days or nasal polypectomy) during the 24-week treatment period, the proportion of patients requiring rescue treatment was lower in omalizumab compared to placebo (2.3% versus 6.2%, respectively). The odds-ratio of having taken rescue treatment in omalizumab compared to placebo was 0.38 (95% CI: 0.10, 1.49). There were no sino-nasal surgeries reported in either study.

The long-term efficacy and safety of omalizumab in patients with CRSwNP who had participated in nasal polyp studies 1 and 2 was assessed in an open-label extension study. Efficacy data from this study suggest that clinical benefit provided at Week 24 was sustained through to Week 52. Safety data were overall consistent with the known safety profile of omalizumab.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma as well as in adult patients with CRSwNP. The general pharmacokinetic characteristics of omalizumab are similar in these patient 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, 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  $78 \pm 32$  ml/kg.

## Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the 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  $2.4 \pm 1.1$  ml/kg/day. In addition, doubling of body weight approximately doubled apparent clearance.

## Characteristics in patient populations

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

The population pharmacokinetics of omalizumab 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 for patients with allergic asthma; 18 to 75 years for patients with CRSwNP), 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**

Arginine hydrochloride  
Histidine hydrochloride monohydrate  
Histidine  
Polysorbate 20  
Water for injections

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

18 months.

The product may be kept for a total of 48 hours at 25°C.

### **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**

#### Xolair 75 mg solution for injection in pre-filled syringe (26-gauge staked needle, blue syringe guard)

Xolair 75 mg solution for injection in pre-filled syringe is supplied as 0.5 ml solution in a pre-filled syringe barrel (type I glass) with 26-gauge staked needle (stainless steel), (type I) plunger stopper and needle cap.

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

#### Xolair 75 mg solution for injection in pre-filled syringe (27-gauge staked needle, blue plunger)

Xolair 75 mg solution for injection in pre-filled syringe is supplied as 0.5 ml solution in a pre-filled syringe barrel (type I glass) with 27-gauge staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack sizes: packs containing 1 pre-filled syringe, and multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled syringes.

#### Xolair 75 mg solution for injection in pre-filled pen

Xolair 75 mg solution for injection in pre-filled pen is supplied as 0.5 ml solution in a pre-filled pen barrel (type I glass) with 27-gauge staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack sizes: packs containing 1 pre-filled pen, and multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled pens.

Not all pack sizes may be marketed.

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

### Pre-filled syringe

The single-use pre-filled syringe is for individual use. It should be taken out of the refrigerator 30 minutes before injecting to allow it to reach room temperature.

### Pre-filled pen

The single-use pre-filled pen is for individual use. It should be taken out of the refrigerator 30 minutes before injecting to allow it to reach room temperature.

### Disposal instructions

Dispose of the used syringe or pen 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  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

## **8. MARKETING AUTHORISATION NUMBER(S)**

### Xolair 75 mg solution for injection in pre-filled syringe

EU/1/05/319/005  
EU/1/05/319/006  
EU/1/05/319/007  
EU/1/05/319/018  
EU/1/05/319/019  
EU/1/05/319/020

### Xolair 75 mg solution for injection in pre-filled pen

EU/1/05/319/021  
EU/1/05/319/022  
EU/1/05/319/023

## **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 in pre-filled syringe  
Xolair 300 mg solution for injection in pre-filled syringe  
Xolair 150 mg solution for injection in pre-filled pen  
Xolair 300 mg solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Xolair 150 mg solution for injection in pre-filled syringe

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

### Xolair 300 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 300 mg of omalizumab\* in 2 ml solution.

### Xolair 150 mg solution for injection in pre-filled pen

Each pre-filled pen contains 150 mg of omalizumab\* in 1 ml solution.

### Xolair 300 mg solution for injection in pre-filled pen

Each pre-filled pen contains 300 mg of omalizumab\* in 2 ml solution.

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

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection (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<sub>1</sub> <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 rhinosinusitis with nasal polyps (CRSwNP)

Xolair is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control.

#### 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**

Treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma, chronic rhinosinusitis with nasal polyps (CRSwNP) or chronic spontaneous urticaria.

#### Posology

##### Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

Dosing for allergic asthma and CRSwNP follows the same dosing principles. The appropriate dose and frequency of omalizumab for these conditions 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 omalizumab in 1 to 4 injections may be needed for each administration.

Allergic asthma patients with baseline 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.

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

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

**Table 1 Conversion from dose to number of pre-filled syringes/pens\*, number of injections\*\* and total injection volume for each administration**

Dose (mg)	Number of syringes/pens*			Number of injections	Total injection volume (ml)
	75 mg	150 mg	300 mg*		
75	1	0	0	1	0.5
150	0	1	0	1	1.0
225	1	1	0	2	1.5
300	0	0	1	1	2.0
375	1	0	1	2	2.5
450	0	1	1	2	3.0
525	1	1	1	3	3.5
600	0	0	2	2	4.0

\*Xolair 300 mg pre-filled syringe and all dose strengths of Xolair pre-filled pen are not intended for use in patients <12 years of age.

\*\*This table represents the least number of injections for the patients, however there are other syringe/pen dosing combinations possible to achieve the desired dose.

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

Baseline IgE (IU/ml)	Body weight (kg)									
	≥20-25*	>25-30*	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75	75	75	150	150	150	150	150	300	300
>100-200	150	150	150	300	300	300	300	300	450	600
>200-300	150	150	225	300	300	450	450	450	600	
>300-400	225	225	300	450	450	450	600	600		
>400-500	225	300	450	450	600	600				
>500-600	300	300	450	600	600					
>600-700	300		450	600						
>700-800										
>800-900										
>900-1 000										
>1 000-1 100										

ADMINISTRATION EVERY 2 WEEKS  
SEE TABLE 3

\*Body weights below 30 kg were not studied in the pivotal trials for CRSwNP.



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

Baseline IgE (IU/ml)	Body weight (kg)									
	≥20- 25*	>25- 30*	>30- 40	>40- 50	>50- 60	>60- 70	>70- 80	>80- 90	>90- 125	>125- 150
≥30-100	ADMINISTRATION EVERY 4 WEEKS									
>100-200	SEE TABLE 2									
>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- 1 000	225	300	375	450	525	600				
>1 000- 1 100	225	300	375	450	600					
>1 100- 1 200	300	300	450	525	600	Insufficient data to recommend a dose				
>1 200- 1 300	300	375	450	525						
>1 300- 1 500	300	375	525	600						

\*Body weights below 30 kg were not studied in the pivotal trials for CRSwNP.

#### Treatment duration, monitoring and dose adjustments

##### *Allergic asthma*

Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for the 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 treatment 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).

##### *Chronic rhinosinusitis with nasal polyps (CRSwNP)*

In clinical trials for CRSwNP, changes in nasal polyps score (NPS) and nasal congestion score (NCS) were observed at 4 weeks. The need for continued therapy should be periodically reassessed based upon the patient's disease severity and level of symptom control.

##### *Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)*

Discontinuation of 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 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 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)*

The recommended dose is 300 mg by subcutaneous injection every four weeks. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

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

Clinical trial experience of long-term treatment in this indication is described in section 5.1.

#### Special populations

##### *Elderly (65 years of age and older)*

There are limited data available on the use of omalizumab 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, omalizumab should be administered with caution (see section 4.4).

##### *Paediatric population*

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

In CRSwNP, the safety and efficacy of omalizumab in patients below the age of 18 years have not been established. No data are available.

In CSU, the safety and efficacy of omalizumab in patients below the age of 12 years have not been established. No data are available.

#### Method of administration

For subcutaneous administration only. Omalizumab must not be administered by the intravenous or intramuscular route.

Xolair 300 mg pre-filled syringe and all dose strengths of Xolair pre-filled pen are not intended for use in children <12 years of age. Xolair 75 mg pre-filled syringe and Xolair 150 mg pre-filled syringe may be used in children 6 to 11 years of age with allergic asthma.

If more than one injection is needed to achieve the required dose, injections should be divided across two or more injection sites (Table 1).

Patients with no known history of anaphylaxis may self-inject Xolair or be injected by a caregiver from the 4th dose onwards if a physician determines that this is appropriate (see section 4.4). The patient or the caregiver must have been trained in the correct injection technique and the recognition of the early signs and symptoms of serious allergic reactions.

Patients or caregivers should be instructed to inject the full amount of Xolair according to the instructions for use provided in 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

### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

### General

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

Omalizumab 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. Omalizumab is not indicated for the treatment of these conditions.

Omalizumab 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 omalizumab in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of omalizumab therapy in allergic asthma or CRSwNP 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, even after a long duration of treatment. However, most of these reactions occurred within 2 hours after the first and subsequent injections of omalizumab but some started beyond 2 hours and even beyond 24 hours after the injection. The majority of anaphylactic reactions occurred within the first 3 doses of omalizumab. Therefore, the first 3 doses must be administered either by or under the supervision of a healthcare professional. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following omalizumab administration. Therefore for patients with a known history of anaphylaxis, omalizumab must be administered by a health care professional, who should always have medicinal products for the treatment of anaphylactic reactions available for immediate use following administration of omalizumab. If an anaphylactic or other serious allergic reaction occurs, administration of omalizumab must be discontinued immediately, and appropriate therapy initiated. Patients should be informed that such reactions are possible, and prompt medical attention should be sought if allergic reactions occur.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-omalizumab 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 omalizumab should be considered.

#### Latex-sensitive individuals (pre-filled syringe)

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

#### Allergic asthma

In clinical studies omalizumab 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 omalizumab was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of omalizumab in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where omalizumab was co-administered with immunotherapy, the safety and efficacy of omalizumab in combination with specific immunotherapy were found to be no different to that of omalizumab alone.

### Chronic rhinosinusitis with nasal polyps (CRSwNP)

In clinical studies omalizumab was used in conjunction with intranasal mometasone spray as per protocol. Other commonly used concomitant medicinal products included other intranasal corticosteroids, bronchodilators antihistamines, leukotriene receptor antagonists, adrenergics/sympathomimetics and local nasal anesthetics. There was no indication that the safety of omalizumab was altered by the concomitant use of these other commonly used medicinal products.

### Chronic spontaneous urticaria (CSU)

In clinical studies in CSU, omalizumab 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 omalizumab 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

A moderate amount of data on pregnant women (between 300-1 000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foeto/neonatal toxicity. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to omalizumab showed the prevalence of major congenital anomalies was similar (8.1% vs. 8.9%) between EXPECT and disease-matched (moderate and severe asthma) patients. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Omalizumab crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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).

If clinically needed, the use of omalizumab may be considered during pregnancy.

### Breast-feeding

Immunoglobulins G (IgGs) are present in human milk and therefore it is expected that omalizumab will be present in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3).

The EXPECT study, with 154 infants who had been exposed to omalizumab during pregnancy and through breast-feeding did not indicate adverse effects on the breast-fed infant. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breast-fed newborns/infants are anticipated. Consequently, if clinically needed, the use of omalizumab may be considered 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 a separate non-clinical genotoxicity study.

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

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

### **4.8 Undesirable effects**

#### Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

##### Summary of the safety profile

During allergic asthma 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. In clinical trials in patients  $\geq 18$  years of age in CRSwNP, the most commonly reported adverse reactions were headache, dizziness, arthralgia, abdominal pain upper and injection site reactions.

##### Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total allergic asthma and CRSwNP 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $<1/10$ ), uncommon ( $\geq 1/1\ 000$  to  $<1/100$ ), rare ( $\geq 1/10\ 000$  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 and CRSwNP**

<b>Infections and infestations</b>	
Uncommon	Pharyngitis
Rare	Parasitic infection
<b>Blood and lymphatic system disorders</b>	
Not known	Idiopathic thrombocytopenia, including severe cases
<b>Immune system disorders</b>	
Rare	Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development
Not known	Serum sickness, may include fever and lymphadenopathy
<b>Nervous system disorders</b>	
Common	Headache*
Uncommon	Syncope, paraesthesia, somnolence, dizziness <sup>#</sup>
<b>Vascular disorders</b>	
Uncommon	Postural hypotension, flushing
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon	Allergic bronchospasm, coughing
Rare	Laryngoedema
Not known	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
<b>Gastrointestinal disorders</b>	
Common	Abdominal pain upper** <sup>#</sup>
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon	Photosensitivity, urticaria, rash, pruritus
Rare	Angioedema
Not known	Alopecia
<b>Musculoskeletal and connective tissue disorders</b>	
Common	Athralgia†
Rare	Systemic lupus erythematosus (SLE)
Not known	Myalgia, joint swelling
<b>General disorders and administration site conditions</b>	
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

<sup>#</sup>: Common in nasal polyp trials

†: Unknown in allergic asthma trials

#### 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 dose and treatment populations (with significantly different risk factors, comorbidities, concomitant medicinal products and ages [e.g. asthma trials included children from 6-12 years of age]).

Table 5 lists the adverse reactions (events occurring in  $\geq 1\%$  of patients in any treatment group and  $\geq 2\%$  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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1\,000$  to  $< 1/100$ ); rare ( $\geq 1/10\,000$  to  $< 1/1\,000$ ); 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.

In a 48-week study, 81 CSU patients received omalizumab 300 mg every 4 weeks (see section 5.1). The safety profile of long-term use was similar to the safety profile observed in 24-week studies in CSU.

#### 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. 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

#### Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

##### Mechanism of action

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (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. 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.

Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils. Omalizumab inhibits IgE-mediated inflammation, as evidenced by reduced blood and tissue eosinophils and reduced inflammatory mediators, including IL-4, IL-5, and IL-13 by innate, adaptive and non-immune cells.

### Pharmacodynamic effects

#### Allergic asthma

The *in vitro* histamine release from basophils isolated from omalizumab-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 omalizumab dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

#### Chronic rhinosinusitis with nasal polyps (CRSwNP)

In clinical studies in patients with CRSwNP, omalizumab treatment led to a reduction in serum free IgE (approx. 95%) and an increase in serum total IgE levels, to a similar extent as observed in patients with allergic asthma. Total IgE levels in serum increased due to the formation of omalizumab-IgE complexes that have a slower elimination rate compared with free IgE.

#### Chronic spontaneous urticaria (CSU)

#### Mechanism of action

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and lowers free IgE levels. 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. 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 omalizumab, free IgE levels increased towards pre-treatment levels over a 16-week treatment-free follow-up period.

### Clinical efficacy and safety

#### Allergic asthma

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

The efficacy and safety of omalizumab 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<sub>1</sub> 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 omalizumab 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 omalizumab 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  $\geq 76$  IU/ml were more likely to experience clinically meaningful benefit to omalizumab. In these patients in study 1 omalizumab reduced the rate

of asthma exacerbations by 40% ( $p = 0.002$ ). In addition more patients had clinically meaningful responses in the total IgE  $\geq 76$  IU/ml population across the omalizumab severe asthma programme. Table 6 includes results in the study 1 population.

**Table 6 Results of study 1**

	Whole study 1 population	
	Omalizumab N=209	Placebo N=210
<b>Asthma exacerbations</b>		
Rate per 28-week period	0.74	0.92
% reduction, p-value for rate ratio	19.4%, p = 0.153	
<b>Severe asthma exacerbations</b>		
Rate per 28-week period	0.24	0.48
% reduction, p-value for rate ratio	50.1%, p = 0.002	
<b>Emergency visits</b>		
Rate per 28-week period	0.24	0.43
% reduction, p-value for rate ratio	43.9%, p = 0.038	
<b>Physician's overall assessment</b>		
% responders*	60.5%	42.8%
p-value**	<0.001	
<b>AQL improvement</b>		
% 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 omalizumab in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with omalizumab 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 omalizumab 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 omalizumab 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 omalizumab were able to reduce their fluticasone dose to  $\leq 500$  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 omalizumab 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 medicinal product use, spirometry and exacerbations. In all five studies a significantly greater proportion of omalizumab-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 omalizumab 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 ( $\geq 500$  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 medicinal product 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.

### *Chronic rhinosinusitis with nasal polyps (CRSwNP)*

The safety and efficacy of omalizumab were evaluated in two randomised, double-blind, placebo-controlled trials in patients with CRSwNP (Table 8). Patients received omalizumab or placebo subcutaneously every 2 or 4 weeks (see section 4.2). All patients received background intranasal mometasone therapy throughout the study. Prior sino-nasal surgery or prior systemic corticosteroid usage were not required for inclusion in the studies. Patients received omalizumab or placebo for 24 weeks followed by a 4-week follow-up period. Demographics and baseline characteristics, including allergic comorbidities, are described in Table 7.

**Table 7 Demographics and baseline characteristics of nasal polyp studies**

<b>Parameter</b>	<b>Nasal polyp study 1 N=138</b>	<b>Nasal polyp study 2 N=127</b>
Mean age (years) (SD)	51.0 (13.2)	50.1 (11.9)
% Male	63.8	65.4
Patients with systemic corticosteroid use in the previous year (%)	18.8	26.0
Bilateral endoscopic nasal polyp score (NPS): mean (SD), range 0-8	6.2 (1.0)	6.3 (0.9)
Nasal congestion score (NCS): mean (SD), range 0-3	2.4 (0.6)	2.3 (0.7)
Sense of smell score: mean (SD), range 0-3	2.7 (0.7)	2.7 (0.7)
SNOT-22 total score: mean (SD) range 0-110	60.1 (17.7)	59.5 (19.3)
Blood eosinophils (cells/ $\mu$ l): mean (SD)	346.1 (284.1)	334.6 (187.6)
Total IgE IU/ml: mean (SD)	160.9 (139.6)	190.2 (200.5)
Asthma (%)	53.6	60.6
Mild (%)	37.8	32.5
Moderate (%)	58.1	58.4
Severe (%)	4.1	9.1
Aspirin exacerbated respiratory disease (%)	19.6	35.4
Allergic rhinitis	43.5	42.5

SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; IgE = Immunoglobulin E; IU = international units. For NPS, NCS, and SNOT-22 higher scores indicate greater disease severity.

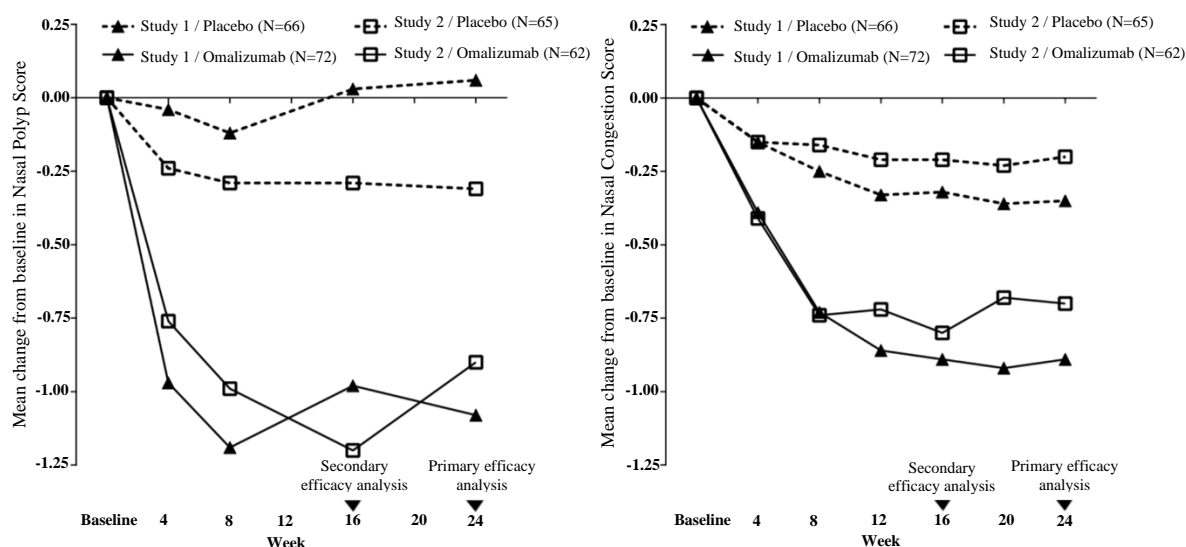
The co-primary endpoints were bilateral nasal polyps score (NPS) and average daily nasal congestion score (NCS) at Week 24. In both nasal polyp studies 1 and 2, patients who received omalizumab had statistically significant greater improvements from baseline at Week 24 in NPS and weekly average NCS than patients who received placebo. Results from nasal polyp studies 1 and 2 are shown in Table 8.

**Table 8      Change from baseline at Week 24 in clinical scores from nasal polyp study 1, nasal polyp study 2, and pooled data**

	Nasal polyp study 1		Nasal polyp study 2		Nasal polyp pooled results	
	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab
N	66	72	65	62	131	134
Nasal polyp score						
Baseline mean	6.32	6.19	6.09	6.44	6.21	6.31
LS mean change at Week 24	0.06	-1.08	-0.31	-0.90	-0.13	-0.99
Difference (95% CI)	-1.14 (-1.59, -0.69)		-0.59 (-1.05, -0.12)		-0.86 (-1.18, -0.54)	
p-value	<0.0001		0.0140		<0.0001	
7-day average of daily nasal congestion score						
Baseline mean	2.46	2.40	2.29	2.26	2.38	2.34
LS mean change at Week 24	-0.35	-0.89	-0.20	-0.70	-0.28	-0.80
Difference (95% CI)	-0.55 (-0.84, -0.25)		-0.50 (-0.80, -0.19)		-0.52 (-0.73, -0.31)	
p-value	0.0004		0.0017		<0.0001	
TNSS						
Baseline mean	9.33	8.56	8.73	8.37	9.03	8.47
LS mean change at Week 24	-1.06	-2.97	-0.44	-2.53	-0.77	-2.75
Difference (95% CI)	-1.91 (-2.85, -0.96)		-2.09 (-3.00, -1.18)		-1.98 (-2.63, -1.33)	
p-value	0.0001		<0.0001		<0.0001	
SNOT-22						
Baseline mean	60.26	59.82	59.80	59.21	60.03	59.54
LS mean change at Week 24	-8.58	-24.70	-6.55	-21.59	-7.73	-23.10
Difference (95% CI)	-16.12 (-21.86, -10.38)		-15.04 (-21.26, -8.82)		-15.36 (-19.57, -11.16)	
p-value	<0.0001		<0.0001		<0.0001	
(MID = 8.9)						
UPSIT						
Baseline mean	13.56	12.78	13.27	12.87	13.41	12.82
LS mean change at Week 24	0.63	4.44	0.44	4.31	0.54	4.38
Difference (95% CI)	3.81 (1.38, 6.24)		3.86 (1.57, 6.15)		3.84 (2.17, 5.51)	
p-value	0.0024		0.0011		<0.0001	

LS=least-square; CI = confidence interval; TNSS = Total nasal symptom score; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; UPSIT = University of Pennsylvania Smell Identification Test; MID = minimal important difference.

**Figure 1 Mean change from baseline in nasal congestion score and mean change from baseline in nasal polyp score by treatment group in nasal polyp study 1 and study 2**



In a pre-specified pooled analysis of rescue treatment (systemic corticosteroids for  $\geq 3$  consecutive days or nasal polypectomy) during the 24-week treatment period, the proportion of patients requiring rescue treatment was lower in omalizumab compared to placebo (2.3% versus 6.2%, respectively). The odds-ratio of having taken rescue treatment in omalizumab compared to placebo was 0.38 (95% CI: 0.10, 1.49). There were no sino-nasal surgeries reported in either study.

The long-term efficacy and safety of omalizumab in patients with CRSwNP who had participated in nasal polyp studies 1 and 2 was assessed in an open-label extension study. Efficacy data from this study suggest that clinical benefit provided at Week 24 was sustained through to Week 52. Safety data were overall consistent with the known safety profile of omalizumab.

### Chronic spontaneous urticaria (CSU)

The efficacy and safety of omalizumab 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 omalizumab 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  $\geq 65$  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  $\geq 16$ , and a weekly itch severity score (which is a component of the UAS7; range 0-21) of  $\geq 8$  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 medicinal products (including H1 antihistamines) for CSU symptoms prior to study enrollment. Patients received omalizumab 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 9). Statistically significant results were further observed in the responder rates for UAS7 $\leq$ 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 9 Change from baseline to week 12 in weekly itch severity score, studies 1, 2 and 3 (mITT population\*)**

	Placebo	Omalizumab 300 mg
<b>Study 1</b>		
N	80	81
Mean (SD)	-3.63 (5.22)	-9.40 (5.73)
Difference in LS means vs. placebo <sup>1</sup>	-	-5.80
95% CI for difference	-	-7.49, -4.10
P-value vs. placebo <sup>2</sup>	-	<0.0001
<b>Study 2</b>		
N	79	79
Mean (SD)	-5.14 (5.58)	-9.77 (5.95)
Difference in LS means vs. placebo <sup>1</sup>	-	-4.81
95% CI for difference	-	-6.49, -3.13
P-value vs. placebo <sup>2</sup>	-	<0.0001
<b>Study 3</b>		
N	83	252
Mean (SD)	-4.01 (5.87)	-8.55 (6.01)
Difference in LS means vs. placebo <sup>1</sup>	-	-4.52
95% CI for difference	-	-5.97, -3.08
P-value vs. placebo <sup>2</sup>	-	<0.0001

\*Modified intent-to-treat (mITT) population: included all patients who were randomised and received at least one dose of study medicinal product.

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

<sup>1</sup> The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (<13 vs.  $\geq$ 13) and baseline weight (<80 kg vs.  $\geq$ 80 kg).

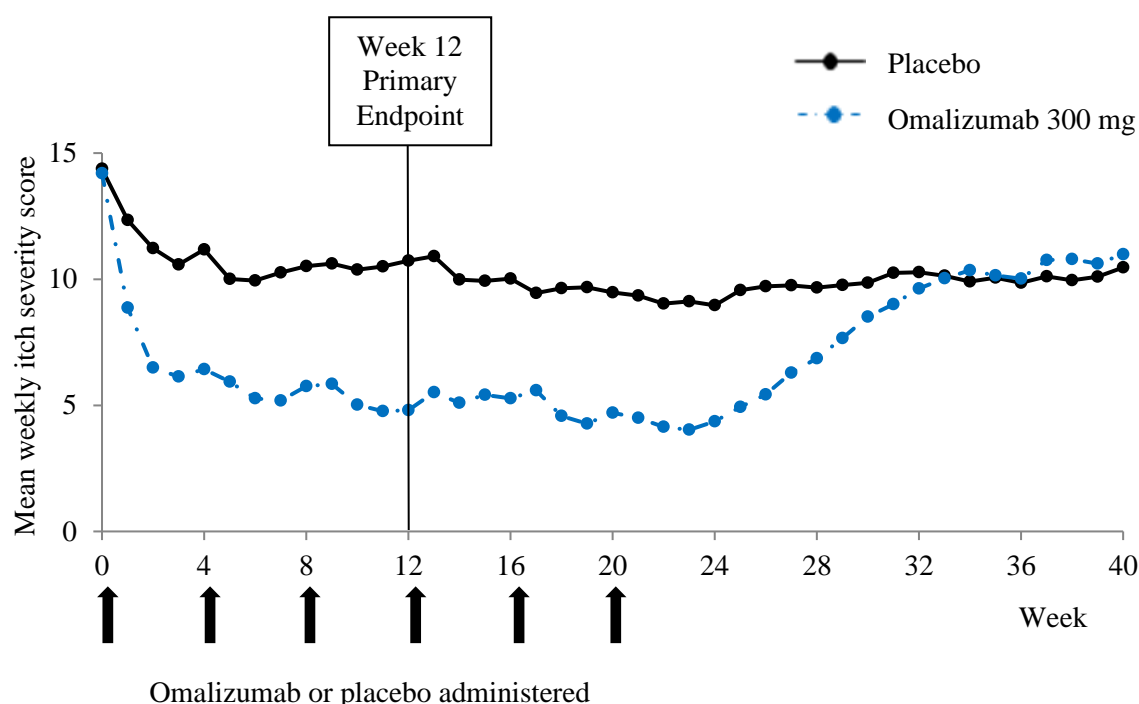
<sup>2</sup> p-value is derived from ANCOVA t-test.

Figure 2 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 2 Mean weekly itch severity score over time, study 1 (mITT population)**



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

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  $UAS7 \leq 6$  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).

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  $UAS7 \leq 6$ .

In a 48-week study, 206 patients aged between 12 and 75 years were enrolled into a 24-week open-label treatment period of omalizumab 300 mg every 4 weeks. Patients who responded to treatment in this open-label period were then randomised to receive omalizumab 300 mg (81 patients) or placebo (53 patients) every 4 weeks for an additional 24 weeks.

Of the patients who remained on omalizumab treatment for 48 weeks, 21% experienced clinical worsening ( $UAS7$  score  $\geq 12$  for at least 2 consecutive weeks post-randomisation between weeks 24 and 48), versus 60.4% of those treated with placebo at week 48 (difference -39.4%,  $p < 0.0001$ , 95% CI: -54.5%, -22.5%).

## 5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma as well as in adult patients with CRSwNP, and adult and adolescent patients with CSU. The general pharmacokinetic characteristics of omalizumab are similar in these patient 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  $78 \pm 32$  ml/kg.

## Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the 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  $2.4 \pm 1.1$  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

### Age, Race/ethnicity, Gender, Body Mass Index

#### *Patients with allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)*

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 for age (6-76 years for patients with allergic asthma; 18 to 75 for patients with CRSwNP), 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**

Arginine hydrochloride  
Histidine hydrochloride monohydrate  
Histidine  
Polysorbate 20  
Water for injections

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

18 months.

The product may be kept for a total of 48 hours at 25°C.

### **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

### Xolair 150 mg solution for injection in pre-filled syringe (26-gauge staked needle, purple syringe guard)

Xolair 150 mg solution for injection in pre-filled syringe is supplied as 1 ml solution in a pre-filled syringe barrel (type I glass) with 26-gauge staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack sizes: packs containing 1 pre-filled syringe, and multipacks containing 4 (4 x 1); 6 (6 x 1) or 10 (10 x 1) pre-filled syringes.

### Xolair 150 mg solution for injection in pre-filled syringe (27-gauge staked needle, purple plunger)

Xolair 150 mg solution for injection in pre-filled syringe is supplied as 1 ml solution in a pre-filled syringe barrel (type I glass) with 27-gauge staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack sizes: packs containing 1 pre-filled syringe, and multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled syringes.

### Xolair 300 mg solution for injection in pre-filled syringe

Xolair 300 mg solution for injection in pre-filled syringe is supplied as 2 ml solution in a pre-filled syringe barrel (type I glass) with 27-gauge staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack sizes: packs containing 1 pre-filled syringe, and multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled syringes.

### Xolair 150 mg solution for injection in pre-filled pen

Xolair 150 mg solution for injection in pre-filled pen is supplied as 1 ml solution in a pre-filled pen barrel (type I glass) with 27-gauge staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack sizes: packs containing 1 pre-filled pen, and multipacks containing 3 (3 x 1), 6 (6 x 1) or 10 (10 x 1) pre-filled pens.

### Xolair 300 mg solution for injection in pre-filled pen

Xolair 300 mg solution for injection in pre-filled pen is supplied as 2 ml solution in a pre-filled pen barrel (type I glass) with 27-gauge staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack sizes: packs containing 1 pre-filled pen, and multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled pens.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

### Pre-filled syringe

The single-use pre-filled syringe is for individual use. It should be taken out of the refrigerator 30 minutes before injecting to allow it to reach room temperature.

### Pre-filled pen

The single-use pre-filled pen is for individual use. It should be taken out of the refrigerator 30 minutes before injecting to allow it to reach room temperature.

### Disposal instructions

Dispose of the used syringe or pen 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  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

## **8. MARKETING AUTHORISATION NUMBER(S)**

### Xolair 150 mg solution for injection in pre-filled syringe

EU/1/05/319/008  
EU/1/05/319/009  
EU/1/05/319/010  
EU/1/05/319/011  
EU/1/05/319/024  
EU/1/05/319/025  
EU/1/05/319/026

### Xolair 300 mg solution for injection in pre-filled syringe

EU/1/05/319/012  
EU/1/05/319/013  
EU/1/05/319/014

### Xolair 150 mg solution for injection in pre-filled pen

EU/1/05/319/027  
EU/1/05/319/028  
EU/1/05/319/029  
EU/1/05/319/030

### Xolair 300 mg solution for injection in pre-filled pen

EU/1/05/319/015  
EU/1/05/319/016  
EU/1/05/319/017

## **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 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 produced in a Chinese hamster ovary (CHO) mammalian cell line by recombinant DNA technology.

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<sub>1</sub> <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 rhinosinusitis with nasal polyps (CRSwNP)

Xolair is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control.

## 4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma or chronic rhinosinusitis with nasal polyps (CRSwNP).

### Posology

Dosing for allergic asthma and CRSwNP follows the same dosing principles. The appropriate dose and frequency of omalizumab for these conditions 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 omalizumab in 1 to 4 injections may be needed for each administration.

Allergic asthma patients with baseline 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.

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

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 <sup>a</sup>	150 mg <sup>b</sup>		
75	1 <sup>c</sup>	0	1	0.6
150	0	1	1	1.2
225	1 <sup>c</sup>	1	2	1.8
300	0	2	2	2.4
375	1 <sup>c</sup>	2	3	3.0
450	0	3	3	3.6
525	1 <sup>c</sup>	3	4	4.2
600	0	4	4	4.8

<sup>a</sup> 0.6 ml = maximum delivered volume per vial (Xolair 75 mg).

<sup>b</sup> 1.2 ml = maximum delivered volume per vial (Xolair 150 mg).

<sup>c</sup> or use 0.6 ml from a 150 mg vial.



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

	<b>Body weight (kg)</b>									
<b>Baseline IgE (IU/ml)</b>	≥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										
>900-1 000										
>1 000-1 100										
	ADMINISTRATION EVERY 2 WEEKS SEE TABLE 3									

\*Body weights below 30 kg were not studied in the pivotal trials for CRSwNP.

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

Baseline IgE (IU/ml)	Body weight (kg)									
	≥20-25*	>25-30*	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	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			
>900-1 000	225	300	375	450	525	600				
>1 000-1 100	225	300	375	450	600					
>1 100-1 200	300	300	450	525	600	Insufficient data to recommend a dose				
>1 200-1 300	300	375	450	525						
>1 300-1 500	300	375	525	600						

\*Body weights below 30 kg were not studied in the pivotal trials for CRSwNP.

#### Treatment duration, monitoring and dose adjustments

##### *Allergic asthma*

Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for the 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 treatment 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).

##### *Chronic rhinosinusitis with nasal polyps (CRSwNP)*

In clinical trials for CRSwNP, changes in nasal polyps score (NPS) and nasal congestion score (NCS) were observed at 4 weeks. The need for continued therapy should be periodically reassessed based upon the patient's disease severity and level of symptom control.

##### *Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)*

Discontinuation of 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 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 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 omalizumab 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, omalizumab should be administered with caution (see section 4.4).

##### *Paediatric population*

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

In CRSwNP, the safety and efficacy of omalizumab in patients below the age of 18 years have not been established. No data are available.

#### Method of administration

For subcutaneous administration only. Omalizumab must not be administered by the intravenous or intramuscular route.

Doses of more than 150 mg (Table 1) should be divided across two or more injection sites.

Xolair powder and solvent for solution for injection 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**

#### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

#### General

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

Omalizumab 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. Omalizumab is not indicated for the treatment of these conditions.

Omalizumab 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 omalizumab in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of omalizumab therapy in allergic asthma or CRSwNP 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, even after a long duration of treatment. However, most of these reactions occurred within 2 hours after the first and subsequent injections of omalizumab but some started beyond 2 hours and even beyond 24 hours after the injection. The majority of anaphylactic reactions occurred within the first 3 doses of omalizumab. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following omalizumab administration. Therefore medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of omalizumab. If an anaphylactic or other serious allergic reaction occurs, administration of omalizumab must be discontinued immediately, and appropriate therapy initiated. Patients should be informed that such reactions are possible, and prompt medical attention should be sought if allergic reactions occur.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-omalizumab 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 omalizumab 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, omalizumab 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 interactions. Medicinal product or vaccine interaction studies have not been performed with omalizumab. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma or CRSwNP will interact with omalizumab.

##### Allergic asthma

In clinical studies omalizumab 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 omalizumab was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of omalizumab in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where omalizumab was co-administered with immunotherapy, the safety and efficacy of omalizumab in combination with specific immunotherapy were found to be no different to that of omalizumab alone.

##### Chronic rhinosinusitis with nasal polyps (CRSwNP)

In clinical studies omalizumab was used in conjunction with intranasal mometasone spray as per protocol. Other commonly used concomitant medicinal products included other intranasal corticosteroids, bronchodilators, antihistamines, leukotriene receptor antagonists, adrenergics/sympathomimetics and local nasal anaesthetics. There was no indication that the safety of omalizumab was altered by the concomitant use of these other commonly used medicinal products.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

A moderate amount of data on pregnant women (between 300-1 000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foeto/neonatal toxicity. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to omalizumab showed the prevalence of major congenital anomalies was similar (8.1% vs. 8.9%) between EXPECT and disease-matched (moderate and severe asthma) patients. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Omalizumab crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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).

If clinically needed, the use of omalizumab may be considered during pregnancy.

### Breast-feeding

Immunoglobulins G (IgGs) are present in human milk and therefore it is expected that omalizumab will be present in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3).

The EXPECT study, with 154 infants who had been exposed to omalizumab during pregnancy and through breast-feeding did not indicate adverse effects on the breast-fed infant. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breast-fed newborns/infants are anticipated. Consequently, if clinically needed, the use of omalizumab may be considered 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 a separate non-clinical genotoxicity study.

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

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

## **4.8 Undesirable effects**

### Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

#### Summary of the safety profile

During allergic asthma 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. In clinical trials in patients  $\geq 18$  years of age in CRSwNP, the most commonly reported adverse reactions were headache, dizziness, arthralgia, abdominal pain upper and injection site reactions.

#### Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total allergic asthma and CRSwNP 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $<1/10$ ), uncommon ( $\geq 1/1\ 000$  to  $<1/100$ ), rare ( $\geq 1/10\ 000$  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 and CRSwNP**

<b>Infections and infestations</b>	
Uncommon	Pharyngitis
Rare	Parasitic infection
<b>Blood and lymphatic system disorders</b>	
Not known	Idiopathic thrombocytopenia, including severe cases
<b>Immune system disorders</b>	
Rare	Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development
Not known	Serum sickness, may include fever and lymphadenopathy
<b>Nervous system disorders</b>	
Common	Headache*
Uncommon	Syncope, paraesthesia, somnolence, dizziness <sup>#</sup>
<b>Vascular disorders</b>	
Uncommon	Postural hypotension, flushing
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon	Allergic bronchospasm, coughing
Rare	Laryngoedema
Not known	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
<b>Gastrointestinal disorders</b>	
Common	Abdominal pain upper** <sup>#</sup>
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon	Photosensitivity, urticaria, rash, pruritus
Rare	Angioedema
Not known	Alopecia
<b>Musculoskeletal and connective tissue disorders</b>	
Common	Athralgia†
Rare	Systemic lupus erythematosus (SLE)
Not known	Myalgia, joint swelling
<b>General disorders and administration site conditions</b>	
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

<sup>#</sup>: Common in nasal polyp trials

†: Unknown in allergic asthma trials

#### 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. 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

#### Mechanism of action

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (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. 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.

Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils. Omalizumab inhibits IgE-mediated inflammation, as evidenced by reduced



blood and tissue eosinophils and reduced inflammatory mediators, including IL-4, IL-5, and IL-13 by innate, adaptive and non-immune cells.

### Pharmacodynamic effects

#### Allergic asthma

The *in vitro* histamine release from basophils isolated from omalizumab-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 omalizumab dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

#### Chronic rhinosinusitis with nasal polyps (CRSwNP)

In clinical studies in patients with CRSwNP, omalizumab treatment led to a reduction in serum free IgE (approx. 95%) and an increase in serum total IgE levels, to a similar extent as observed in patients with allergic asthma. Total IgE levels in serum increased due to the formation of omalizumab-IgE complexes that have a slower elimination rate compared with free IgE.

### Clinical efficacy and safety

#### Allergic asthma

##### *Adults and adolescents $\geq 12$ years of age*

The efficacy and safety of omalizumab 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<sub>1</sub> 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 omalizumab 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 omalizumab 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  $\geq 76$  IU/ml were more likely to experience clinically meaningful benefit to omalizumab. In these patients in study 1 omalizumab reduced the rate of asthma exacerbations by 40% ( $p = 0.002$ ). In addition more patients had clinically meaningful responses in the total IgE  $\geq 76$  IU/ml population across the omalizumab severe asthma programme. Table 5 includes results in the study 1 population.

**Table 5 Results of study 1**

	Whole study 1 population	
	Omalizumab N=209	Placebo N=210
<b>Asthma exacerbations</b>		
Rate per 28-week period	0.74	0.92
% reduction, p-value for rate ratio	19.4%, p = 0.153	
<b>Severe asthma exacerbations</b>		
Rate per 28-week period	0.24	0.48
% reduction, p-value for rate ratio	50.1%, p = 0.002	
<b>Emergency visits</b>		
Rate per 28-week period	0.24	0.43
% reduction, p-value for rate ratio	43.9%, p = 0.038	
<b>Physician's overall assessment</b>		
% responders*	60.5%	42.8%
p-value**	<0.001	
<b>AQL improvement</b>		
% 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 omalizumab in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with omalizumab 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 omalizumab 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 omalizumab 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 omalizumab were able to reduce their fluticasone dose to  $\leq 500$  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 omalizumab 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 medicinal product use, spirometry and exacerbations. In all five studies a significantly greater proportion of omalizumab-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 omalizumab 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 ( $\geq 500$  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 medicinal product 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.

#### Chronic rhinosinusitis with nasal polyps (CRSwNP)

The safety and efficacy of omalizumab were evaluated in two randomised, double-blind, placebo-controlled trials in patients with CRSwNP (Table 7). Patients received omalizumab or placebo subcutaneously every 2 or 4 weeks (see section 4.2). All patients received background intranasal mometasone therapy throughout the study. Prior sino-nasal surgery or prior systemic corticosteroid usage were not required for inclusion in the studies. Patients received omalizumab or placebo for 24 weeks followed by a 4-week follow-up period. Demographics and baseline characteristics, including allergic comorbidities, are described in Table 6.

**Table 6 Demographics and baseline characteristics of nasal polyp studies**

<b>Parameter</b>	<b>Nasal polyp study 1 N=138</b>	<b>Nasal polyp study 2 N=127</b>
Mean age (years) (SD)	51.0 (13.2)	50.1 (11.9)
% Male	63.8	65.4
Patients with systemic corticosteroid use in the previous year (%)	18.8	26.0
Bilateral endoscopic nasal polyp score (NPS): mean (SD), range 0-8	6.2 (1.0)	6.3 (0.9)
Nasal congestion score (NCS): mean (SD), range 0-3	2.4 (0.6)	2.3 (0.7)
Sense of smell score: mean (SD), range 0-3	2.7 (0.7)	2.7 (0.7)
SNOT-22 total score: mean (SD) range 0-110	60.1 (17.7)	59.5 (19.3)
Blood eosinophils (cells/ $\mu$ l): mean (SD)	346.1 (284.1)	334.6 (187.6)
Total IgE IU/ml: mean (SD)	160.9 (139.6)	190.2 (200.5)
Asthma (%)	53.6	60.6
Mild (%)	37.8	32.5
Moderate (%)	58.1	58.4
Severe (%)	4.1	9.1
Aspirin exacerbated respiratory disease (%)	19.6	35.4
Allergic rhinitis	43.5	42.5

SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; IgE = Immunoglobulin E; IU = international units. For NPS, NCS, and SNOT-22 higher scores indicate greater disease severity.

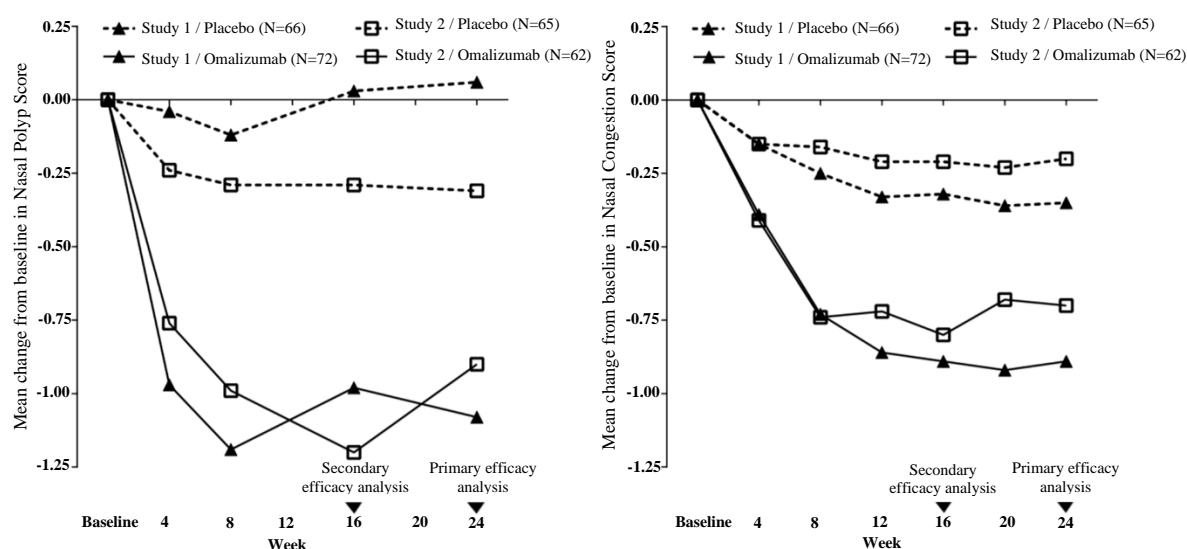
The co-primary endpoints were bilateral nasal polyps score (NPS) and average daily nasal congestion score (NCS) at Week 24. In both nasal polyp studies 1 and 2, patients who received omalizumab had statistically significant greater improvements from baseline at Week 24 in NPS and weekly average NCS than patients who received placebo. Results from nasal polyp studies 1 and 2 are shown in Table 7.

**Table 7** Change from baseline at Week 24 in clinical scores from nasal polyp study 1, nasal polyp study 2, and pooled data

	Nasal polyp study 1		Nasal polyp study 2		Nasal polyp pooled results	
	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab
N	66	72	65	62	131	134
Nasal polyp score						
Baseline mean	6.32	6.19	6.09	6.44	6.21	6.31
LS mean change at Week 24	0.06	-1.08	-0.31	-0.90	-0.13	-0.99
Difference (95% CI)	-1.14 (-1.59, -0.69)		-0.59 (-1.05, -0.12)		-0.86 (-1.18, -0.54)	
p-value	<0.0001		0.0140		<0.0001	
7-day average of daily nasal congestion score						
Baseline mean	2.46	2.40	2.29	2.26	2.38	2.34
LS mean change at Week 24	-0.35	-0.89	-0.20	-0.70	-0.28	-0.80
Difference (95% CI)	-0.55 (-0.84, -0.25)		-0.50 (-0.80, -0.19)		-0.52 (-0.73, -0.31)	
p-value	0.0004		0.0017		<0.0001	
TNSS						
Baseline mean	9.33	8.56	8.73	8.37	9.03	8.47
LS mean change at Week 24	-1.06	-2.97	-0.44	-2.53	-0.77	-2.75
Difference (95% CI)	-1.91 (-2.85, -0.96)		-2.09 (-3.00, -1.18)		-1.98 (-2.63, -1.33)	
p-value	0.0001		<0.0001		<0.0001	
SNOT-22						
Baseline mean	60.26	59.82	59.80	59.21	60.03	59.54
LS mean change at Week 24	-8.58	-24.70	-6.55	-21.59	-7.73	-23.10
Difference (95% CI)	-16.12 (-21.86, -10.38)		-15.04 (-21.26, -8.82)		-15.36 (-19.57, -11.16)	
p-value (MID = 8.9)	<0.0001		<0.0001		<0.0001	
UPSIT						
Baseline mean	13.56	12.78	13.27	12.87	13.41	12.82
LS mean change at Week 24	0.63	4.44	0.44	4.31	0.54	4.38
Difference (95% CI)	3.81 (1.38, 6.24)		3.86 (1.57, 6.15)		3.84 (2.17, 5.51)	
p-value	0.0024		0.0011		<0.0001	

LS=least-square; CI = confidence interval; TNSS = Total nasal symptom score; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; UPSIT = University of Pennsylvania Smell Identification Test; MID = minimal important difference.

**Figure 1 Mean change from baseline in nasal congestion score and mean change from baseline in nasal polyp score by treatment group in nasal polyp study 1 and study 2**



In a pre-specified pooled analysis of rescue treatment (systemic corticosteroids for  $\geq 3$  consecutive days or nasal polypectomy) during the 24-week treatment period, the proportion of patients requiring rescue treatment was lower in omalizumab compared to placebo (2.3% versus 6.2%, respectively). The odds-ratio of having taken rescue treatment in omalizumab compared to placebo was 0.38 (95% CI: 0.10, 1.49). There were no sino-nasal surgeries reported in either study.

The long-term efficacy and safety of omalizumab in patients with CRSwNP who had participated in nasal polyp studies 1 and 2 was assessed in an open-label extension study. Efficacy data from this study suggest that clinical benefit provided at Week 24 was sustained through to Week 52. Safety data were overall consistent with the known safety profile of omalizumab.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma as well as in adult patients with CRSwNP. The general pharmacokinetic characteristics of omalizumab are similar in these patient 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, 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  $78 \pm 32$  ml/kg.

## Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the 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  $2.4 \pm 1.1$  ml/kg/day. In addition, doubling of body weight approximately doubled apparent clearance.

## Characteristics in patient populations

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

The population pharmacokinetics of omalizumab 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 for patients with allergic asthma; 18 to 75 years for patients with CRSwNP), 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  
Histidine  
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**

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).



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.

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

## **7. MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

## **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 produced in a Chinese hamster ovary (CHO) mammalian cell line by recombinant DNA technology.

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<sub>1</sub> <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 rhinosinusitis with nasal polyps (CRSwNP)

Xolair is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control.

## 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**

Treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma, chronic rhinosinusitis with nasal polyps (CRSwNP) or chronic spontaneous urticaria.

#### Posology

##### Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

Dosing for allergic asthma and CRSwNP follows the same dosing principles. The appropriate dose and frequency of omalizumab for these conditions 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 omalizumab in 1 to 4 injections may be needed for each administration.

Allergic asthma patients with baseline 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.

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

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 <sup>a</sup>	150 mg <sup>b</sup>		
75	1 <sup>c</sup>	0	1	0.6
150	0	1	1	1.2
225	1 <sup>c</sup>	1	2	1.8
300	0	2	2	2.4
375	1 <sup>c</sup>	2	3	3.0
450	0	3	3	3.6
525	1 <sup>c</sup>	3	4	4.2
600	0	4	4	4.8

<sup>a</sup> 0.6 ml = maximum delivered volume per vial (Xolair 75 mg).

<sup>b</sup> 1.2 ml = maximum delivered volume per vial (Xolair 150 mg).

<sup>c</sup> or use 0.6 ml from a 150 mg vial.

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

	<b>Body weight (kg)</b>									
<b>Baseline IgE (IU/ml)</b>	≥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										
>900-1 000										
>1 000-1 100										

ADMINISTRATION EVERY 2 WEEKS  
SEE TABLE 3

\*Body weights below 30 kg were not studied in the pivotal trials for CRSwNP.

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

Baseline IgE (IU/ml)	Body weight (kg)									
	≥20-25*	>25-30*	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	ADMINISTRATION EVERY 4 WEEKS									
>100-200	SEE TABLE 2									
>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			
>900-1 000	225	300	375	450	525	600				
>1 000-1 100	225	300	375	450	600					
>1 100-1 200	300	300	450	525	600	Insufficient data to recommend a dose				
>1 200-1 300	300	375	450	525						
>1 300-1 500	300	375	525	600						

\*Body weights below 30 kg were not studied in the pivotal trials for CRSwNP.

#### Treatment duration, monitoring and dose adjustments

##### *Allergic asthma*

Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for the 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 treatment 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).

##### *Chronic rhinosinusitis with nasal polyps (CRSwNP)*

In clinical trials for CRSwNP, changes in nasal polyps score (NPS) and nasal congestion score (NCS) were observed at 4 weeks. The need for continued therapy should be periodically reassessed based upon the patient's disease severity and level of symptom control.

##### *Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)*

Discontinuation of 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 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 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)

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 in this indication is described in section 5.1.

#### Special populations

##### *Elderly (65 years of age and older)*

There are limited data available on the use of omalizumab 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, omalizumab should be administered with caution (see section 4.4).

##### *Paediatric population*

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

In CRSwNP, the safety and efficacy of omalizumab in patients below the age of 18 years have not been established. No data are available.

In CSU, the safety and efficacy of omalizumab in patients below the age of 12 years have not been established. No data are available.

#### Method of administration

For subcutaneous administration only. Omalizumab must not be administered by the intravenous or intramuscular route.

Doses of more than 150 mg (Table 1) should be divided across two or more injection sites.

Xolair powder and solvent for solution for injection 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**

#### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

## General

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

Omalizumab 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. Omalizumab is not indicated for the treatment of these conditions.

Omalizumab 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 omalizumab in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of omalizumab therapy in allergic asthma or CRSwNP 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, even after a long duration of treatment. However, most of these reactions occurred within 2 hours after the first and subsequent injections of omalizumab but some started beyond 2 hours and even beyond 24 hours after the injection. The majority of anaphylactic reactions occurred within the first 3 doses of omalizumab. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following omalizumab administration. Therefore medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of omalizumab. If an anaphylactic or other serious allergic reaction occurs, administration of omalizumab must be discontinued immediately, and appropriate therapy initiated. Patients should be informed that such reactions are possible, and prompt medical attention should be sought if allergic reactions occur.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-omalizumab 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 omalizumab 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, omalizumab 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 interactions. Medicinal product or vaccine interaction studies have not been performed with omalizumab. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma, CRSwNP or CSU will interact with omalizumab.

#### Allergic asthma

In clinical studies omalizumab 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 omalizumab was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of omalizumab in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where omalizumab was co-administered with immunotherapy, the safety and efficacy of omalizumab in combination with specific immunotherapy were found to be no different to that of omalizumab alone.

#### Chronic rhinosinusitis with nasal polyps (CRSwNP)

In clinical studies omalizumab was used in conjunction with intranasal mometasone spray as per protocol. Other commonly used concomitant medicinal products included other intranasal corticosteroids, bronchodilators, antihistamines, leukotriene receptor antagonists, adrenergics/sympathomimetics and local nasal anaesthetics. There was no indication that the safety of omalizumab was altered by the concomitant use of these other commonly used medicinal products.

#### Chronic spontaneous urticaria (CSU)

In clinical studies in CSU, omalizumab 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 omalizumab 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

A moderate amount of data on pregnant women (between 300-1 000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foeto/neonatal toxicity. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to omalizumab showed the prevalence of major congenital anomalies was similar (8.1% vs. 8.9%) between EXPECT and disease-matched (moderate and severe asthma) patients. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Omalizumab crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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).

If clinically needed, the use of omalizumab may be considered during pregnancy.

### Breast-feeding

Immunoglobulins G (IgGs) are present in human milk and therefore it is expected that omalizumab will be present in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3).

The EXPECT study, with 154 infants who had been exposed to omalizumab during pregnancy and through breast-feeding did not indicate adverse effects on the breast-fed infant. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breast-fed newborns/infants are anticipated. Consequently, if clinically needed, the use of omalizumab may be considered 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 a separate non-clinical genotoxicity study.

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

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

## 4.8 Undesirable effects

### Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

#### Summary of safety profile

During allergic asthma 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. In clinical trials in patients  $\geq 18$  years of age in CRSwNP, the most commonly reported adverse reactions were headache, dizziness, arthralgia, abdominal pain upper and injection site reactions.

#### Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total allergic asthma and CRSwNP 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ), rare ( $\geq 1/10\ 000$  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 and CRSwNP**

<b>Infections and infestations</b>	
Uncommon	Pharyngitis
Rare	Parasitic infection
<b>Blood and lymphatic system disorders</b>	
Not known	Idiopathic thrombocytopenia, including severe cases
<b>Immune system disorders</b>	
Rare	Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development
Not known	Serum sickness, may include fever and lymphadenopathy
<b>Nervous system disorders</b>	
Common	Headache*
Uncommon	Syncope, paraesthesia, somnolence, dizziness <sup>#</sup>
<b>Vascular disorders</b>	
Uncommon	Postural hypotension, flushing
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon	Allergic bronchospasm, coughing
Rare	Laryngoedema
Not known	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
<b>Gastrointestinal disorders</b>	
Common	Abdominal pain upper** <sup>#</sup>
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon	Photosensitivity, urticaria, rash, pruritus
Rare	Angioedema
Not known	Alopecia
<b>Musculoskeletal and connective tissue disorders</b>	
Common	Athralgia†
Rare	Systemic lupus erythematosus (SLE)
Not known	Myalgia, joint swelling
<b>General disorders and administration site conditions</b>	
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

<sup>#</sup>: Common in nasal polyp trials

†: Unknown in allergic asthma trials

#### 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 dose and treatment populations (with significantly different risk factors, comorbidities, concomitant medicinal products and ages [e.g. asthma trials included children from 6-12 years of age]).

Table 5 lists the adverse reactions (events occurring in  $\geq 1\%$  of patients in any treatment group and  $\geq 2\%$  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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1\,000$  to  $< 1/100$ ); rare ( $\geq 1/10\,000$  to  $< 1/1\,000$ ); 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	
<b>Infections and infestations</b>			
Sinusitis	5 (2.1%)	20 (4.9%)	Common
<b>Nervous system disorders</b>			
Headache	7 (2.9%)	25 (6.1%)	Common
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia	1 (0.4%)	12 (2.9%)	Common
<b>General disorder and administration site conditions</b>			
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	
<b>Infections and infestations</b>			
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.

In a 48-week study, 81 CSU patients received omalizumab 300 mg every 4 weeks (see section 5.1). The safety profile of long-term use was similar to the safety profile observed in 24-week studies in CSU.

#### 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. 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

#### Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

##### Mechanism of action

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (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. 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.

Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils. Omalizumab inhibits IgE-mediated inflammation, as evidenced by reduced

blood and tissue eosinophils and reduced inflammatory mediators, including IL-4, IL-5, and IL-13 by innate, adaptive and non-immune cells.

### Pharmacodynamic effects

#### Allergic asthma

The *in vitro* histamine release from basophils isolated from omalizumab-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 omalizumab dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

#### Chronic rhinosinusitis with nasal polyps (CRSwNP)

In clinical studies in patients with CRSwNP, omalizumab treatment led to a reduction in serum free IgE (approx. 95%) and an increase in serum total IgE levels, to a similar extent as observed in patients with allergic asthma. Total IgE levels in serum increased due to the formation of omalizumab-IgE complexes that have a slower elimination rate compared with free IgE.

#### Chronic spontaneous urticaria (CSU)

#### Mechanism of action

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and lowers free IgE levels. 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. 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 omalizumab, free IgE levels increased towards pre-treatment levels over a 16-week treatment-free follow-up period.

### Clinical efficacy and safety

#### Allergic asthma

##### Adults and adolescents ≥12 years of age

The efficacy and safety of omalizumab 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<sub>1</sub> 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 omalizumab 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 omalizumab 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  $\geq 76$  IU/ml were more likely to experience clinically meaningful benefit to omalizumab. In these patients in study 1 omalizumab reduced the rate of asthma exacerbations by 40% ( $p = 0.002$ ). In addition more patients had clinically meaningful responses in the total IgE  $\geq 76$  IU/ml population across the omalizumab severe asthma programme. Table 6 includes results in the study 1 population.

**Table 6 Results of study 1**

	Whole study 1 population	
	Omalizumab N=209	Placebo N=210
<b>Asthma exacerbations</b>		
Rate per 28-week period	0.74	0.92
% reduction, p-value for rate ratio	19.4%, p = 0.153	
<b>Severe asthma exacerbations</b>		
Rate per 28-week period	0.24	0.48
% reduction, p-value for rate ratio	50.1%, p = 0.002	
<b>Emergency visits</b>		
Rate per 28-week period	0.24	0.43
% reduction, p-value for rate ratio	43.9%, p = 0.038	
<b>Physician's overall assessment</b>		
% responders*	60.5%	42.8%
p-value**	<0.001	
<b>AQL improvement</b>		
% 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 omalizumab in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with omalizumab 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 omalizumab 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 omalizumab 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 omalizumab were able to reduce their fluticasone dose to  $\leq 500$  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 omalizumab 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 medicinal product use, spirometry and exacerbations. In all five studies a significantly greater proportion of omalizumab-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 omalizumab 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 ( $\geq 500$  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 medicinal product 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.

#### *Chronic rhinosinusitis with nasal polyps (CRSwNP)*

The safety and efficacy of omalizumab were evaluated in two randomised, double-blind, placebo-controlled trials in patients with CRSwNP (Table 8). Patients received omalizumab or placebo subcutaneously every 2 or 4 weeks (see section 4.2). All patients received background intranasal mometasone therapy throughout the study. Prior sino-nasal surgery or prior systemic corticosteroid usage were not required for inclusion in the studies. Patients received omalizumab or placebo for 24 weeks followed by a 4-week follow-up period. Demographics and baseline characteristics, including allergic comorbidities, are described in Table 7.



**Table 7 Demographics and baseline characteristics of nasal polyp studies**

<b>Parameter</b>	<b>Nasal polyp study 1 N=138</b>	<b>Nasal polyp study 2 N=127</b>
Mean age (years) (SD)	51.0 (13.2)	50.1 (11.9)
% Male	63.8	65.4
Patients with systemic corticosteroid use in the previous year (%)	18.8	26.0
Bilateral endoscopic nasal polyp score (NPS): mean (SD), range 0-8	6.2 (1.0)	6.3 (0.9)
Nasal congestion score (NCS): mean (SD), range 0-3	2.4 (0.6)	2.3 (0.7)
Sense of smell score: mean (SD), range 0-3	2.7 (0.7)	2.7 (0.7)
SNOT-22 total score: mean (SD) range 0-110	60.1 (17.7)	59.5 (19.3)
Blood eosinophils (cells/ $\mu$ l): mean (SD)	346.1 (284.1)	334.6 (187.6)
Total IgE IU/ml: mean (SD)	160.9 (139.6)	190.2 (200.5)
Asthma (%)	53.6	60.6
Mild (%)	37.8	32.5
Moderate (%)	58.1	58.4
Severe (%)	4.1	9.1
Aspirin exacerbated respiratory disease (%)	19.6	35.4
Allergic rhinitis	43.5	42.5

SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; IgE = Immunoglobulin E; IU = international units. For NPS, NCS, and SNOT-22 higher scores indicate greater disease severity.

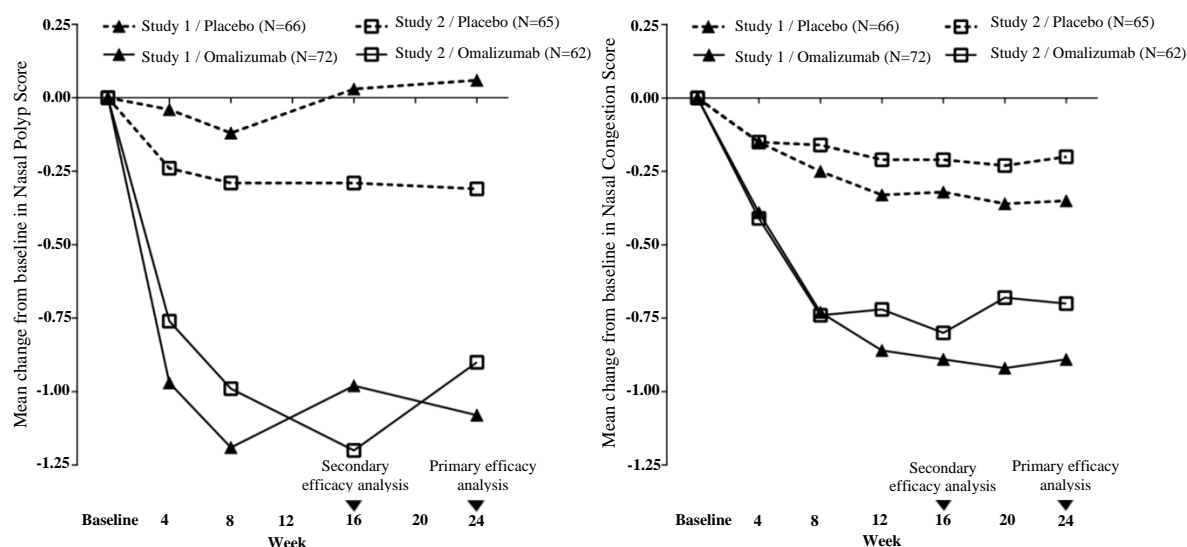
The co-primary endpoints were bilateral nasal polyps score (NPS) and average daily nasal congestion score (NCS) at Week 24. In both nasal polyp studies 1 and 2, patients who received omalizumab had statistically significant greater improvements from baseline at Week 24 in NPS and weekly average NCS than patients who received placebo. Results from nasal polyp studies 1 and 2 are shown in Table 8.

**Table 8      Change from baseline at Week 24 in clinical scores from nasal polyp study 1, nasal polyp study 2, and pooled data**

	Nasal polyp study 1		Nasal polyp study 2		Nasal polyp pooled results	
	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab
N	66	72	65	62	131	134
Nasal polyp score						
Baseline mean	6.32	6.19	6.09	6.44	6.21	6.31
LS mean change at Week 24	0.06	-1.08	-0.31	-0.90	-0.13	-0.99
Difference (95% CI)	-1.14 (-1.59, -0.69)		-0.59 (-1.05, -0.12)		-0.86 (-1.18, -0.54)	
p-value	<0.0001		0.0140		<0.0001	
7-day average of daily nasal congestion score						
Baseline mean	2.46	2.40	2.29	2.26	2.38	2.34
LS mean change at Week 24	-0.35	-0.89	-0.20	-0.70	-0.28	-0.80
Difference (95% CI)	-0.55 (-0.84, -0.25)		-0.50 (-0.80, -0.19)		-0.52 (-0.73, -0.31)	
p-value	0.0004		0.0017		<0.0001	
TNSS						
Baseline mean	9.33	8.56	8.73	8.37	9.03	8.47
LS mean change at Week 24	-1.06	-2.97	-0.44	-2.53	-0.77	-2.75
Difference (95% CI)	-1.91 (-2.85, -0.96)		-2.09 (-3.00, -1.18)		-1.98 (-2.63, -1.33)	
p-value	0.0001		<0.0001		<0.0001	
SNOT-22						
Baseline mean	60.26	59.82	59.80	59.21	60.03	59.54
LS mean change at Week 24	-8.58	-24.70	-6.55	-21.59	-7.73	-23.10
Difference (95% CI)	-16.12 (-21.86, -10.38)		-15.04 (-21.26, -8.82)		-15.36 (-19.57, -11.16)	
p-value (MID = 8.9)	<0.0001		<0.0001		<0.0001	
UPSIT						
Baseline mean	13.56	12.78	13.27	12.87	13.41	12.82
LS mean change at Week 24	0.63	4.44	0.44	4.31	0.54	4.38
Difference (95% CI)	3.81 (1.38, 6.24)		3.86 (1.57, 6.15)		3.84 (2.17, 5.51)	
p-value	0.0024		0.0011		<0.0001	

LS=least-square; CI = confidence interval; TNSS = Total nasal symptom score; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; UPSIT = University of Pennsylvania Smell Identification Test; MID = minimal important difference.

**Figure 1 Mean change from baseline in nasal congestion score and mean change from baseline in nasal polyp score by treatment group in nasal polyp study 1 and study 2**



In a pre-specified pooled analysis of rescue treatment (systemic corticosteroids for  $\geq 3$  consecutive days or nasal polypectomy) during the 24-week treatment period, the proportion of patients requiring rescue treatment was lower in omalizumab compared to placebo (2.3% versus 6.2%, respectively). The odds-ratio of having taken rescue treatment in omalizumab compared to placebo was 0.38 (95% CI: 0.10, 1.49). There were no sino-nasal surgeries reported in either study.

The long-term efficacy and safety of omalizumab in patients with CRSwNP who had participated in nasal polyp studies 1 and 2 was assessed in an open-label extension study. Efficacy data from this study suggest that clinical benefit provided at Week 24 was sustained through to Week 52. Safety data were overall consistent with the known safety profile of omalizumab.

### Chronic spontaneous urticaria (CSU)

The efficacy and safety of omalizumab 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 omalizumab 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  $\geq 65$  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  $\geq 16$ , and a weekly itch severity score (which is a component of the UAS7; range 0-21) of  $\geq 8$  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 medicinal products (including H1 antihistamines) for CSU symptoms prior to study enrollment. Patients received omalizumab 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 9). Statistically significant results were further observed in the responder rates for UAS7 $\leq$ 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 9 Change from baseline to week 12 in weekly itch severity score, studies 1, 2 and 3 (mITT population\*)**

	Placebo	Omalizumab 300 mg
<b>Study 1</b>		
N	80	81
Mean (SD)	-3.63 (5.22)	-9.40 (5.73)
Difference in LS means vs. placebo <sup>1</sup>	-	-5.80
95% CI for difference	-	-7.49, -4.10
P-value vs. placebo <sup>2</sup>	-	<0.0001
<b>Study 2</b>		
N	79	79
Mean (SD)	-5.14 (5.58)	-9.77 (5.95)
Difference in LS means vs. placebo <sup>1</sup>	-	-4.81
95% CI for difference	-	-6.49, -3.13
P-value vs. placebo <sup>2</sup>	-	<0.0001
<b>Study 3</b>		
N	83	252
Mean (SD)	-4.01 (5.87)	-8.55 (6.01)
Difference in LS means vs. placebo <sup>1</sup>	-	-4.52
95% CI for difference	-	-5.97, -3.08
P-value vs. placebo <sup>2</sup>	-	<0.0001

\*Modified intent-to-treat (mITT) population: included all patients who were randomised and received at least one dose of study medicinal product.

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

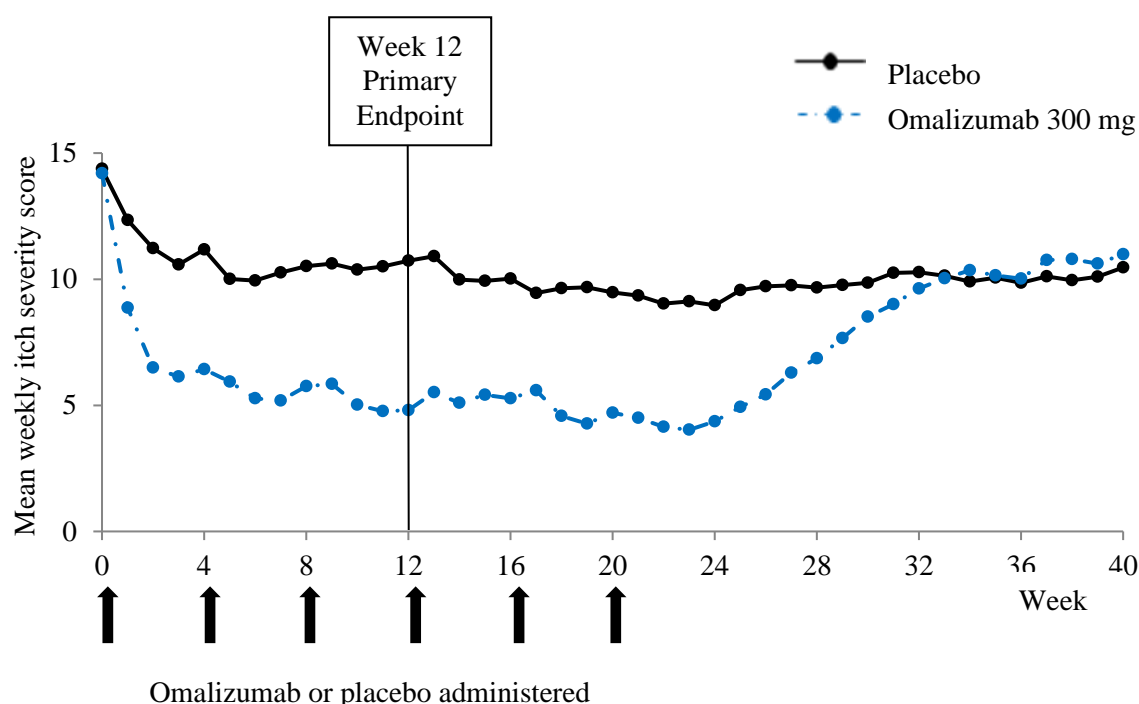
<sup>1</sup> The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (<13 vs.  $\geq$ 13) and baseline weight (<80 kg vs.  $\geq$ 80 kg).

<sup>2</sup> p-value is derived from ANCOVA t-test.

Figure 2 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 2 Mean weekly itch severity score over time, study 1 (mITT population)**



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

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  $UAS7 \leq 6$  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).

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  $UAS7 \leq 6$ .

In a 48-week study, 206 patients aged between 12 and 75 years were enrolled into a 24-week open-label treatment period of omalizumab 300 mg every 4 weeks. Patients who responded to treatment in this open-label period were then randomised to receive omalizumab 300 mg (81 patients) or placebo (53 patients) every 4 weeks for an additional 24 weeks.

Of the patients who remained on omalizumab treatment for 48 weeks, 21% experienced clinical worsening ( $UAS7$  score  $\geq 12$  for at least 2 consecutive weeks post-randomisation between weeks 24 and 48), versus 60.4% of those treated with placebo at week 48 (difference -39.4%,  $p < 0.0001$ , 95% CI: -54.5%, -22.5%).

## 5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma as well as in adult patients with CRSwNP, and adult and adolescent patients with CSU. The general pharmacokinetic characteristics of omalizumab are similar in these patient 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  $78 \pm 32$  ml/kg.

## Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the 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  $2.4 \pm 1.1$  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

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

#### *Patients with allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)*

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 for age (6-76 years for patients with allergic asthma; 18 to 75 years for patients with CRSwNP), 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  
Histidine  
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 x 1) vials of powder and 4 (4 x 1) ampoules of water for injections or 10 (10 x 1) vials of powder and 10 (10 x 1) ampoules of water for injections.

Not all pack sizes may be marketed.

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

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).

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.

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

### **7. MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

### **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>

## **ANNEX II**

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE  
SUBSTANCE AND MANUFACTURERS 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE  
AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers of the biological active substance

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

Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.  
BioProduction Operations Singapore  
8 Tuas Bay Lane  
Singapore 636986  
Singapore

Name and address of the manufacturers responsible for batch release

*Powder and solvent for solution for injection*

Novartis Farmacéutica S.A.  
Gran Via de les Corts Catalanes, 764  
08013 Barcelona  
Spain

Lek Pharmaceuticals d.d.  
Verovškova ulica 57  
Ljubljana, 1526  
Slovenia

Novartis Pharma GmbH  
Roonstrasse 25  
D-90429 Nuremberg  
Germany

Novartis Pharma GmbH  
Sophie-Germain-Strasse 10  
90443 Nuremberg  
Germany

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

Novartis Farmacéutica S.A.  
Gran Via de les Corts Catalanes, 764  
08013 Barcelona  
Spain

Novartis Pharma GmbH  
Roonstrasse 25  
D-90429 Nuremberg  
Germany

Novartis Pharma GmbH  
Sophie-Germain-Strasse 10  
90443 Nuremberg  
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## **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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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 OF UNIT PACK****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 75 mg solution for injection in pre-filled syringe  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled syringe

1 pre-filled syringe

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/005	75 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, blue syringe guard)
EU/1/05/319/018	75 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, blue plunger)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN



**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 in pre-filled syringe  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled syringe

Multipack: 3 (3 x 1) pre-filled syringes

Multipack: 4 (4 x 1) pre-filled syringes

Multipack: 6 (6 x 1) pre-filled syringes

Multipack: 10 (10 x 1) pre-filled syringes

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/006	75 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, blue syringe guard) (4 x 1)
EU/1/05/319/007	75 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, blue syringe guard) (10 x 1)
EU/1/05/319/019	75 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, blue plunger) (3 x 1)
EU/1/05/319/020	75 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, blue plunger) (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

**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 in pre-filled syringe  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled syringe

1 pre-filled syringe. Component of a multipack. Not to be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/006	75 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, blue syringe guard) (4 x 1)
EU/1/05/319/007	75 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, blue syringe guard) (10 x 1)
EU/1/05/319/019	75 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, blue plunger) (3 x 1)
EU/1/05/319/020	75 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, blue plunger) (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER OF PRE-FILLED SYRINGE</b>
--------------------------------------

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xolair 75 mg solution for injection in pre-filled syringe  
omalizumab

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Novartis Europharm Limited

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
-----------------

Subcutaneous use  
Single use

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>PRE-FILLED SYRINGE LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b>
--

Xolair 75 mg injection  
omalizumab  
SC

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

0.5 ml

<b>6. OTHER</b>
-----------------

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON OF UNIT PACK****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 75 mg solution for injection in pre-filled pen  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled pen

1 pre-filled pen

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/021

75 mg solution for injection in pre-filled pen

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**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 in pre-filled pen  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled pen

Multipack: 3 (3 x 1) pre-filled pens

Multipack: 6 (6 x 1) pre-filled pens

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/022	75 mg solution for injection in pre-filled pen (3 x 1)
EU/1/05/319/023	75 mg solution for injection in pre-filled pen (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**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 in pre-filled pen  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled pen

1 pre-filled pen. Component of a multipack. Not to be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/022	75 mg solution for injection in pre-filled pen (3 x 1)
EU/1/05/319/023	75 mg solution for injection in pre-filled pen (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>PRE-FILLED PEN LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b>
--

Xolair 75 mg injection  
omalizumab  
SC

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

0.5 ml

<b>6. OTHER</b>
-----------------

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON OF UNIT PACK****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 150 mg solution for injection in pre-filled syringe  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled syringe

1 pre-filled syringe

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/008	150 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, purple syringe guard)
EU/1/05/319/024	150 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, purple plunger)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN



**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 in pre-filled syringe  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled syringe

Multipack: 3 (3 x 1) pre-filled syringes

Multipack: 4 (4 x 1) pre-filled syringes

Multipack: 6 (6 x 1) pre-filled syringes

Multipack: 10 (10 x 1) pre-filled syringes

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/009	150 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, purple syringe guard) (4 x 1)
EU/1/05/319/010	150 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, purple syringe guard) (10 x 1)
EU/1/05/319/011	150 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, purple syringe guard) (6 x 1)
EU/1/05/319/025	150 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, purple plunger) (3 x 1)
EU/1/05/319/026	150 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, purple plunger) (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

**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 in pre-filled syringe  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled syringe

1 pre-filled syringe. Component of a multipack. Not to be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/009	150 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, purple syringe guard) (4 x 1)
EU/1/05/319/010	150 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, purple syringe guard) (10 x 1)
EU/1/05/319/011	150 mg solution for injection in pre-filled syringe (with 26-gauge staked needle, purple syringe guard) (6 x 1)
EU/1/05/319/025	150 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, purple plunger) (3 x 1)
EU/1/05/319/026	150 mg solution for injection in pre-filled syringe (with 27-gauge staked needle, purple plunger) (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER OF PRE-FILLED SYRINGE</b>
--------------------------------------

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xolair 150 mg solution for injection in pre-filled syringe  
omalizumab

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Novartis Europharm Limited

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
-----------------

Subcutaneous use  
Single use

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>PRE-FILLED SYRINGE LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b>
--

Xolair 150 mg injection  
omalizumab  
SC

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

1 ml

<b>6. OTHER</b>
-----------------



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON OF UNIT PACK****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 300 mg solution for injection in pre-filled syringe  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe contains 300 mg of omalizumab in 2 ml solution.

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled syringe

1 pre-filled syringe

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/012

300 mg solution for injection in pre-filled syringe

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 300 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 300 mg solution for injection in pre-filled syringe  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe contains 300 mg of omalizumab in 2 ml solution.

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled syringe

Multipack: 3 (3 x 1) pre-filled syringes

Multipack: 6 (6 x 1) pre-filled syringes

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/013	300 mg solution for injection in pre-filled syringe (3 x 1)
EU/1/05/319/014	300 mg solution for injection in pre-filled syringe (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 300 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 300 mg solution for injection in pre-filled syringe  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe contains 300 mg of omalizumab in 2 ml solution.

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled syringe

1 pre-filled syringe. Component of a multipack. Not to be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/013	300 mg solution for injection in pre-filled syringe (3 x 1)
EU/1/05/319/014	300 mg solution for injection in pre-filled syringe (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 300 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER OF PRE-FILLED SYRINGE</b>
--------------------------------------

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xolair 300 mg solution for injection in pre-filled syringe  
omalizumab

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Novartis Europharm Limited

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
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Subcutaneous use  
Single use

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>PRE-FILLED SYRINGE LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b>
--

Xolair 300 mg injection  
omalizumab  
SC

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

2 ml

<b>6. OTHER</b>
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**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON OF UNIT PACK****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 150 mg solution for injection in pre-filled pen  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled pen

1 pre-filled pen

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/027

150 mg solution for injection in pre-filled pen

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**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 in pre-filled pen  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled pen

Multipack: 3 (3 x 1) pre-filled pens

Multipack: 6 (6 x 1) pre-filled pens

Multipack: 10 (10 x 1) pre-filled pens

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Subcutaneous use.

Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/028	150 mg solution for injection in pre-filled pen (3 x 1)
EU/1/05/319/029	150 mg solution for injection in pre-filled pen (6 x 1)
EU/1/05/319/030	150 mg solution for injection in pre-filled pen (10 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**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 in pre-filled pen  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled pen

1 pre-filled pen. Component of a multipack. Not to be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/028	150 mg solution for injection in pre-filled pen (3 x 1)
EU/1/05/319/029	150 mg solution for injection in pre-filled pen (6 x 1)
EU/1/05/319/030	150 mg solution for injection in pre-filled pen (10 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>PRE-FILLED PEN LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b>
--

Xolair 150 mg injection  
omalizumab  
SC

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

1 ml

<b>6. OTHER</b>
-----------------

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON OF UNIT PACK****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 300 mg solution for injection in pre-filled pen  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled pen contains 300 mg of omalizumab in 2 ml solution.

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled pen

1 pre-filled pen

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/015

300 mg solution for injection in pre-filled pen

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 300 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 300 mg solution for injection in pre-filled pen  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled pen contains 300 mg of omalizumab in 2 ml solution.

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled pen

Multipack: 3 (3 x 1) pre-filled pens

Multipack: 6 (6 x 1) pre-filled pens

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/016	300 mg solution for injection in pre-filled pen (3 x 1)
EU/1/05/319/017	300 mg solution for injection in pre-filled pen (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 300 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

Xolair 300 mg solution for injection in pre-filled pen  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled pen contains 300 mg of omalizumab in 2 ml solution.

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in pre-filled pen

1 pre-filled pen. Component of a multipack. Not to be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.  
Single 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.

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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/016	300 mg solution for injection in pre-filled pen (3 x 1)
EU/1/05/319/017	300 mg solution for injection in pre-filled pen (6 x 1)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 300 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>PRE-FILLED PEN LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b>
--

Xolair 300 mg injection  
omalizumab  
SC

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

2 ml

<b>6. OTHER</b>
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**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, histidine, 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**

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.

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  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN



**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.

**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, histidine, 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**

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.

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  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTON OF 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, histidine, 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**

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.

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  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**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****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**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, histidine, histidine hydrochloride monohydrate and polysorbate 20.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for solution for injection

Multipack: 4 (4 x 1) vials and 4 (4 x 1) ampoules

Multipack: 10 (10 x 1) vials and 10 (10 x 1) ampoules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

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.

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  
Vista Building  
Elm Park, Merrion Road  
Dublin 4  
Ireland

**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****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**



**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.

**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**

## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **Xolair 75 mg solution for injection in pre-filled syringe** (pre-filled syringe with 26-gauge staked needle, blue syringe guard) 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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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
2. What you need to know before you use Xolair
3. How to use Xolair
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

Xolair contains the active substance 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 is used for the treatment of:

- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps

##### Allergic asthma

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

##### Chronic rhinosinusitis with nasal polyps

This medicine is used to treat chronic rhinosinusitis with nasal polyps in adults (18 years of age and older) who are already receiving intranasal corticosteroids (corticosteroid nasal spray), but whose symptoms are not well controlled by these medicines. Nasal polyps are small growths on the lining of the nose. Xolair helps to reduce the size of the polyps and improves symptoms including nasal congestion, loss of sense of smell, mucus in the back of the throat and runny nose.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE contributes to a type of inflammation that plays a key role in causing allergic asthma and chronic rhinosinusitis with nasal polyps.

#### **2. What you need to know before you use Xolair**

##### **Do not use 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 use Xolair.

### **Warnings and precautions**

Talk to your doctor before using 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 are travelling to region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.
- if you have ever had an allergic reaction to latex. The needle cap of the syringe may contain dry rubber (latex).

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.

### **Look out for signs of allergic reactions and other serious side effects**

Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a severe allergic reaction or other serious side effects. Such signs are listed under “Serious side effects” in section 4.

It is important that you receive training from your doctor in how to recognise early symptoms of severe allergic reactions, and how to manage these reactions if they occur, before you inject Xolair yourself or before a non-healthcare professional gives you a Xolair injection (see section 3, “How to use Xolair”). The majority of severe allergic reactions occur within the first 3 doses of Xolair.

### **Children and adolescents**

#### Allergic asthma

Xolair is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

#### Chronic rhinosinusitis with nasal polyps

Xolair is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age 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**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Your doctor will discuss with you the benefits and potential risks of using this medicine during pregnancy.

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

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

### **Driving and using machines**

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

## **3. How to use Xolair**

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

### **How Xolair is used**

Xolair is used as an injection under your skin (known as a subcutaneous injection).

#### Injecting Xolair

- You and your doctor will decide if you should inject Xolair yourself. The first 3 doses are always given by or under the supervision of a healthcare professional (see section 2).
- It is important to be properly trained on how to inject the medicine before injecting yourself.
- A caregiver (for example a parent) may also give you your Xolair injection after he or she has received proper training.

For detailed instructions on how to inject Xolair, see “Instructions for use of Xolair pre-filled syringe” at the end of this leaflet.

#### Training to recognise serious allergic reactions

It is also important that you do not inject Xolair yourself until you have been trained by your doctor or nurse on:

- how to recognise the early signs and symptoms of serious allergic reactions.
- what to do if the symptoms occur.

For more information about the early signs and symptoms of serious allergic reactions, see section 4.

### **How much to use**

Your doctor will decide how much Xolair you need and how often you will need 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 need 1 to 4 injections at a time. You will need the injections either every two weeks, or every four weeks.

Keep taking your current asthma and/or nasal polyps medicine during Xolair treatment. Do not stop taking any asthma and/or nasal polyps medicine without talking to your doctor.

You may not see an immediate improvement after beginning Xolair treatment. In patients with nasal polyps effects have been seen 4 weeks after the start of the treatment. In asthma patients it usually takes between 12 and 16 weeks to have the full effect.

### **Use in children and adolescents**

#### Allergic asthma

Xolair can be used in children and adolescents aged 6 years and older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers and 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.

Children (6 to 11 years of age) are not expected to self-administer Xolair. However, if considered appropriate by their doctor, a caregiver may give them their Xolair injection after proper training.

#### Chronic rhinosinusitis with nasal polyps

Xolair should not be used in children and adolescents under 18 years of age.

#### **If a dose of Xolair is missed**

If you have missed an appointment, contact your doctor or hospital as soon as possible to re-schedule it.

If you have forgotten to give yourself a dose of Xolair, inject the dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

#### **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 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.

#### Serious side effects:

Seek medical attention immediately if you notice any signs of the following side effects:

Rare (may affect up to 1 in 1 000 people)

- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

#### Other side effects include:

Very common (may affect more than 1 in 10 people)

- fever (in children)

Common (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
- headache (very common in children)
- feeling dizzy
- pain in joints (arthralgia)

Uncommon (may affect up to 1 in 100 people)

- feeling 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 (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 after EXP. The expiry date refers to the last day of that month. The carton containing the pre-filled syringe can be stored for a total time of 48 hours at room temperature (25°C) before use.
- 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 arginine hydrochloride, histidine hydrochloride monohydrate, 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 in pre-filled syringe with 26-gauge staked needle and blue syringe guard is available in packs containing 1 pre-filled syringe and in multipacks containing 4 (4 x 1) or 10 (10 x 1) pre-filled syringes.

Not all pack sizes may be marketed.



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**This leaflet was last revised in**

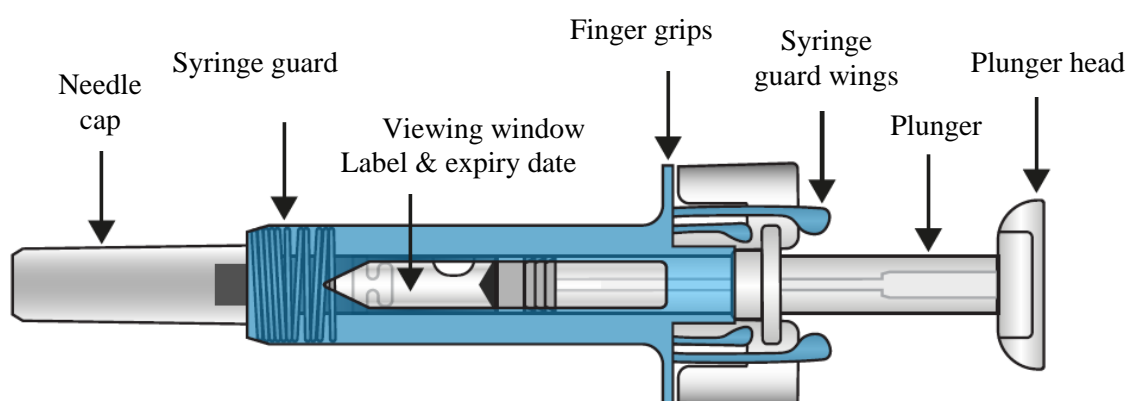
**Other sources of information**

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

## INSTRUCTIONS FOR USE OF XOLAIR PRE-FILLED SYRINGE

Read ALL the way through these instructions before injecting. If your doctor decides that you or a caregiver may be able to give your injections of Xolair at home, you need to be trained by your doctor, nurse or pharmacist before you inject yourself or others. Children (6 to less than 12 years of age) are not expected to inject Xolair themselves, however, if deemed appropriate by their doctor, a caregiver may give them their Xolair injection after proper training. The box contains Xolair pre-filled syringe(s) individually sealed in a plastic tray.

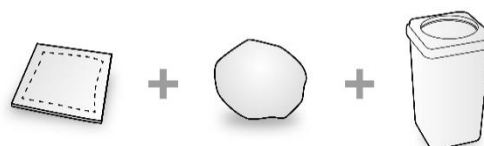
### Your Xolair 75 mg solution for injection in pre-filled syringe



After the medicine has been injected, the syringe guard will be activated to cover the needle. This is intended to protect against accidental needlestick injuries.

### Other items you need for your injection:

- Alcohol swab.
- Cotton ball or gauze.
- Sharps disposal container.



### Important safety information

#### Caution: Keep the syringe out of the sight and reach of children.

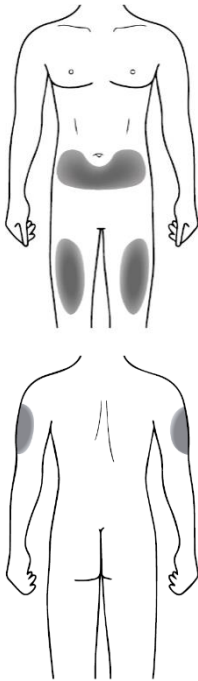
- The needle cap of the syringe may contain dry rubber (latex), which should not be handled by anyone who is sensitive to this substance.
- Do not open the sealed outer box until you are ready to use this medicine.
- Do not use this medicine if either the seal on the outer box or the seal of the plastic tray is broken, as it may not be safe for you to use.
- Do not use if the syringe has been dropped onto a hard surface or dropped after removing the needle cap.
- Never leave the syringe where others might tamper with it.
- Do not shake the syringe.
- Be careful not to touch the syringe guard wings before use. If the wings are touched, the syringe guard may be activated too early.
- Do not remove the needle cap until just before you give the injection.
- The syringe cannot be re-used. Dispose of the used syringe immediately after use in a sharps container.

### Storage of Xolair solution for injection in pre-filled syringe

- Store this medicine sealed in its outer box to protect it from light. Store in the refrigerator between 2°C and 8°C. DO NOT FREEZE.

- Remember to take the syringe out of the refrigerator and allow it to reach room temperature (25°C) before preparing it for injection (it will take about 30 minutes). Leave the syringe in the box to protect it from light. The total time that the syringe is kept at room temperature (25°C) before use must not exceed 48 hours.
- Do not use the syringe after the expiry date which is stated on the outer box and syringe label. If it has expired, return the entire pack to the pharmacy.

### The injection site














The injection site is the place on the body where you are going to use the syringe.

- The recommended site is the front of the thighs. You may also use the lower abdomen, but **not** the area 5 centimetres around the navel (belly button).
- If you need to give more than one injection for the full dose, choose a different injection site each time you inject.
- Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

If a caregiver is giving the injection, the outer upper arms may also be used.

## Preparing Xolair solution for injection in pre-filled syringe for use

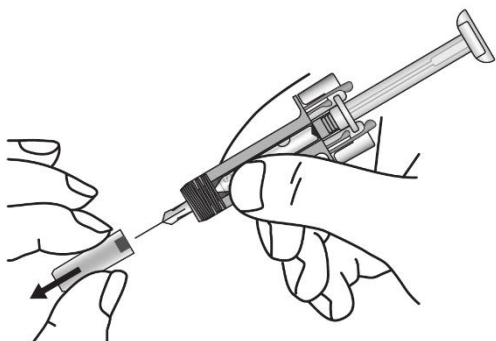
Note: Depending on the dose prescribed to you by your doctor, you may need to prepare one or more pre-filled syringes, and inject the contents of them all. The following table gives examples of how many injections of each dose strength you need for a given dose:

Dose	Syringes needed for the dose	
75 mg	1 blue	
150 mg	1 purple (150 mg)	
225 mg	1 blue (75 mg) + 1 purple (150 mg)	 
300 mg	2 purple (150 mg)	
375 mg	1 blue (75 mg) + 2 purple (150 mg)	 
450 mg	3 purple (150 mg)	
525 mg	1 blue (75 mg) + 3 purple (150 mg)	 
600 mg	4 purple (150 mg)	

1. Take the box containing the syringe out of the refrigerator and leave it **unopened** for about 30 minutes so that it reaches room temperature (leave the syringe in the box to protect it from light).
2. When you are ready to use the syringe, wash your hands thoroughly with soap and water.
3. Clean the injection site with an alcohol swab.
4. Remove the plastic tray from the box, peel back the paper cover. Gripping the middle of the blue syringe guard, lift the syringe out of the tray.
5. Inspect the syringe. The liquid should be clear to slightly cloudy. Its colour may vary from colourless to pale brownish-yellow. You may see an air bubble, which is normal. **DO NOT USE** if the syringe is broken or if the liquid looks distinctly cloudy or distinctly brown, or contains particles. In all these cases, return the entire pack to the pharmacy.
6. Holding the syringe horizontally look into the viewing window to check the expiry date printed on the label. Note: It is possible to rotate the inner part of the syringe assembly so that the label can be read in the viewing window. **DO NOT USE** if the product has expired. If expired, return the entire pack to the pharmacy.

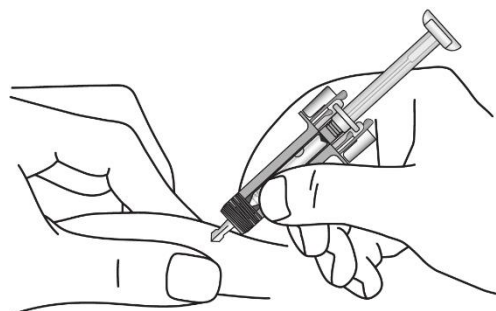
## How to use Xolair solution for injection in pre-filled syringe

1



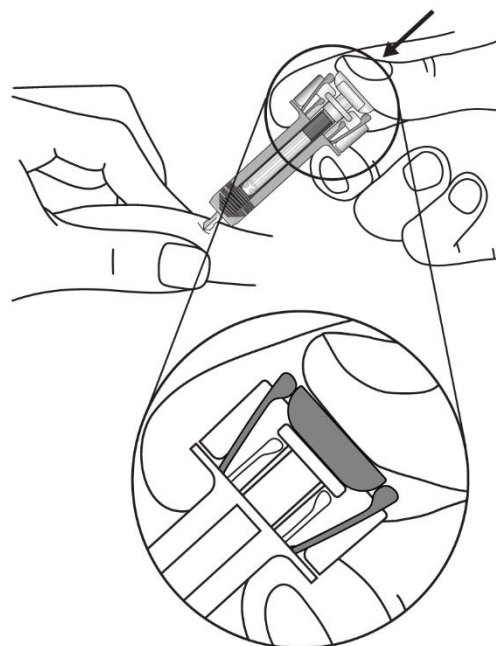
Carefully remove the needle cap from the syringe. Discard the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

2



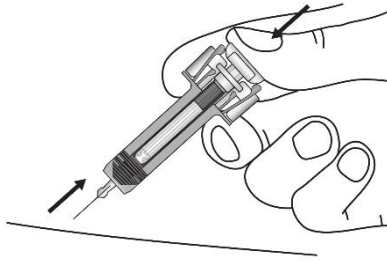
Gently pinch the skin at the injection site and insert the needle as shown. Push the needle all the way in to ensure that the medicine can be fully administered.

3



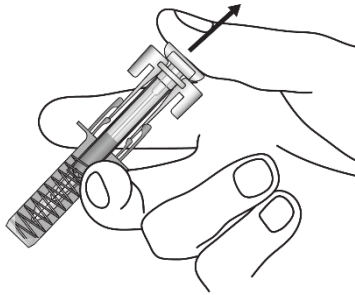
Hold the syringe as shown. **Slowly** depress the plunger **as far as it will go** so that the plunger head is completely between the syringe guard wings.

4



**Keep the plunger fully depressed** while you carefully lift the needle straight out from the injection site.

5



Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle.

There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 30 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

### Disposal instructions



Dispose of the used syringe immediately in a sharps container (closable, puncture resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **Package leaflet: Information for the user**

### **Xolair 75 mg solution for injection in pre-filled syringe** (pre-filled syringe with 27-gauge staked needle, blue plunger) 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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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
2. What you need to know before you use Xolair
3. How to use Xolair
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

Xolair contains the active substance 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 is used for the treatment of:

- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps

##### Allergic asthma

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

##### Chronic rhinosinusitis with nasal polyps

This medicine is used to treat chronic rhinosinusitis with nasal polyps in adults (18 years of age and older) who are already receiving intranasal corticosteroids (corticosteroid nasal spray), but whose symptoms are not well controlled by these medicines. Nasal polyps are small growths on the lining of the nose. Xolair helps to reduce the size of the polyps and improves symptoms including nasal congestion, loss of sense of smell, mucus in the back of the throat and runny nose.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE contributes to a type of inflammation that plays a key role in causing allergic asthma and chronic rhinosinusitis with nasal polyps.

#### **2. What you need to know before you use Xolair**

##### **Do not use 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 use Xolair.

### **Warnings and precautions**

Talk to your doctor before using 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 are travelling to region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.

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.

### **Look out for signs of allergic reactions and other serious side effects**

Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a severe allergic reaction or other serious side effects. Such signs are listed under “Serious side effects” in section 4.

It is important that you receive training from your doctor in how to recognise early symptoms of severe allergic reactions, and how to manage these reactions if they occur, before you inject Xolair yourself or before a non-healthcare professional gives you a Xolair injection (see section 3, “How to use Xolair”). The majority of severe allergic reactions occur within the first 3 doses of Xolair.

### **Children and adolescents**

#### Allergic asthma

Xolair is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

#### Chronic rhinosinusitis with nasal polyps

Xolair is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age 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**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Your doctor will discuss with you the benefits and potential risks of using this medicine during pregnancy.

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

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

### **Driving and using machines**

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

## **3. How to use Xolair**

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

### **How Xolair is used**

Xolair is used as an injection under your skin (known as a subcutaneous injection).

#### Injecting Xolair

- You and your doctor will decide if you should inject Xolair yourself. The first 3 doses are always given by or under the supervision of a healthcare professional (see section 2).
- It is important to be properly trained on how to inject the medicine before injecting yourself.
- A caregiver (for example a parent) may also give you your Xolair injection after he or she has received proper training.

For detailed instructions on how to inject Xolair, see “Instructions for use of Xolair pre-filled syringe” at the end of this leaflet.

#### Training to recognise serious allergic reactions

It is also important that you do not inject Xolair yourself until you have been trained by your doctor or nurse on:

- how to recognise the early signs and symptoms of serious allergic reactions.
- what to do if the symptoms occur.

For more information about the early signs and symptoms of serious allergic reactions, see section 4.

### **How much to use**

Your doctor will decide how much Xolair you need and how often you will need 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 need 1 to 4 injections at a time. You will need the injections either every two weeks, or every four weeks.

Keep taking your current asthma and/or nasal polyps medicine during Xolair treatment. Do not stop taking any asthma and/or nasal polyps medicine without talking to your doctor.

You may not see an immediate improvement after beginning Xolair treatment. In patients with nasal polyps effects have been seen 4 weeks after the start of the treatment. In asthma patients it usually takes between 12 and 16 weeks to have the full effect.

### **Use in children and adolescents**

#### Allergic asthma

Xolair can be used in children and adolescents aged 6 years and older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers and 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.

Children (6 to 11 years of age) are not expected to self-administer Xolair. However, if considered appropriate by their doctor, a caregiver may give them their Xolair injection after proper training.

#### Chronic rhinosinusitis with nasal polyps

Xolair should not be used in children and adolescents under 18 years of age.

#### **If a dose of Xolair is missed**

If you have missed an appointment, contact your doctor or hospital as soon as possible to re-schedule it.

If you have forgotten to give yourself a dose of Xolair, inject the dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

#### **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 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.

#### Serious side effects:

Seek medical attention immediately if you notice any signs of the following side effects:

Rare (may affect up to 1 in 1 000 people)

- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

#### Other side effects include:

Very common (may affect more than 1 in 10 people)

- fever (in children)

Common (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
- headache (very common in children)
- feeling dizzy
- pain in joints (arthralgia)

Uncommon (may affect up to 1 in 100 people)

- feeling 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 (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 after EXP. The expiry date refers to the last day of that month. The carton containing the pre-filled syringe can be stored for a total time of 48 hours at room temperature (25°C) before use.
- 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 arginine hydrochloride, histidine hydrochloride monohydrate, histidine, Polysorbate 20 and water for injections.

### **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 in pre-filled syringe with 27-gauge staked needle and blue plunger is available in packs containing 1 pre-filled syringe and in multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled syringes.

Not all pack sizes may be marketed.

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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>

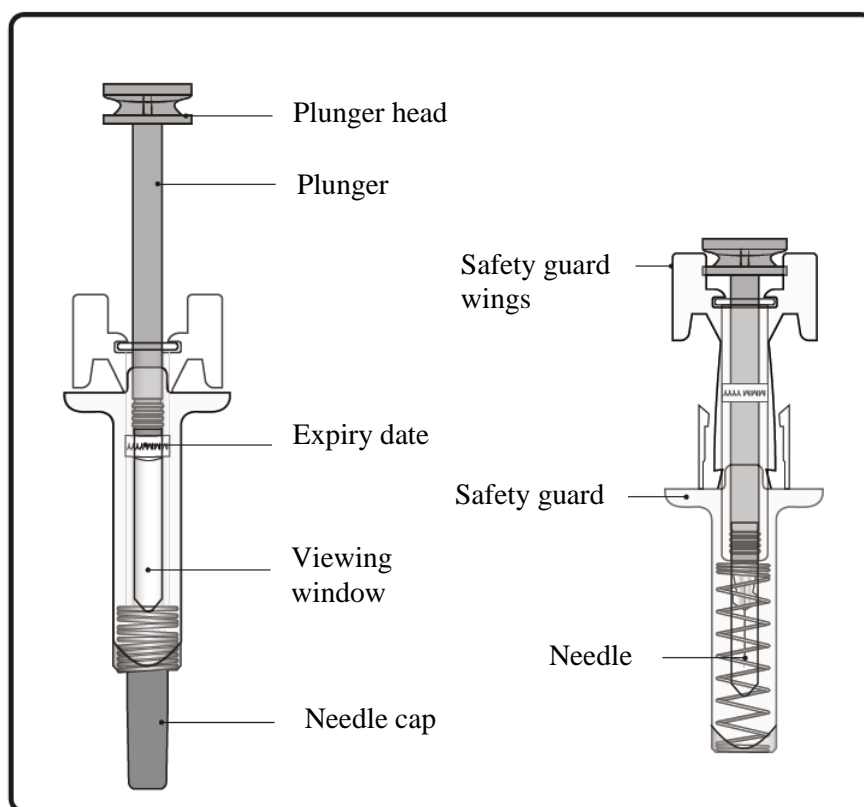
## INSTRUCTIONS FOR USE OF XOLAIR PRE-FILLED SYRINGE

These “Instructions for Use” contain information on how to inject Xolair.

If your doctor decides that you or your caregiver may be able to give your injections of Xolair at home, ensure that your doctor or nurse shows you or your caregiver how to prepare and inject with the Xolair pre-filled syringe before you use it for the first time.

Children below 12 years of age are not expected to inject Xolair themselves, however, if deemed appropriate by their doctor, a caregiver may give them their Xolair injections after proper training.

Be sure that you read and understand these “Instructions for Use” before injecting with the Xolair pre-filled syringe. Talk to your doctor if you have any questions.



### Important information you need to know before injecting Xolair

- Xolair is for subcutaneous injection only (inject directly into fatty layer under the skin).
- **Do not** use the pre-filled syringe if either the seal on the outer carton or the seal of the plastic tray is broken.
- **Do not** use if the pre-filled syringe has been dropped onto a hard surface or dropped after removing the needle cap.
- **Do not** inject if the pre-filled syringe has been kept out of the refrigerator for more than a total of 48 hours. Dispose of it (see Step 12) and use a new pre-filled syringe for your injection.
- The pre-filled syringe has a safety guard that will be activated to cover the needle after the injection is finished. The safety guard will help to prevent needlestick injuries to anyone who handles the pre-filled syringe after injection.
- **Do not** try to re-use or take apart the pre-filled syringe.
- **Do not** pull back on the plunger.


## Store Xolair

- Store in a refrigerator (2°C to 8°C). The carton containing the pre-filled syringe can be stored for a total time of 48 hours at room temperature (25°C) before use.
- **Do not** freeze.
- Keep the pre-filled syringe in the original carton until ready to use in order to protect from light.
- Keep the pre-filled syringe out of sight and reach of children.

## DOSING TABLE

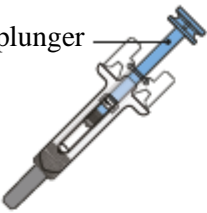

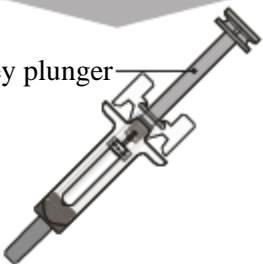






























Xolair pre-filled syringes are available in 3 dose strengths (one pre-filled syringe in each carton). These instructions are to be used for all 3 dose strengths.

Depending on the dose prescribed to you by your doctor, you may need to select one or more pre-filled syringes, and inject the contents of them all in order to deliver your full dose. The Dosing Table below shows the combination of pre-filled syringes needed to deliver your full dose.

	<b>Important:</b> If the dose is for a child under age 12 it is recommended to use only blue (75 mg) and purple (150 mg) pre-filled syringes. Refer to the Dosing Table below for the recommended combination of pre-filled syringes for children under age 12.
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Contact your doctor if you have questions on the Dosing Table.



Xolair 75 mg pre-filled syringe with a blue plunger		Xolair 150 mg pre-filled syringe with a purple plunger		Xolair 300 mg pre-filled syringe with a grey plunger	
Blue plunger 		Purple plunger 		Grey plunger 	
DOSE	Pre-filled syringes needed for dose	Blue 75 mg	Purple 150 mg	Grey 300 mg	
75 mg	1 blue				
150 mg	1 purple				
225 mg	1 blue + 1 purple				
300 mg (ages 12 and up)	1 grey				
300 mg (children under age 12)	2 purple		 		
375 mg (ages 12 and up)	1 blue + 1 grey				
375 mg (children under age 12)	1 blue + 2 purple		 		
450 mg (ages 12 and up)	1 purple + 1 grey				
450 mg (children under age 12)	3 purple		  		
525 mg (ages 12 and up)	1 blue + 1 purple + 1 grey				
525 mg (children under age 12)	1 blue + 3 purple		  		
600 mg (ages 12 and up)	2 grey			 	
600 mg (children under age 12)	4 purple		   		

## Prepare to inject Xolair

### Step 1. Bring to room temperature

Take the carton containing the pre-filled syringe out of the refrigerator **and leave it unopened so that it reaches room temperature (minimum 30 minutes)**.

Note: If you need more than one pre-filled syringe (one pre-filled syringe per carton) to deliver your full dose (see Dosing Table), take all the cartons out of the refrigerator at the same time.

### Step 2. Gather supplies

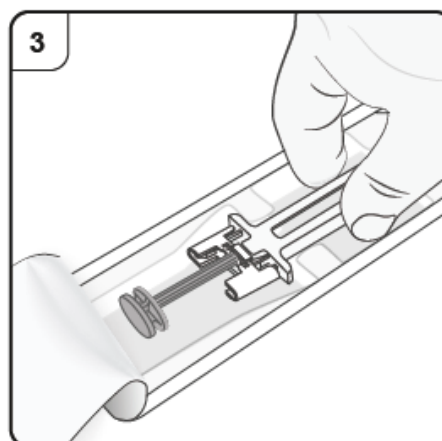
You will need the following supplies (not included in the carton):

- Alcohol wipe
- Cotton ball or gauze pad
- Sharps disposal container
- Adhesive plaster

### Step 3. Unpack

Open the plastic tray by peeling away the cover. Remove the pre-filled syringe by holding it in the middle as shown.

**Do not** remove the needle cap until you are ready to inject.



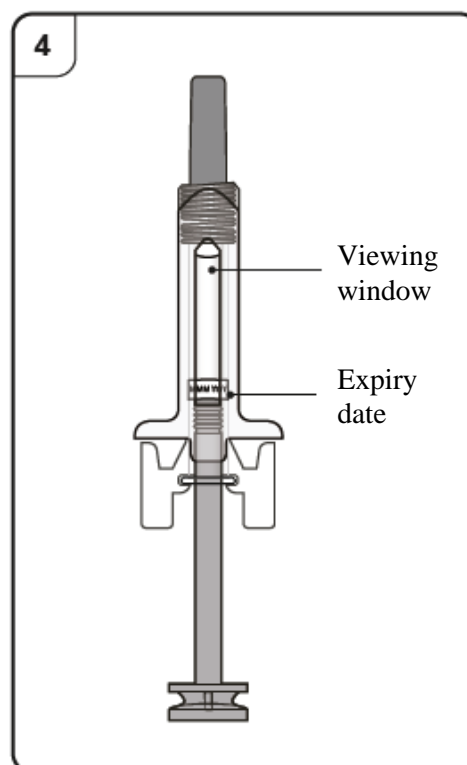
#### Step 4. Inspect the pre-filled syringe

Look through the viewing window of the pre-filled syringe. The liquid inside should be clear to slightly cloudy. Its colour may vary from colourless to pale brownish-yellow. You may see air bubbles in the liquid, which is normal.

**Do not** try to remove the air.

- **Do not** use the pre-filled syringe if the liquid contains particles, or if the liquid looks distinctly cloudy or distinctly brown.
- **Do not** use the pre-filled syringe if it looks damaged or if it has leaked.
- **Do not** use the pre-filled syringe after the expiry date (EXP), which is printed on the pre-filled syringe label and carton.

In all of these cases, contact your doctor, nurse or pharmacist.

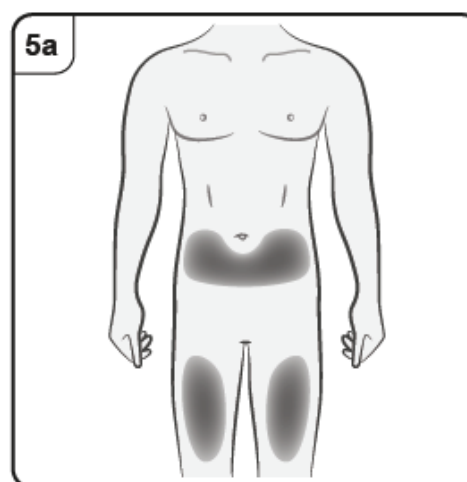


#### Step 5. Choose injection site

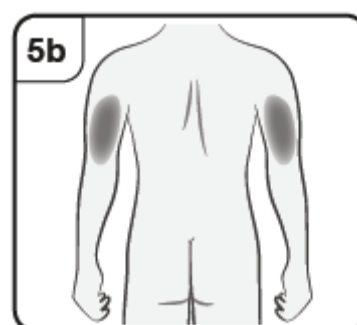
You should inject into the front of the thighs or the lower stomach area but not the area 5 cm around the belly button.

**Do not** inject into skin that is tender, bruised, red, scaly or hard or into areas with scars or stretch marks.

Note: If you need more than one pre-filled syringe to deliver your full dose, make sure your injections are at least 2 cm apart.



If your caregiver, doctor or nurse is giving you the injection, they may also inject into the outer upper arm.



## Inject with Xolair

### Step 6. Clean injection site

Clean your hands.

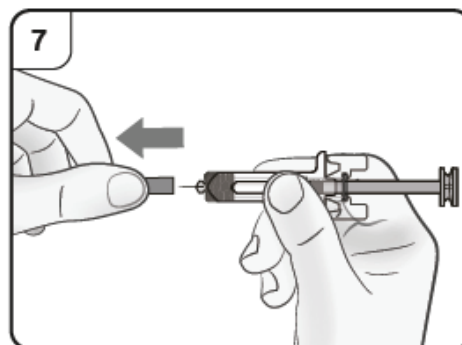
Clean the chosen injection site with an alcohol wipe. Leave it to dry before injecting.

**Do not** touch or blow on the cleaned skin before injecting.

### Step 7. Remove needle cap

Firmly pull straight to remove the needle cap from the pre-filled syringe. You may see a drop of liquid at the end of the needle. This is normal.

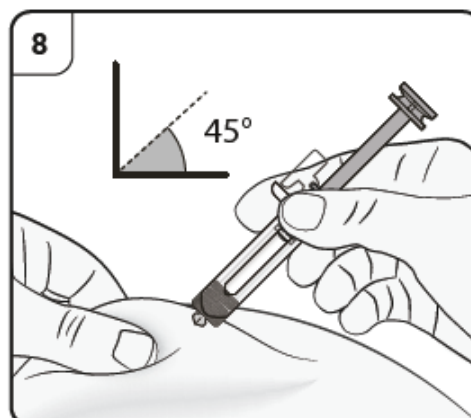
**Do not** put the needle cap back on. Throw away the needle cap.



### Step 8. Insert needle

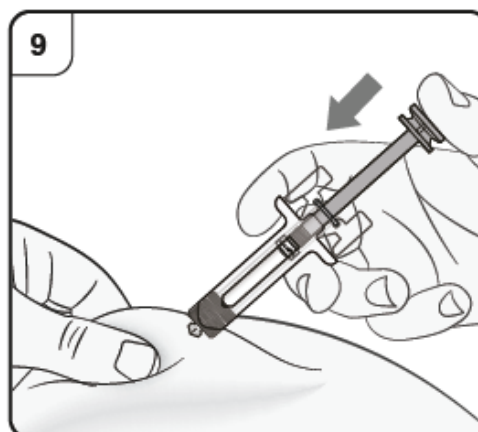
Gently pinch the skin at the injection site and hold the pinch throughout the injection. With the other hand insert the needle into the skin at an angle of approximately 45 degrees as shown.

**Do not** press the plunger while inserting the needle.



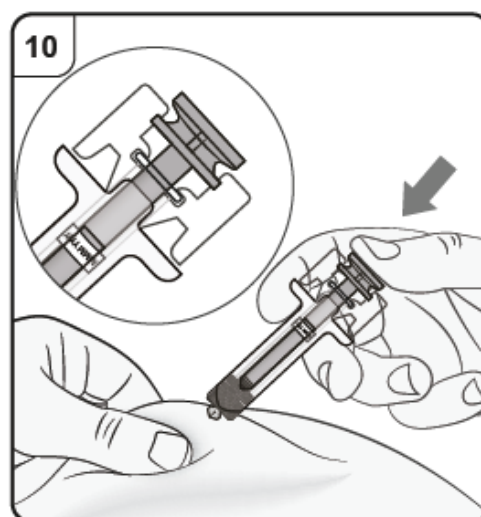
### Step 9. Start injection

Continue to pinch the skin. Slowly press the plunger **as far as it will go**. This will ensure that a full dose is injected.



### Step 10. Complete injection

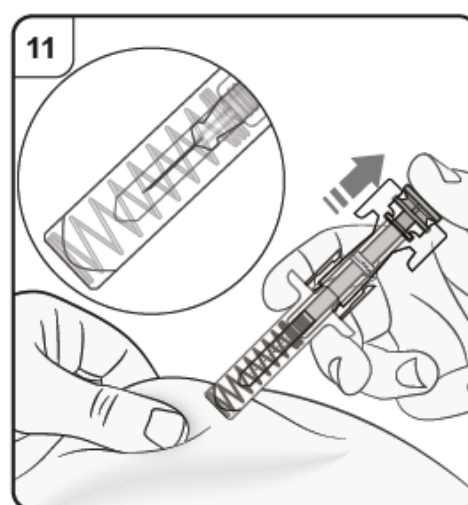
Confirm that the plunger head is between the safety guard wings as shown. This will ensure that the safety guard has been activated and will cover the needle after the injection is finished.



### Step 11. Release plunger

Keeping the pre-filled syringe at the injection site, slowly release the plunger until the needle is automatically covered by the safety guard. Remove the pre-filled syringe from the injection site and release the pinch.

There may be a small amount of blood at the injection site. You can press a cotton ball or gauze pad over the injection site until any bleeding stops. **Do not** rub the injection site. If needed, cover the injection site with a small adhesive plaster.



**Note:** If you need more than one pre-filled syringe to deliver your full dose, throw away the used pre-filled syringe as described in Step 12.

Repeat Step 2 to Step 12 again for all the pre-filled syringes needed to deliver your full dose.

Carry out the injections immediately one after another.

Make sure the injections are at least 2 cm apart.

## **After the injection**

### **Step 12. Dispose of the pre-filled syringe**

Put the used pre-filled syringe in a sharps disposal container (i.e. a puncture-resistant closable container, or similar) immediately after use.

**Do not** try to put the needle cap back onto the syringe.

Talk to your doctor or pharmacist about proper disposal of the sharps disposal container. There may be local regulations for disposal.

## **Package leaflet: Information for the user**

### **Xolair 75 mg solution for injection in pre-filled pen** 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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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
2. What you need to know before you use Xolair
3. How to use Xolair
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

Xolair contains the active substance 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 is used for the treatment of:

- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps

##### Allergic asthma

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

##### Chronic rhinosinusitis with nasal polyps

This medicine is used to treat chronic rhinosinusitis with nasal polyps in adults (18 years of age and older) who are already receiving intranasal corticosteroids (corticosteroid nasal spray), but whose symptoms are not well controlled by these medicines. Nasal polyps are small growths on the lining of the nose. Xolair helps to reduce the size of the polyps and improves symptoms including nasal congestion, loss of sense of smell, mucus in the back of the throat and runny nose.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE contributes to a type of inflammation that plays a key role in causing allergic asthma and chronic rhinosinusitis with nasal polyps.

#### **2. What you need to know before you use Xolair**

##### **Do not use 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 use Xolair.

### **Warnings and precautions**

Talk to your doctor before using 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 are travelling to region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.

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.

### **Look out for signs of allergic reactions and other serious side effects**

Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a severe allergic reaction or other serious side effects. Such signs are listed under “Serious side effects” in section 4.

It is important that you receive training from your doctor in how to recognise early symptoms of severe allergic reactions, and how to manage these reactions if they occur, before you inject Xolair yourself or before a non-healthcare professional gives you a Xolair injection (see section 3, “How to use Xolair”). The majority of severe allergic reactions occur within the first 3 doses of Xolair.

### **Children and adolescents**

#### Allergic asthma

Xolair is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

#### Chronic rhinosinusitis with nasal polyps

Xolair is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age 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**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Your doctor will discuss with you the benefits and potential risks of using this medicine during pregnancy.

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



Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

### **Driving and using machines**

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

## **3. How to use Xolair**

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

### **How Xolair is used**

Xolair is used as an injection under your skin (known as a subcutaneous injection).

#### Injecting Xolair

- You and your doctor will decide if you should inject Xolair yourself. The first 3 doses are always given by or under the supervision of a healthcare professional (see section 2).
- It is important to be properly trained on how to inject the medicine before injecting yourself.
- A caregiver (for example a parent) may also give you your Xolair injection after he or she has received proper training.

For detailed instructions on how to inject Xolair, see “Instructions for use of Xolair pre-filled pen” at the end of this leaflet.

#### Training to recognise serious allergic reactions

It is also important that you do not inject Xolair yourself until you have been trained by your doctor or nurse on:

- how to recognise the early signs and symptoms of serious allergic reactions.
- what to do if the symptoms occur.

For more information about the early signs and symptoms of serious allergic reactions, see section 4.

### **How much to use**

Your doctor will decide how much Xolair you need and how often you will need 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 need 1 to 4 injections at a time. You will need the injections either every two weeks, or every four weeks.

Keep taking your current asthma and/or nasal polyps medicine during Xolair treatment. Do not stop taking any asthma and/or nasal polyps medicine without talking to your doctor.

You may not see an immediate improvement after beginning Xolair treatment. In patients with nasal polyps effects have been seen 4 weeks after the start of the treatment. In asthma patients it usually takes between 12 and 16 weeks to have the full effect.

### **Use in children and adolescents**

#### Allergic asthma

Xolair can be used in children and adolescents aged 6 years and older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers and 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.

Children (6 to 11 years of age) are not expected to self-administer Xolair. However, if considered appropriate by their doctor, a caregiver may give them their Xolair injection after proper training.

Xolair pre-filled pens are not intended for use in children under 12 years of age. Xolair 75 mg pre-filled syringe and Xolair 150 mg pre-filled syringe or Xolair powder and solvent for solution for injection may be used in children 6-11 years of age with allergic asthma.

#### Chronic rhinosinusitis with nasal polyps

Xolair should not be used in children and adolescents under 18 years of age.

#### **If a dose of Xolair is missed**

If you have missed an appointment, contact your doctor or hospital as soon as possible to re-schedule it.

If you have forgotten to give yourself a dose of Xolair, inject the dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

#### **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 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.

#### Serious side effects:

Seek medical attention immediately if you notice any signs of the following side effects:

Rare (may affect up to 1 in 1 000 people)

- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

#### Other side effects include:

Very common (may affect more than 1 in 10 people)

- fever (in children)

Common (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
- headache (very common in children)
- feeling dizzy

- pain in joints (arthralgia)

Uncommon (may affect up to 1 in 100 people)

- feeling 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 (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 after EXP. The expiry date refers to the last day of that month. The carton containing the pre-filled pen can be stored for a total time of 48 hours at room temperature (25°C) before use.
- 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 pen of 0.5 ml solution contains 75 mg omalizumab.
- The other ingredients are arginine hydrochloride, histidine hydrochloride monohydrate, histidine, Polysorbate 20 and water for injections.

### **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 pen.

Xolair 75 mg solution for injection in pre-filled pen is available in packs containing 1 pre-filled pen and in multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled pens.

Not all pack sizes may be marketed.

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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>

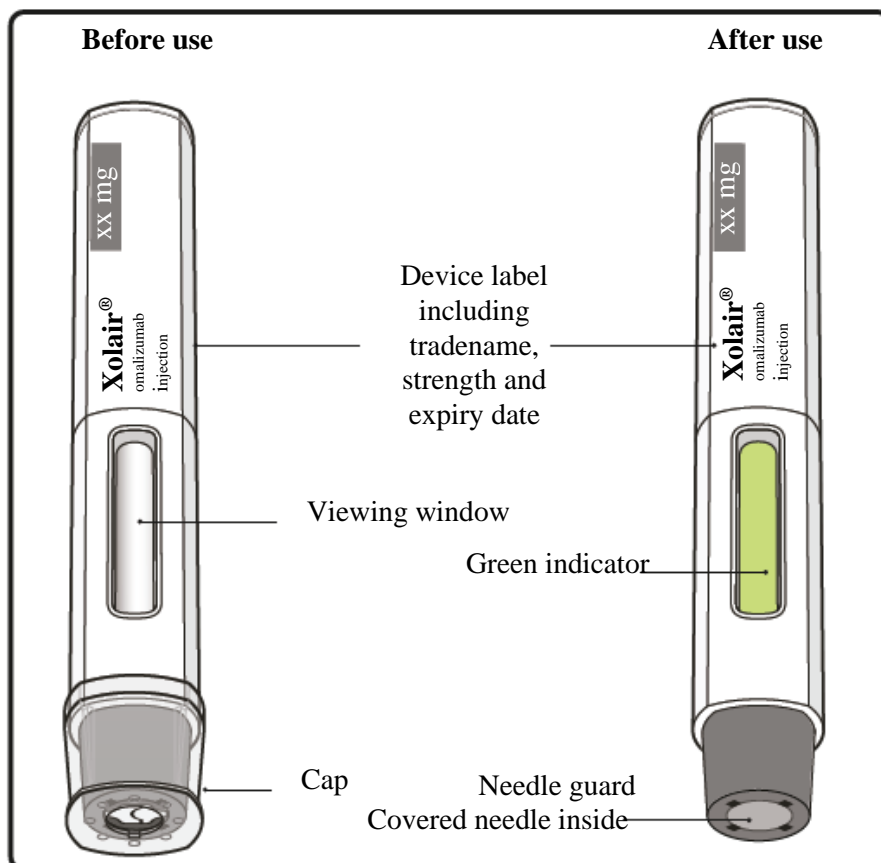
## INSTRUCTIONS FOR USE OF XOLAIR PRE-FILLED PEN

These “Instructions for Use” contain information on how to inject Xolair.

If your doctor decides that you or your caregiver may be able to give your injections of Xolair at home, ensure that your doctor or nurse shows you or your caregiver how to prepare and inject with the Xolair pen before you use it for the first time.

This Xolair pen is intended to be used for patients ages 12 and up.

Be sure that you read and understand these “Instructions for Use” before injecting with the Xolair pen. Talk to your doctor if you have any questions.



### Important information you need to know before injecting Xolair

- Xolair is for subcutaneous injection only (inject directly into fatty layer under the skin).
- **Do not** use the pen if the seal on the outer carton is broken.
- **Do not** use if the pen has been dropped after removing the cap.
- **Do not** inject if the pen has been kept out of the refrigerator for more than a total of 48 hours. Dispose of it (see Step 13) and use a new pen for your injection.
- **Do not** touch or push the needle guard as you could get injured. Touching or pushing on the needle guard could cause a needlestick injury.
- **Do not** try to re-use or take apart the pen.
- **Do not** try to reattach the cap once it has been taken off.

### Store Xolair

- Store in a refrigerator (2°C - 8°C). The carton containing the pen can be stored for a total time of 48 hours at room temperature (25°C) before use.

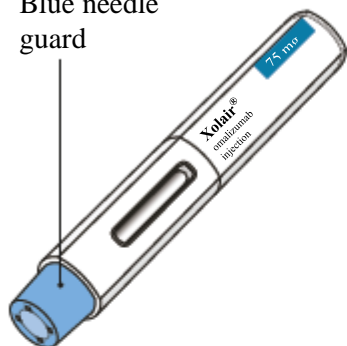
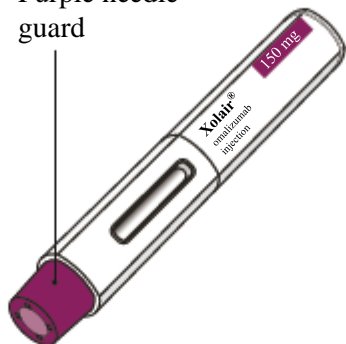
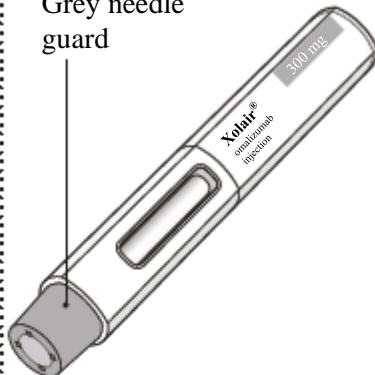














- **Do not** freeze.
- Keep the pen in the original carton until ready to use in order to protect from light.
- Keep the pen out of sight and reach of children.

## **DOSING TABLE**

Xolair pens are available in 3 dose strengths (one pen in each carton). These instructions are to be used for all 3 dose strengths.

Depending on the dose prescribed to you by your doctor, you may need to select one or more pens, and inject the contents of them all in order to deliver your full dose. The Dosing Table below shows the combination of pens needed to deliver your full dose.

Contact your doctor if you have questions on the Dosing Table.

Xolair 75 mg pen with a blue needle guard		Xolair 150 mg pen with a purple needle guard		Xolair 300 mg pen with a grey needle guard	
<p>Blue needle guard</p> 		<p>Purple needle guard</p> 		<p>Grey needle guard</p> 	
Dose	Number of pens needed for the dose	Blue 75 mg	Purple 150 mg	Grey 300 mg	
75 mg	1 blue				
150 mg	1 purple				
225 mg	1 blue + 1 purple				
300 mg	1 grey				
375 mg	1 blue + 1 grey				
450 mg	1 purple + 1 grey				
525 mg	1 blue + 1 purple + 1 grey				
600 mg	1 grey + 1 grey			 	



## Prepare to inject Xolair

### Step 1. Bring to room temperature

Take the carton containing the pen out of the refrigerator **and leave it unopened so that it reaches room temperature (minimum 30 minutes)**.

Note: If you need more than one pen (one pen in each carton) to deliver your full dose (see Dosing Table), take all the cartons out of the refrigerator at the same time.

### Step 2. Gather supplies

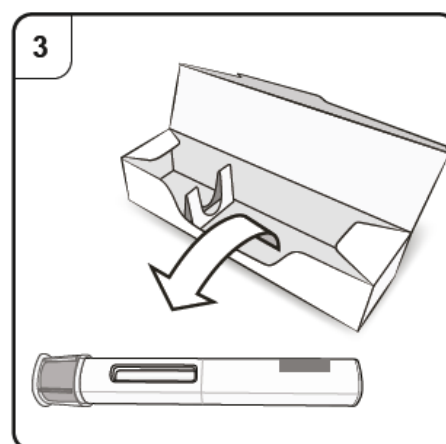
You will need the following supplies (not included in the carton):

- Alcohol wipe
- Cotton ball or gauze pad
- Sharps disposal container
- Adhesive plaster

### Step 3. Unpack

Take the pen out of the outer carton.

**Do not** remove the cap until you are ready to inject.

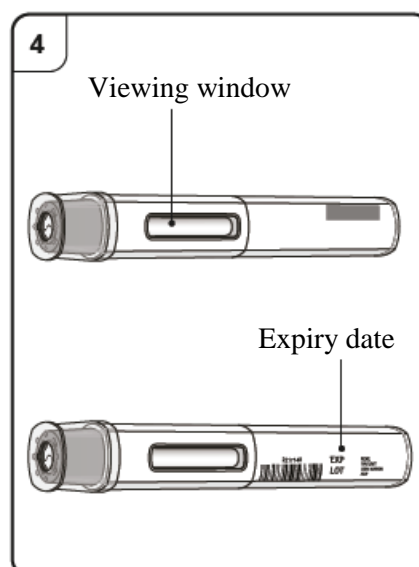


#### Step 4. Inspect the pen

Look through the viewing window of the pen. The liquid inside should be clear to slightly cloudy. Its colour may vary from colourless to pale brownish-yellow. You may see air bubbles in the liquid, which is normal.

- **Do not** use the pen if the liquid contains particles, or if the liquid looks distinctly cloudy or distinctly brown.
- **Do not** use the pen if it looks damaged.
- **Do not** use the pen after the expiry date (EXP), which is printed on the pen label and carton.

In all of these cases, contact your doctor, nurse or pharmacist.

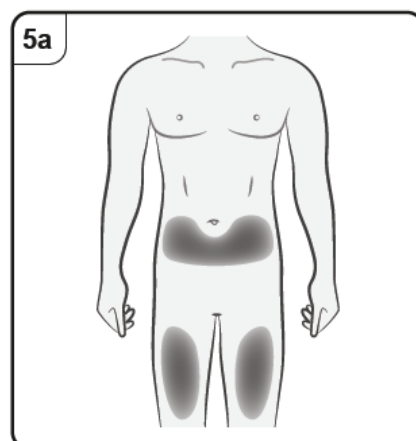


#### Step 5. Choose injection site

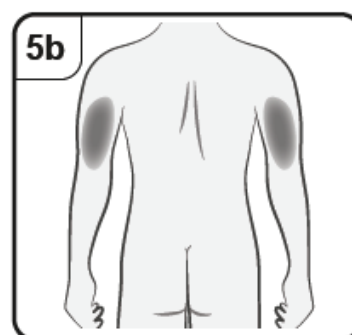
You should inject into the front of the thighs or the lower stomach area but not the area 5 cm around the belly button.

**Do not** inject into skin that is tender, bruised, red, scaly or hard or into areas with scars or stretch marks.

Note: If you need more than one pen to deliver your full dose, make sure your injections are at least 2 cm apart.



If a caregiver, doctor or nurse is giving the injection, they may also inject into the outer upper arm.



## Inject with Xolair

### Step 6. Clean injection site

Clean your hands.

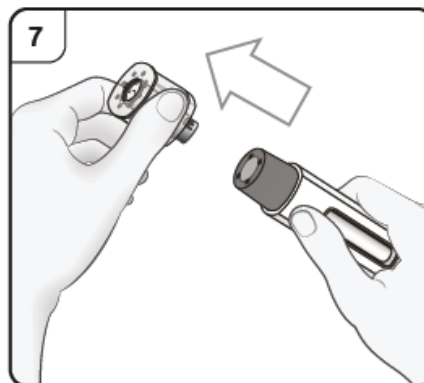
Clean the chosen injection site with an alcohol wipe. Leave it to dry before injecting.

**Do not** touch or blow on the cleaned skin before injecting.

### Step 7. Remove cap

Pull the cap straight off in the direction of the arrow.

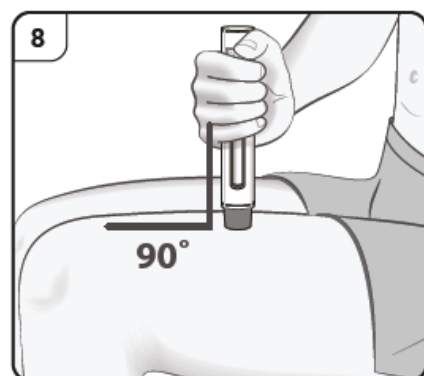
**Do not** put the cap back on. Throw away the cap.



### Step 8. Position the pen

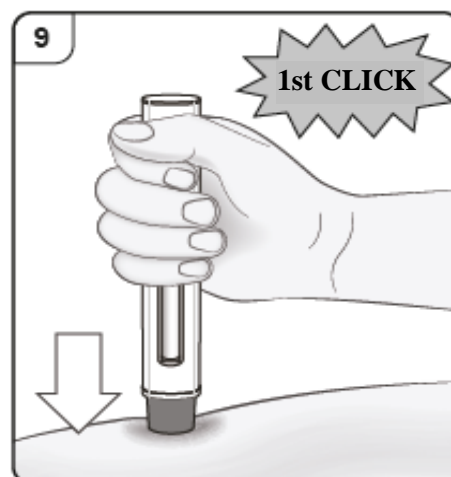
Hold the pen comfortably **with the needle guard directly against the skin**.

The pen should be at a 90° angle to the skin as shown.



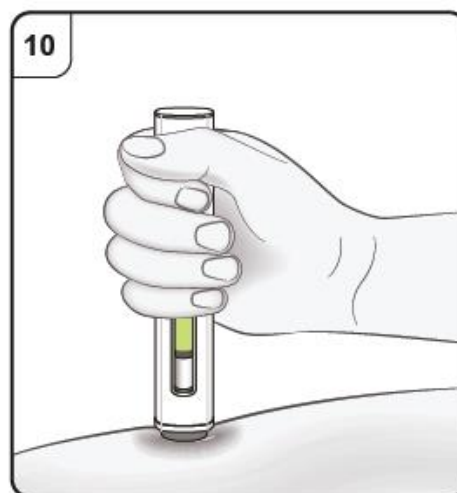
### Step 9. Start injection

Push and hold the pen firmly against the skin. Listen for the **1st click** which indicates that the injection has started.



### Step 10. Monitor injection

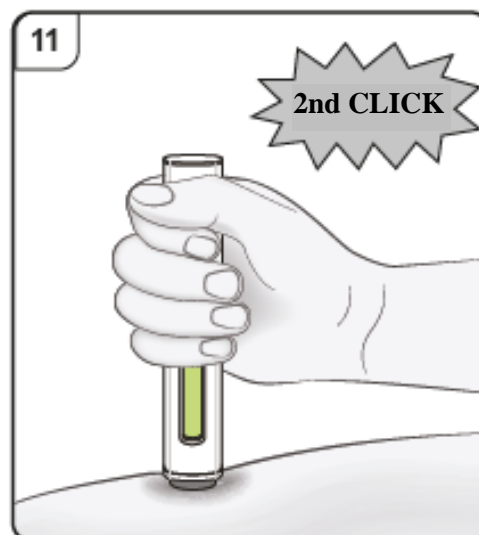
Keep holding the pen firmly down against the skin. The green indicator shows the progress of the injection.



### Step 11. Complete injection

Listen for the **2nd click**. This indicates the injection is **almost** complete.

**Keep holding the pen in position until the green indicator has stopped moving to make sure the injection is complete.** Remove the pen from the skin. The needle is automatically covered by the needle guard. The injection is now complete.



### After the injection

#### Step 12. Check green indicator

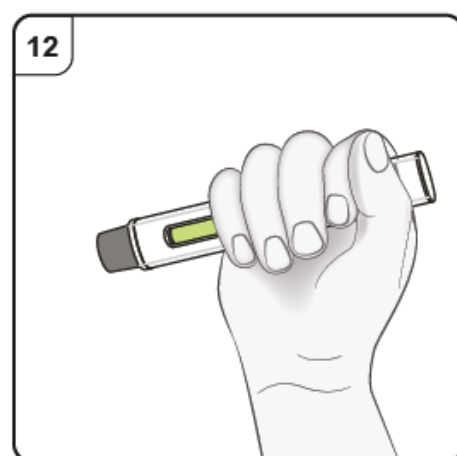
If the green indicator has not completely filled the viewing window, contact your doctor or nurse.

There may be a small amount of blood at the injection site.

You can press a cotton ball or gauze pad over the injection site until any bleeding stops.

**Do not** rub the injection site. If needed, cover your injection site with a small adhesive plaster.

Note: If you need more than one pen to deliver your full dose, throw away the used pen as described in Step 13.



Repeat Step 2 to Step 13 again for all the pens needed to deliver your full dose.

Carry out the injections immediately one after another.

Make sure the injections are at least 2 cm apart.

### **Step 13. Dispose of the pen**

Put the used pen in a sharps disposal container (i.e. a puncture-resistant closable container, or similar) right away after use.

Talk to your doctor or pharmacist about proper disposal of the sharps disposal container. There may be local regulations for disposal.

## **Package leaflet: Information for the user**

### **Xolair 150 mg solution for injection in pre-filled syringe** (pre-filled syringe with 26-gauge staked needle, purple syringe guard) 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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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
2. What you need to know before you use Xolair
3. How to use Xolair
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

Xolair contains the active substance 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 is used for the treatment of:

- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps
- chronic spontaneous urticaria (CSU)

##### Allergic asthma

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

##### Chronic rhinosinusitis with nasal polyps

This medicine is used to treat chronic rhinosinusitis with nasal polyps in adults (18 years of age and older) who are already receiving intranasal corticosteroids (corticosteroid nasal spray), but whose symptoms are not well controlled by these medicines. Nasal polyps are small growths on the lining of the nose. Xolair helps to reduce the size of the polyps and improves symptoms including nasal congestion, loss of sense of smell, mucus in the back of the throat and runny nose.

##### Chronic spontaneous urticaria (CSU)

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

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE contributes to a type of inflammation that plays a key role in causing allergic asthma, chronic rhinosinusitis with nasal polyps and CSU.

## **2. What you need to know before you use Xolair**

### **Do not use 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 use Xolair.

### **Warnings and precautions**

Talk to your doctor before using 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 are travelling to region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.
- if you have ever had an allergic reaction to latex. The needle cap of the syringe may contain dry rubber (latex).

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.

### **Look out for signs of allergic reactions and other serious side effects**

Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a severe allergic reaction or other serious side effects. Such signs are listed under “Serious side effects” in section 4.

It is important that you receive training from your doctor in how to recognise early symptoms of severe allergic reactions, and how to manage these reactions if they occur, before you inject Xolair yourself or before a non-healthcare professional gives you a Xolair injection (see section 3, “How to use Xolair”). The majority of severe allergic reactions occur within the first 3 doses of Xolair.

### **Children and adolescents**

#### Allergic asthma

Xolair is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

#### Chronic rhinosinusitis with nasal polyps

Xolair is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age has not been studied.

#### Chronic spontaneous urticaria (CSU)

Xolair is not recommended for children under 12 years of age. Its use in children under 12 years of age 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**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Your doctor will discuss with you the benefits and potential risks of using this medicine during pregnancy.

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

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

### **Driving and using machines**

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

## **3. How to use Xolair**

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure

### **How Xolair is used**

Xolair is used as an injection under your skin (known as a subcutaneous injection).

#### Injecting Xolair

- You and your doctor will decide if you should inject Xolair yourself. The first 3 doses are always given by or under the supervision of a healthcare professional (see section 2).
- It is important to be properly trained on how to inject the medicine before injecting yourself.
- A caregiver (for example a parent) may also give you your Xolair injection after he or she has received proper training.

For detailed instructions on how to inject Xolair, see “Instructions for use of Xolair pre-filled syringe” at the end of this leaflet.

#### Training to recognise serious allergic reactions

It is also important that you do not inject Xolair yourself until you have been trained by your doctor or nurse on:

- how to recognise the early signs and symptoms of serious allergic reactions
- what to do if the symptoms occur.

For more information about the early signs and symptoms of serious allergic reactions, see section 4.

### **How much to use**

#### Allergic asthma and chronic rhinosinusitis with nasal polyps

Your doctor will decide how much Xolair you need and how often you will need 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 need 1 to 4 injections at a time. You will need the injections either every two weeks, or every four weeks.

Keep taking your current asthma and/or nasal polyps medicine during Xolair treatment. Do not stop taking any asthma and/or nasal polyps medicine without talking to your doctor.



You may not see an immediate improvement after beginning Xolair treatment. In patients with nasal polyps effects have been seen 4 weeks after the start of the treatment. In asthma patients it usually takes between 12 and 16 weeks to have the full effect.

#### Chronic spontaneous urticaria (CSU)

You will need two 150 mg injections at a time every four weeks.

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

#### **Use in children and adolescents**

##### Allergic asthma

Xolair can be used in children and adolescents aged 6 years and older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers and 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.

Children (6 to 11 years of age) are not expected to self-administer Xolair. However, if considered appropriate by their doctor, a caregiver may give them their Xolair injection after proper training.

##### Chronic rhinosinusitis with nasal polyps

Xolair should not be used in children and adolescents under 18 years of age.

##### Chronic spontaneous urticaria (CSU)

Xolair can be used in adolescents aged 12 years of age and older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines. The dose for adolescents aged 12 years and above is the same as for adults.

#### **If a dose of Xolair is missed**

If you have missed an appointment, contact your doctor or hospital as soon as possible to re-schedule it.

If you have forgotten to give yourself a dose of Xolair, inject the dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

#### **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 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:

Seek medical attention immediately if you notice any signs of the following side effects:

Rare (may affect up to 1 in 1 000 people)

- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or

trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

Other side effects include:

Very common (may affect more than 1 in 10 people)

- fever (in children)

Common (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
- 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)
- feeling dizzy

Uncommon (may affect up to 1 in 100 people)

- feeling 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 (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 after EXP. The expiry date refers to the last day of that month. The carton containing the pre-filled syringe can be stored for a total time of 48 hours at room temperature (25°C) before use.
- 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 arginine hydrochloride, histidine hydrochloride monohydrate, 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 in pre-filled syringe with 26-gauge staked needle and purple syringe guard is available in packs containing 1 pre-filled syringe and in multipacks containing 4 (4 x 1), 6 (6 x 1) or 10 (10 x 1) pre-filled syringes.

Not all pack sizes may be marketed.

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**This leaflet was last revised in**

**Other sources of information**

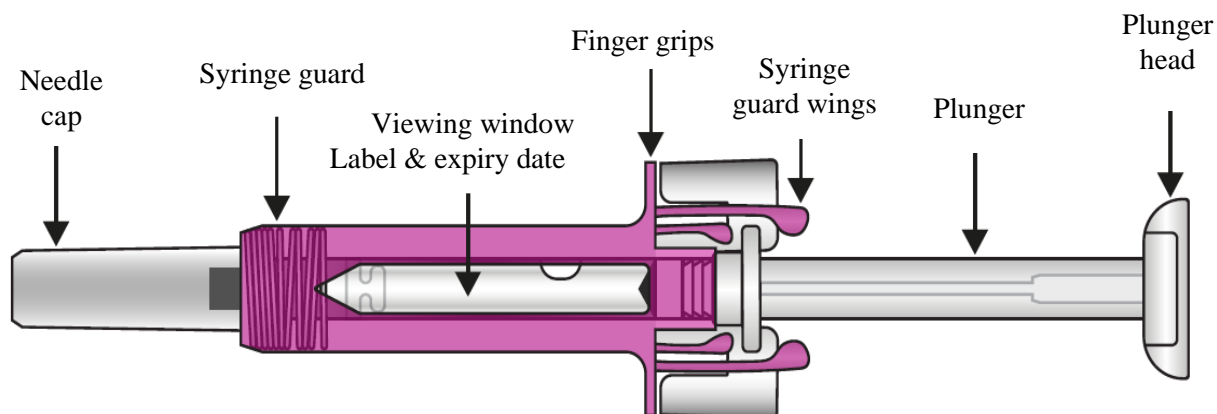
Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

## INSTRUCTIONS FOR USE OF XOLAIR PRE-FILLED SYRINGE

Read ALL the way through these instructions before injecting. If your doctor decides that you or a caregiver may be able to give your injections of Xolair at home, you need to be trained by your doctor, nurse or pharmacist before you inject yourself or others. Children (6 to less than 12 years of age) are not expected to inject Xolair themselves, however, if deemed appropriate by their doctor, a caregiver may give them their Xolair injection after proper training. The box contains Xolair pre-filled syringe(s) individually sealed in a plastic tray.

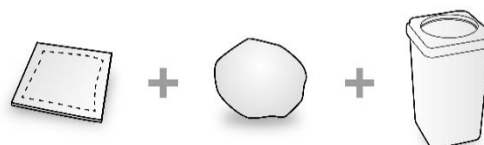
### Your Xolair 150 mg solution for injection in pre-filled syringe



After the medicine has been injected, the syringe guard will be activated to cover the needle. This is intended to protect against accidental needlestick injuries.

### Other items you need for your injection:

- Alcohol swab.
- Cotton ball or gauze.
- Sharps disposal container.



### Important safety information

#### Caution: Keep the syringe out of the sight and reach of children.

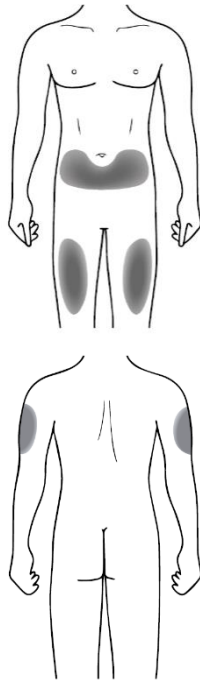
- The needle cap of the syringe may contain dry rubber (latex), which should not be handled by anyone who is sensitive to this substance.
- Do not open the sealed outer box until you are ready to use this medicine.
- Do not use this medicine if either the seal on the outer box or the seal of the plastic tray is broken, as it may not be safe for you to use.
- Do not use if the syringe has been dropped onto a hard surface or dropped after removing the needle cap.
- Never leave the syringe where others might tamper with it.
- Do not shake the syringe.
- Be careful not to touch the syringe guard wings before use. If the wings are touched, the syringe guard may be activated too early.
- Do not remove the needle cap until just before you give the injection.
- The syringe cannot be re-used. Dispose of the used syringe immediately after use in a sharps container.

### Storage of Xolair solution for injection in pre-filled syringe

- Store this medicine sealed in its outer box to protect it from light. Store in the refrigerator between 2°C and 8°C. DO NOT FREEZE.

- Remember to take the syringe out of the refrigerator and allow it to reach room temperature (25°C) before preparing it for injection (it will take about 30 minutes). Leave the syringe in the box to protect it from light. The total time that the syringe is kept at room temperature (25°C) before use must not exceed 48 hours.
- Do not use the syringe after the expiry date which is stated on the outer box and syringe label. If it has expired, return the entire pack to the pharmacy.

### The injection site














The injection site is the place on the body where you are going to use the syringe.

- The recommended site is the front of the thighs. You may also use the lower abdomen, but **not** the area 5 centimetres around the navel (belly button).
- If you need to give more than one injection for the full dose, choose a different injection site each time you inject.
- Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

If a caregiver is giving the injection, the outer upper arms may also be used.

## Preparing Xolair solution for injection in pre-filled syringe for use

Note: Depending on the dose prescribed to you by your doctor, you may need to prepare one or more pre-filled syringes, and inject the contents of them all. The following table gives examples of how many injections of each dose strength you need for a given dose:

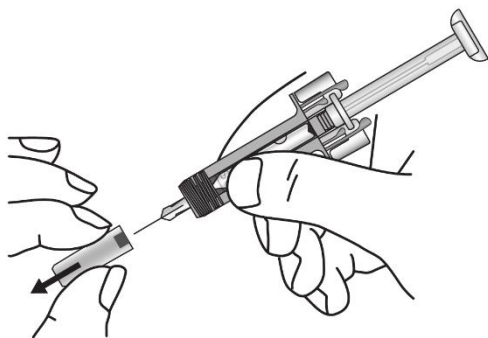
Dose	Syringes needed for the dose	
75 mg	1 blue	
150 mg	1 purple (150 mg)	
225 mg	1 blue (75 mg) + 1 purple (150 mg)	 
300 mg	2 purple (150 mg)	
375 mg	1 blue (75 mg) + 2 purple (150 mg)	 
450 mg	3 purple (150 mg)	
525 mg	1 blue (75 mg) + 3 purple (150 mg)	 
600 mg	4 purple (150 mg)	

1. Take the box containing the syringe out of the refrigerator and leave it **unopened** for about 30 minutes so that it reaches room temperature (leave the syringe in the box to protect it from light).
2. When you are ready to use the syringe, wash your hands thoroughly with soap and water.
3. Clean the injection site with an alcohol swab.
4. Remove the plastic tray from the box and peel back the paper cover. Gripping the middle of the purple syringe guard, lift the syringe out of the tray.
5. Inspect the syringe. The liquid should be clear to slightly cloudy. Its colour may vary from colourless to pale brownish-yellow. You may see an air bubble, which is normal. **DO NOT USE** if the syringe is broken or if the liquid looks distinctly cloudy or distinctly brown, or contains particles. In all these cases, return the entire pack to the pharmacy.
6. Holding the syringe horizontally, look into the viewing window to check the expiry date printed on the label. Note: It is possible to rotate the inner part of the syringe assembly so that the label can be read in the viewing window. **DO NOT USE** if the product has expired. If expired, return the entire pack to the pharmacy.



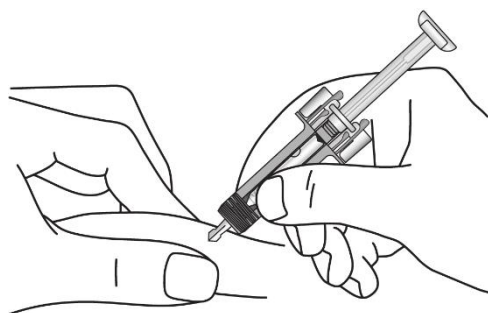
## How to use Xolair solution for injection in pre-filled syringe

1



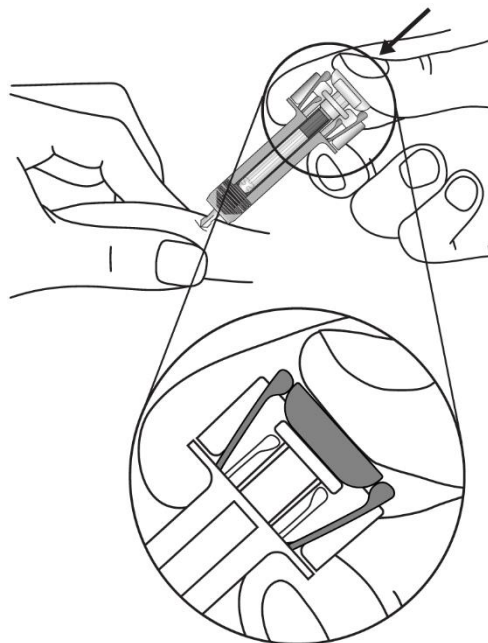
Carefully remove the needle cap from the syringe. Discard the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

2



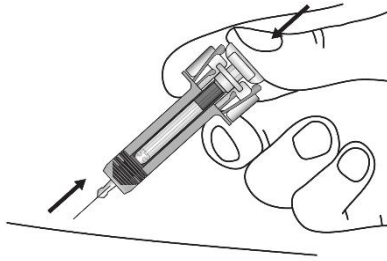
Gently pinch the skin at the injection site and insert the needle as shown. Push the needle all the way in to ensure that the medicine can be fully administered.

3



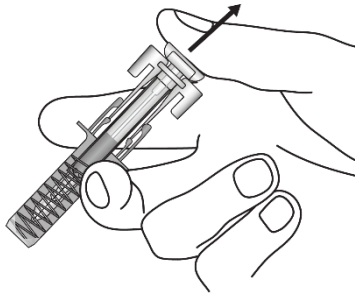
Hold the syringe as shown. **Slowly** depress the plunger **as far as it will go** so that the plunger head is completely between the syringe guard wings.

4



**Keep the plunger fully depressed** while you carefully lift the needle straight out from the injection site.

5



Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle.

There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 30 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

### Disposal instructions



Dispose of the used syringe immediately in a sharps container (closable, puncture resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **Package leaflet: Information for the user**

### **Xolair 150 mg solution for injection in pre-filled syringe** (pre-filled syringe with 27-gauge staked needle, purple plunger) **Xolair 300 mg solution for injection in pre-filled syringe** 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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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
2. What you need to know before you use Xolair
3. How to use Xolair
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

Xolair contains the active substance 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 is used for the treatment of:

- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps
- chronic spontaneous urticaria (CSU)

##### Allergic asthma

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

##### Chronic rhinosinusitis with nasal polyps

This medicine is used to treat chronic rhinosinusitis with nasal polyps in adults (18 years of age and older) who are already receiving intranasal corticosteroids (corticosteroid nasal spray), but whose symptoms are not well controlled by these medicines. Nasal polyps are small growths on the lining of the nose. Xolair helps to reduce the size of the polyps and improves symptoms including nasal congestion, loss of sense of smell, mucus in the back of the throat and runny nose.

##### Chronic spontaneous urticaria (CSU)

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

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE contributes to a type of inflammation that plays a key role in causing allergic asthma, chronic rhinosinusitis with nasal polyps and CSU.

## **2. What you need to know before you use Xolair**

### **Do not use 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 use Xolair.

### **Warnings and precautions**

Talk to your doctor before using 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 are travelling to region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.

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.

### **Look out for signs of allergic reactions and other serious side effects**

Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a severe allergic reaction or other serious side effects. Such signs are listed under “Serious side effects” in section 4.

It is important that you receive training from your doctor in how to recognise early symptoms of severe allergic reactions, and how to manage these reactions if they occur, before you inject Xolair yourself or before a non-healthcare professional gives you a Xolair injection (see section 3, “How to use Xolair”). The majority of severe allergic reactions occur within the first 3 doses of Xolair.

### **Children and adolescents**

#### Allergic asthma

Xolair is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

#### Chronic rhinosinusitis with nasal polyps

Xolair is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age has not been studied.

#### Chronic spontaneous urticaria (CSU)

Xolair is not recommended for children under 12 years of age. Its use in children under 12 years of age 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**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Your doctor will discuss with you the benefits and potential risks of using this medicine during pregnancy.

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

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

### **Driving and using machines**

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

## **3. How to use Xolair**

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure

### **How Xolair is used**

Xolair is used as an injection under your skin (known as a subcutaneous injection).

#### Injecting Xolair

- You and your doctor will decide if you should inject Xolair yourself. The first 3 doses are always given by or under the supervision of a healthcare professional (see section 2).
- It is important to be properly trained on how to inject the medicine before injecting yourself.
- A caregiver (for example a parent) may also give you your Xolair injection after he or she has received proper training.

For detailed instructions on how to inject Xolair, see “Instructions for use of Xolair pre-filled syringe” at the end of this leaflet.

#### Training to recognise serious allergic reactions

It is also important that you do not inject Xolair yourself until you have been trained by your doctor or nurse on:

- how to recognise the early signs and symptoms of serious allergic reactions
- what to do if the symptoms occur.

For more information about the early signs and symptoms of serious allergic reactions, see section 4.

### **How much to use**

#### Allergic asthma and chronic rhinosinusitis with nasal polyps

Your doctor will decide how much Xolair you need and how often you will need 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 need 1 to 4 injections at a time. You will need the injections either every two weeks, or every four weeks.

Keep taking your current asthma and/or nasal polyps medicine during Xolair treatment. Do not stop taking any asthma and/or nasal polyps medicine without talking to your doctor.

You may not see an immediate improvement after beginning Xolair treatment. In patients with nasal polyps effects have been seen 4 weeks after the start of the treatment. In asthma patients it usually takes between 12 and 16 weeks to have the full effect.

#### Chronic spontaneous urticaria (CSU)

You will need two 150 mg injections at a time or one 300 mg injection every four weeks.

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

#### **Use in children and adolescents**

##### Allergic asthma

Xolair can be used in children and adolescents aged 6 years and older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers and 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.

Children (6 to 11 years of age) are not expected to self-administer Xolair. However, if considered appropriate by their doctor, a caregiver may give them their Xolair injection after proper training.

Xolair 300 mg pre-filled syringe is not intended for use in children under 12 years of age. Xolair 75 mg pre-filled syringe and Xolair 150 mg pre-filled syringe or Xolair powder and solvent for solution for injection may be used in children 6-11 years of age with allergic asthma.

##### Chronic rhinosinusitis with nasal polyps

Xolair should not be used in children and adolescents under 18 years of age.

##### Chronic spontaneous urticaria (CSU)

Xolair can be used in adolescents aged 12 years of age and older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines. The dose for adolescents aged 12 years and above is the same as for adults.

#### **If a dose of Xolair is missed**

If you have missed an appointment, contact your doctor or hospital as soon as possible to re-schedule it.

If you have forgotten to give yourself a dose of Xolair, inject the dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

#### **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 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:

Seek medical attention immediately if you notice any signs of the following side effects:

Rare (may affect up to 1 in 1 000 people)

- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

### Other side effects include:

Very common (may affect more than 1 in 10 people)

- fever (in children)

Common (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
- 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)
- feeling dizzy

Uncommon (may affect up to 1 in 100 people)

- feeling 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 (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 after EXP. The expiry date refers to the last day of that month. The carton containing the pre-filled syringe can be stored for a total time of 48 hours at room temperature (25°C) before use.
- 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.
  - One syringe of 2 ml solution contains 300 mg omalizumab.
- The other ingredients are arginine hydrochloride, histidine hydrochloride monohydrate, histidine, Polysorbate 20 and water for injections.

### **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 in pre-filled syringe with 27-gauge staked needle and purple plunger is supplied in packs containing 1 pre-filled syringe, and in multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled syringes.

Xolair 300 mg solution for injection in pre-filled syringe is supplied in packs containing 1 pre-filled syringe, and in multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled syringes.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Novartis Europharm Limited  
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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>

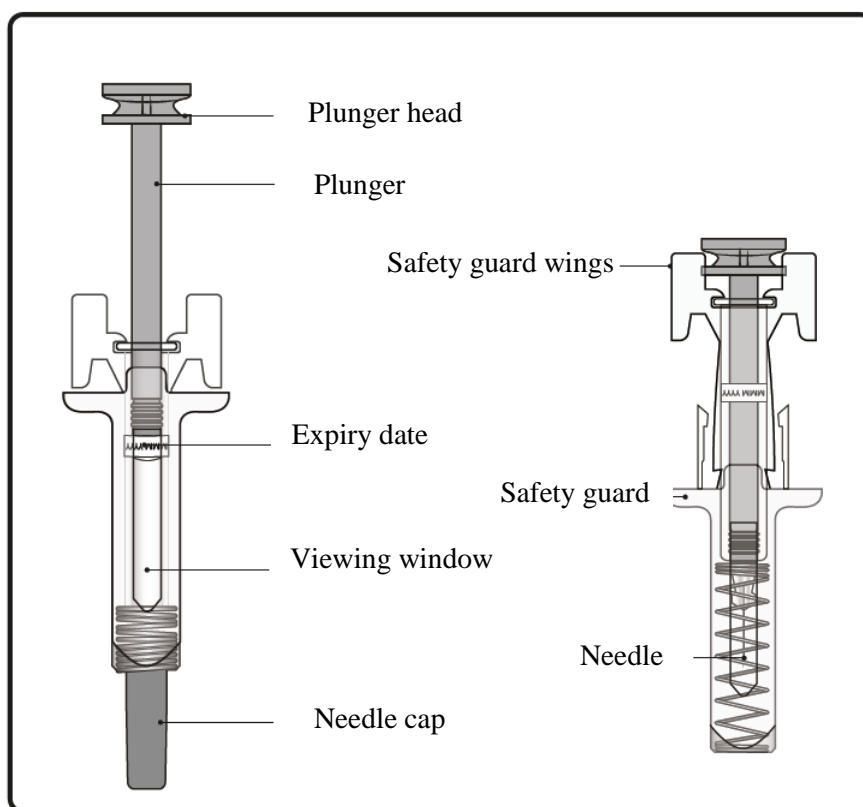
## INSTRUCTIONS FOR USE OF XOLAIR PRE-FILLED SYRINGE

These “Instructions for Use” contain information on how to inject Xolair.

If your doctor decides that you or your caregiver may be able to give your injections of Xolair at home, ensure that your doctor or nurse shows you or your caregiver how to prepare and inject with the Xolair pre-filled syringe before you use it for the first time.

Children below 12 years of age are not expected to inject Xolair themselves, however, if deemed appropriate by their doctor, a caregiver may give them their Xolair injections after proper training.

Be sure that you read and understand these “Instructions for Use” before injecting with the Xolair pre-filled syringe. Talk to your doctor if you have any questions.



### Important information you need to know before injecting Xolair

- Xolair is for subcutaneous injection only (inject directly into fatty layer under the skin).
- **Do not** use the pre-filled syringe if either the seal on the outer carton or the seal of the plastic tray is broken.
- **Do not** use if the pre-filled syringe has been dropped onto a hard surface or dropped after removing the needle cap.
- **Do not** inject if the pre-filled syringe has been kept out of the refrigerator for more than a total of 48 hours. Dispose of it (see Step 12) and use a new pre-filled syringe for your injection.
- The pre-filled syringe has a safety guard that will be activated to cover the needle after the injection is finished. The safety guard will help to prevent needlestick injuries to anyone who handles the pre-filled syringe after injection.
- **Do not** try to re-use or take apart the pre-filled syringe.
- **Do not** pull back on the plunger.


## Store Xolair

- Store in a refrigerator (2°C to 8°C). The carton containing the pre-filled syringe can be stored for a total time of 48 hours at room temperature (25°C) before use.
- **Do not** freeze.
- Keep the pre-filled syringe in the original carton until ready to use in order to protect from light.
- Keep the pre-filled syringe out of sight and reach of children.

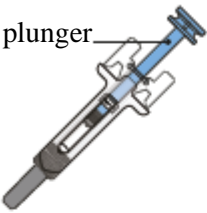

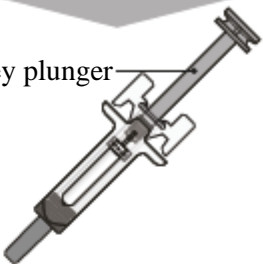






























## DOSING TABLE

Xolair pre-filled syringes are available in 3 dose strengths (one pre-filled syringe in each carton). These instructions are to be used for all 3 dose strengths.

Depending on the dose prescribed to you by your doctor, you may need to select one or more pre-filled syringes, and inject the contents of them all in order to deliver your full dose. The Dosing Table below shows the combination of pre-filled syringes needed to deliver your full dose.

	<b>Important:</b> If the dose is for a child under age 12 it is recommended to use only blue (75 mg) and purple (150 mg) pre-filled syringes. Refer to the Dosing Table below for the recommended combination of pre-filled syringes for children under age 12.
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Contact your doctor if you have questions on the Dosing Table.

Xolair 75 mg pre-filled syringe with a blue plunger		Xolair 150 mg pre-filled syringe with a purple plunger		Xolair 300 mg pre-filled syringe with a grey plunger	
Blue plunger 		Purple plunger 		Grey plunger 	
DOSE	Pre-filled syringes needed for dose	Blue 75 mg	Purple 150 mg	Grey 300 mg	
75 mg	1 blue				
150 mg	1 purple				
225 mg	1 blue + 1 purple				
300 mg (ages 12 and up)	1 grey				
300 mg (children under age 12)	2 purple		 		
375 mg (ages 12 and up)	1 blue + 1 grey				
375 mg (children under age 12)	1 blue + 2 purple		 		
450 mg (ages 12 and up)	1 purple + 1 grey				
450 mg (children under age 12)	3 purple		  		
525 mg (ages 12 and up)	1 blue + 1 purple + 1 grey				
525 mg (children under age 12)	1 blue + 3 purple		  		
600 mg (ages 12 and up)	2 grey			 	
600 mg (children under age 12)	4 purple		   		

## Prepare to inject Xolair

### Step 1. Bring to room temperature

Take the carton containing the pre-filled syringe out of the refrigerator **and leave it unopened so that it reaches room temperature (minimum 30 minutes)**.

Note: If you need more than one pre-filled syringe (one pre-filled syringe per carton) to deliver your full dose (see Dosing Table), take all the cartons out of the refrigerator at the same time.

### Step 2. Gather supplies

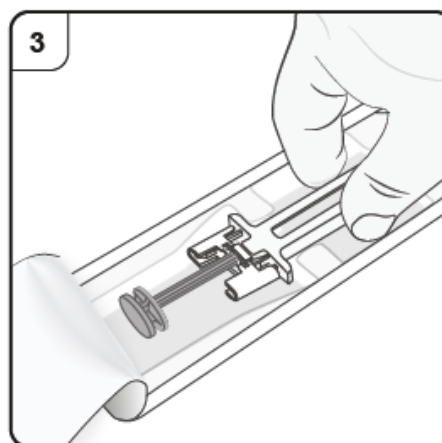
You will need the following supplies (not included in the carton):

- Alcohol wipe
- Cotton ball or gauze pad
- Sharps disposal container
- Adhesive plaster

### Step 3. Unpack

Open the plastic tray by peeling away the cover. Remove the pre-filled syringe by holding it in the middle as shown.

**Do not** remove the needle cap until you are ready to inject.



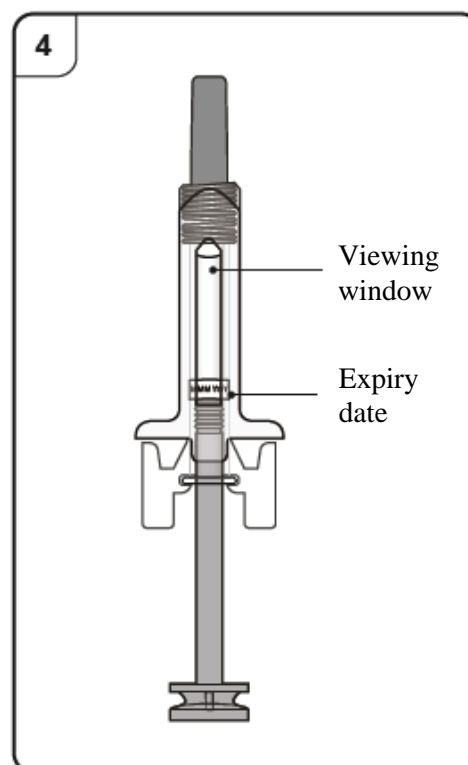
#### Step 4. Inspect the pre-filled syringe

Look through the viewing window of the pre-filled syringe. The liquid inside should be clear to slightly cloudy. Its colour may vary from colourless to pale brownish-yellow. You may see air bubbles in the liquid, which is normal.

**Do not** try to remove the air.

- **Do not** use the pre-filled syringe if the liquid contains particles, or if the liquid looks distinctly cloudy or distinctly brown.
- **Do not** use the pre-filled syringe if it looks damaged or if it has leaked.
- **Do not** use the pre-filled syringe after the expiry date (EXP), which is printed on the pre-filled syringe label and carton.

In all of these cases, contact your doctor, nurse or pharmacist.

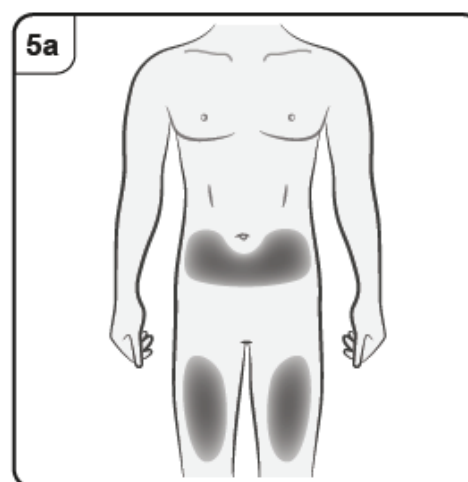


#### Step 5. Choose injection site

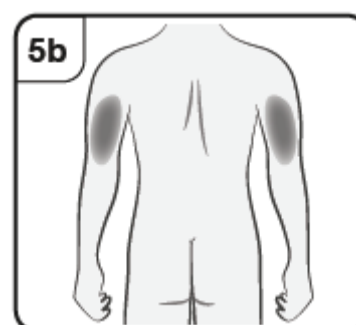
You should inject into the front of the thighs or the lower stomach area but not the area 5 cm around the belly button.

**Do not** inject into skin that is tender, bruised, red, scaly or hard or into areas with scars or stretch marks.

Note: If you need more than one pre-filled syringe to deliver your full dose, make sure your injections are at least 2 cm apart.



If your caregiver, doctor or nurse is giving you the injection, they may also inject into the outer upper arm.



## Inject with Xolair

### Step 6. Clean injection site

Clean your hands.

Clean the chosen injection site with an alcohol wipe. Leave it to dry before injecting.

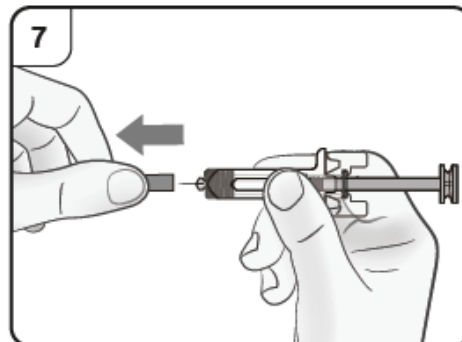
**Do not** touch or blow on the cleaned skin before injecting.

### Step 7. Remove needle cap

Firmly pull straight to remove the needle cap from the pre-filled syringe. You may see a drop of liquid at the end of the needle. This is normal.

**Do not** put the needle cap back on.

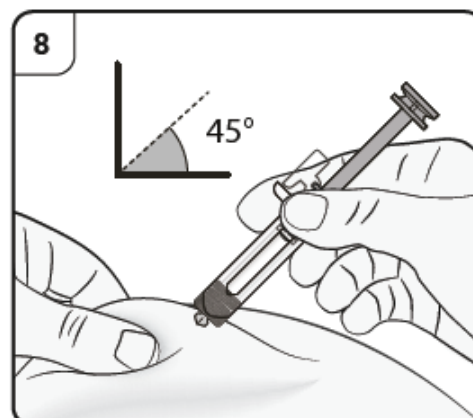
Throw away the needle cap.



### Step 8. Insert needle

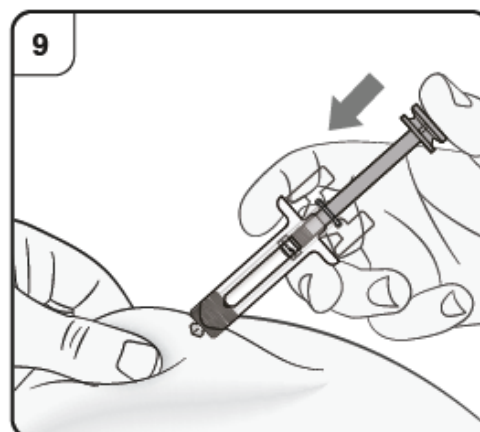
Gently pinch the skin at the injection site and hold the pinch throughout the injection. With the other hand insert the needle into the skin at an angle of approximately 45 degrees as shown.

**Do not** press the plunger while inserting the needle.



### Step 9. Start injection

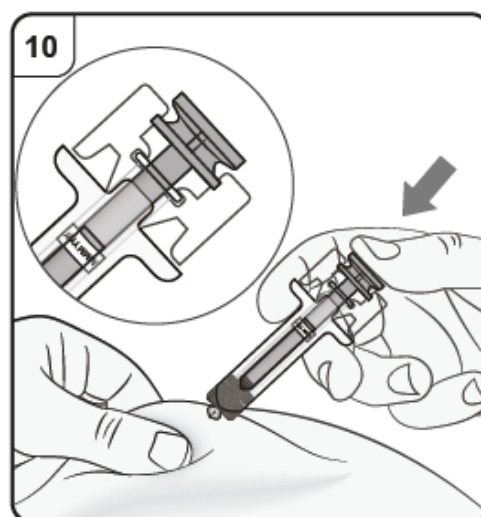
Continue to pinch the skin. Slowly press the plunger **as far as it will go**. This will ensure that a full dose is injected.





### Step 10. Complete injection

Confirm that the plunger head is between the safety guard wings as shown. This will ensure that the safety guard has been activated and will cover the needle after the injection is finished.



### Step 11. Release plunger

Keeping the pre-filled syringe at the injection site, slowly release the plunger until the needle is automatically covered by the safety guard. Remove the pre-filled syringe from the injection site and release the pinch.

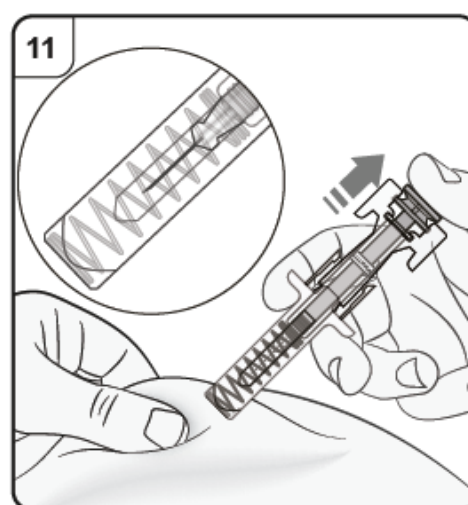
There may be a small amount of blood at the injection site. You can press a cotton ball or gauze pad over the injection site until any bleeding stops. **Do not** rub the injection site. If needed, cover the injection site with a small adhesive plaster.

Note: If you need more than one pre-filled syringe to deliver your full dose, throw away the used pre-filled syringe as described in Step 12.

Repeat Step 2 to Step 12 again for all the pre-filled syringes needed to deliver your full dose.

Carry out the injections immediately one after another.

Make sure the injections are at least 2 cm apart.



## **After the injection**

### **Step 12. Dispose of the pre-filled syringe**

Put the used pre-filled syringe in a sharps disposal container (i.e. a puncture-resistant closable container, or similar) immediately after use.

**Do not** try to put the needle cap back onto the syringe.

Talk to your doctor or pharmacist about proper disposal of the sharps disposal container. There may be local regulations for disposal.

## **Package leaflet: Information for the user**

### **Xolair 150 mg solution for injection in pre-filled pen**

### **Xolair 300 mg solution for injection in pre-filled pen**

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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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
2. What you need to know before you use Xolair
3. How to use Xolair
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

### **1. What Xolair is and what it is used for**

Xolair contains the active substance 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 is used for the treatment of:

- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps
- chronic spontaneous urticaria (CSU)

#### Allergic asthma

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

#### Chronic rhinosinusitis with nasal polyps

This medicine is used to treat chronic rhinosinusitis with nasal polyps in adults (18 years of age and older) who are already receiving intranasal corticosteroids (corticosteroid nasal spray), but whose symptoms are not well controlled by these medicines. Nasal polyps are small growths on the lining of the nose. Xolair helps to reduce the size of the polyps and improves symptoms including nasal congestion, loss of sense of smell, mucus in the back of the throat and runny nose.

#### Chronic spontaneous urticaria (CSU)

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

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE contributes to a type of inflammation that plays a key role in causing allergic asthma, chronic rhinosinusitis with nasal polyps and CSU.

## **2. What you need to know before you use Xolair**

### **Do not use 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 use Xolair.

### **Warnings and precautions**

Talk to your doctor before using 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 are travelling to region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.

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.

### **Look out for signs of allergic reactions and other serious side effects**

Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a severe allergic reaction or other serious side effects. Such signs are listed under “Serious side effects” in section 4.

It is important that you receive training from your doctor in how to recognise early symptoms of severe allergic reactions, and how to manage these reactions if they occur, before you inject Xolair yourself or before a non-healthcare professional gives you a Xolair injection (see section 3, “How to use Xolair”). The majority of severe allergic reactions occur within the first 3 doses of Xolair.

### **Children and adolescents**

#### Allergic asthma

Xolair is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

#### Chronic rhinosinusitis with nasal polyps

Xolair is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age has not been studied.

#### Chronic spontaneous urticaria (CSU)

Xolair is not recommended for children under 12 years of age. Its use in children under 12 years of age 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**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Your doctor will discuss with you the benefits and potential risks of using this medicine during pregnancy.

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

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

### **Driving and using machines**

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

## **3. How to use Xolair**

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure

### **How Xolair is used**

Xolair is used as an injection under your skin (known as a subcutaneous injection).

#### Injecting Xolair

- You and your doctor will decide if you should inject Xolair yourself. The first 3 doses are always given by or under the supervision of a healthcare professional (see section 2).
- It is important to be properly trained on how to inject the medicine before injecting yourself.
- A caregiver (for example a parent) may also give you your Xolair injection after he or she has received proper training.

For detailed instructions on how to inject Xolair, see “Instructions for use of Xolair pre-filled pen” at the end of this leaflet.

#### Training to recognise serious allergic reactions

It is also important that you do not inject Xolair yourself until you have been trained by your doctor or nurse on:

- how to recognise the early signs and symptoms of serious allergic reactions
- what to do if the symptoms occur.

For more information about the early signs and symptoms of serious allergic reactions, see section 4.

### **How much to use**

#### Allergic asthma and chronic rhinosinusitis with nasal polyps

Your doctor will decide how much Xolair you need and how often you will need 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 need 1 to 3 injections at a time. You will need the injections either every two weeks, or every four weeks.

Keep taking your current asthma and/or nasal polyps medicine during Xolair treatment. Do not stop taking any asthma and/or nasal polyps medicine without talking to your doctor.

You may not see an immediate improvement after beginning Xolair treatment. In patients with nasal polyps effects have been seen 4 weeks after the start of the treatment. In asthma patients it usually takes between 12 and 16 weeks to have the full effect.

#### Chronic spontaneous urticaria (CSU)

You will need two 150 mg injections at a time or one 300 mg injection every four weeks.

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

#### **Use in children and adolescents**

##### Allergic asthma

Xolair can be used in children and adolescents aged 6 years and older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers and 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.

Children (6 to 11 years of age) are not expected to self-administer Xolair. However, if considered appropriate by their doctor, a caregiver may give them their Xolair injection after proper training.

Xolair pre-filled pens are not intended for use in children under 12 years of age. Xolair 75 mg pre-filled syringe and Xolair 150 mg pre-filled syringe or Xolair powder and solvent for solution for injection may be used in children 6-11 years of age with allergic asthma.

##### Chronic rhinosinusitis with nasal polyps

Xolair should not be used in children and adolescents under 18 years of age.

##### Chronic spontaneous urticaria (CSU)

Xolair can be used in adolescents aged 12 years of age and older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines. The dose for adolescents aged 12 years and above is the same as for adults.

#### **If a dose of Xolair is missed**

If you have missed an appointment, contact your doctor or hospital as soon as possible to re-schedule it.

If you have forgotten to give yourself a dose of Xolair, inject the dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

#### **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 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:

Seek medical attention immediately if you notice any signs of the following side effects:

Rare (may affect up to 1 in 1 000 people)

- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

### Other side effects include:

Very common (may affect more than 1 in 10 people)

- fever (in children)

Common (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
- 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)
- feeling dizzy

Uncommon (may affect up to 1 in 100 people)

- feeling 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 (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 after EXP. The expiry date refers to the last day of that month. The carton containing the pre-filled pen can be stored for a total time of 48 hours at room temperature (25°C) before use.
- 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 pen of 1 ml solution contains 150 mg omalizumab.
  - One pen of 2 ml solution contains 300 mg omalizumab.
- The other ingredients are arginine hydrochloride, histidine hydrochloride monohydrate, histidine, Polysorbate 20 and water for injections.

### **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 pen.

Xolair 150 mg solution for injection in pre-filled pen is supplied in packs containing 1 pre-filled pen, and in multipacks containing 3 (3 x 1), 6 (6 x 1) or 10 (10 x 1) pre-filled pens.

Xolair 300 mg solution for injection in pre-filled pen is supplied in packs containing 1 pre-filled pen, and in multipacks containing 3 (3 x 1) or 6 (6 x 1) pre-filled pens.

Not all pack sizes may be marketed.

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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>

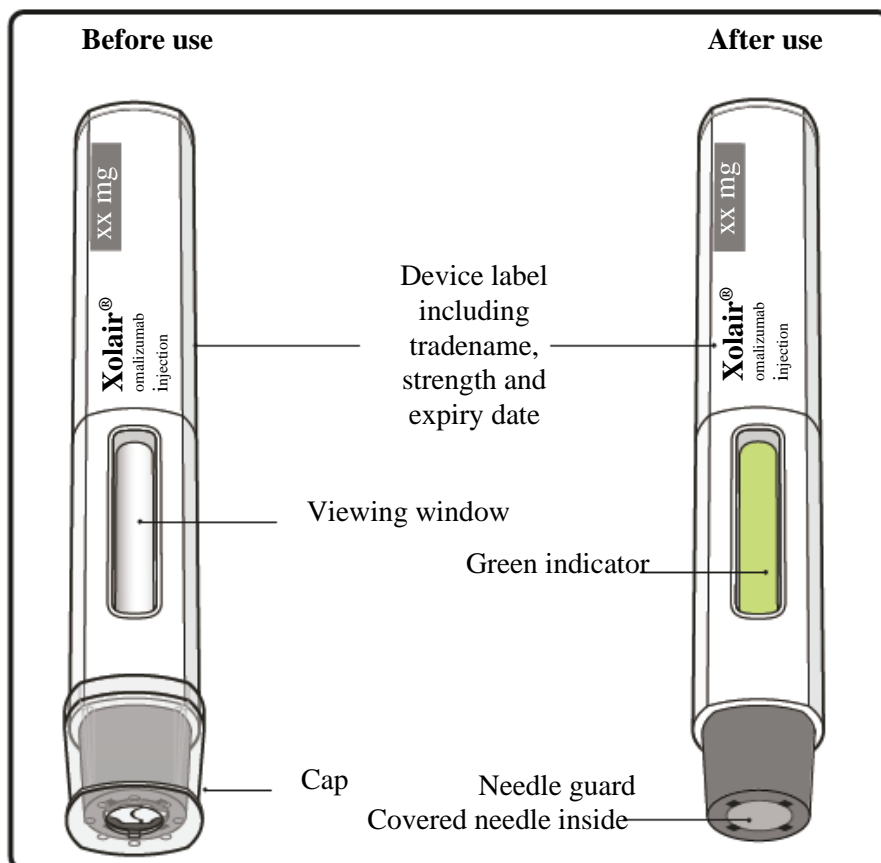
## INSTRUCTIONS FOR USE OF XOLAIR PRE-FILLED PEN

These “Instructions for Use” contain information on how to inject Xolair.

If your doctor decides that you or your caregiver may be able to give your injections of Xolair at home, ensure that your doctor or nurse shows you or your caregiver how to prepare and inject with the Xolair pen before you use it for the first time.

This Xolair pen is intended to be used for patients ages 12 and up.

Be sure that you read and understand these “Instructions for Use” before injecting with the Xolair pen. Talk to your doctor if you have any questions.



### Important information you need to know before injecting Xolair

- Xolair is for subcutaneous injection only (inject directly into fatty layer under the skin).
- **Do not** use the pen if the seal on the outer carton is broken.
- **Do not** use if the pen has been dropped after removing the cap.
- **Do not** inject if the pen has been kept out of the refrigerator for more than a total of 48 hours. Dispose of it (see Step 13) and use a new pen for your injection.
- **Do not** touch or push the needle guard as you could get injured. Touching or pushing on the needle guard could cause a needlestick injury.
- **Do not** try to re-use or take apart the pen.
- **Do not** try to reattach the cap once it has been taken off.

### Store Xolair

- Store in a refrigerator (2°C - 8°C). The carton containing the pen can be stored for a total time of 48 hours at room temperature (25°C) before use.

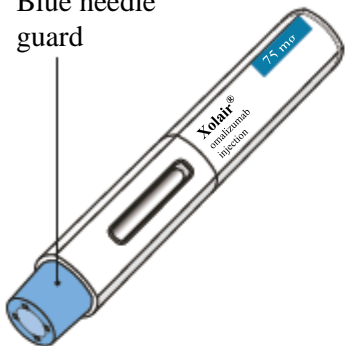
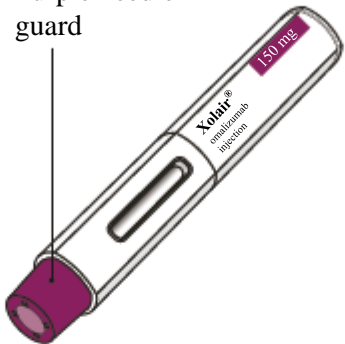
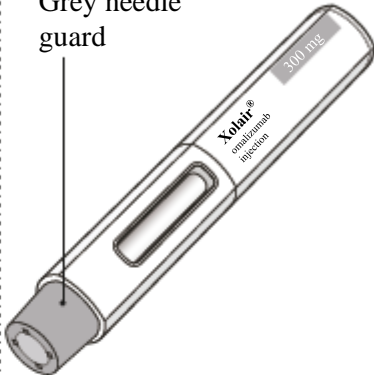













- **Do not** freeze.
- Keep the pen in the original carton until ready to use in order to protect from light.
- Keep the pen out of sight and reach of children.

## **DOSING TABLE**

Xolair pens are available in 3 dose strengths (one pen in each carton). These instructions are to be used for all 3 dose strengths.

Depending on the dose prescribed to you by your doctor, you may need to select one or more pens, and inject the contents of them all in order to deliver your full dose. The Dosing Table below shows the combination of pens needed to deliver your full dose.

Contact your doctor if you have questions on the Dosing Table.

Xolair 75 mg pen with a blue needle guard		Xolair 150 mg pen with a purple needle guard		Xolair 300 mg pen with a grey needle guard	
<p>Blue needle guard</p> 		<p>Purple needle guard</p> 		<p>Grey needle guard</p> 	
Dose	Number of pens needed for the dose	Blue 75 mg	Purple 150 mg	Grey 300 mg	
75 mg	1 blue				
150 mg	1 purple				
225 mg	1 blue + 1 purple				
300 mg	1 grey				
375 mg	1 blue + 1 grey				
450 mg	1 purple + 1 grey				
525 mg	1 blue + 1 purple + 1 grey				
600 mg	1 grey + 1 grey				

## Prepare to inject Xolair

### Step 1. Bring to room temperature

Take the carton containing the pen out of the refrigerator **and leave it unopened so that it reaches room temperature (minimum 30 minutes)**.

Note: If you need more than one pen (one pen in each carton) to deliver your full dose (see Dosing Table), take all the cartons out of the refrigerator at the same time.

### Step 2. Gather supplies

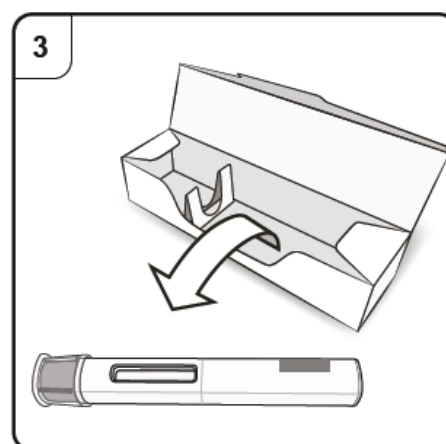
You will need the following supplies (not included in the carton):

- Alcohol wipe
- Cotton ball or gauze pad
- Sharps disposal container
- Adhesive plaster

### Step 3. Unpack

Take the pen out of the outer carton.

**Do not** remove the cap until you are ready to inject.

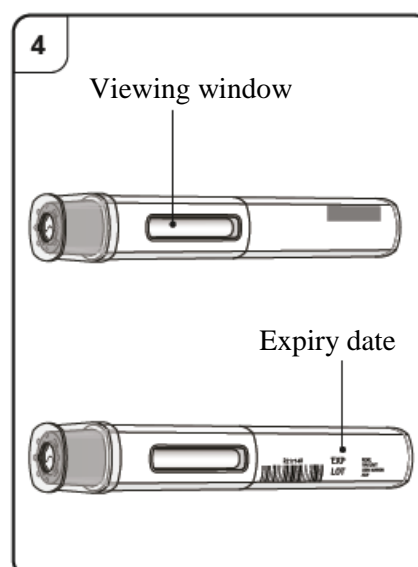


### Step 4. Inspect the pen

Look through the viewing window of the pen. The liquid inside should be clear to slightly cloudy. Its colour may vary from colourless to pale brownish-yellow. You may see air bubbles in the liquid, which is normal.

- **Do not** use the pen if the liquid contains particles, or if the liquid looks distinctly cloudy or distinctly brown.
- **Do not** use the pen if it looks damaged.
- **Do not** use the pen after the expiry date (EXP), which is printed on the pen label and carton.

In all of these cases, contact your doctor, nurse or pharmacist.

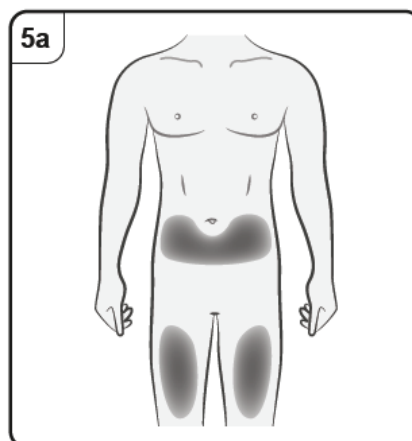


### Step 5. Choose injection site

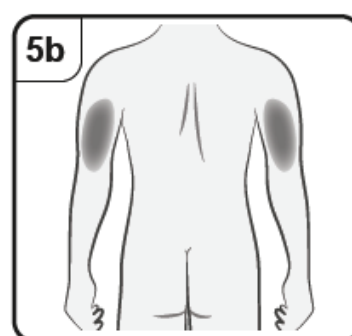
You should inject into the front of the thighs or the lower stomach area but not the area 5 cm around the belly button.

**Do not** inject into skin that is tender, bruised, red, scaly or hard or into areas with scars or stretch marks.

Note: If you need more than one pen to deliver your full dose, make sure your injections are at least 2 cm apart.



If a caregiver, doctor or nurse is giving the injection, they may also inject into the outer upper arm.



## Inject with Xolair

### Step 6. Clean injection site

Clean your hands.

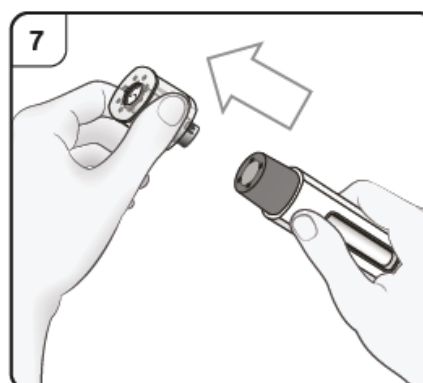
Clean the chosen injection site with an alcohol wipe. Leave it to dry before injecting.

**Do not** touch or blow on the cleaned skin before injecting.

### Step 7. Remove cap

Pull the cap straight off in the direction of the arrow.

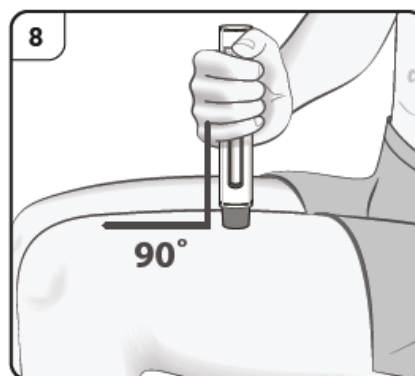
**Do not** put the cap back on. Throw away the cap.



### Step 8. Position the pen

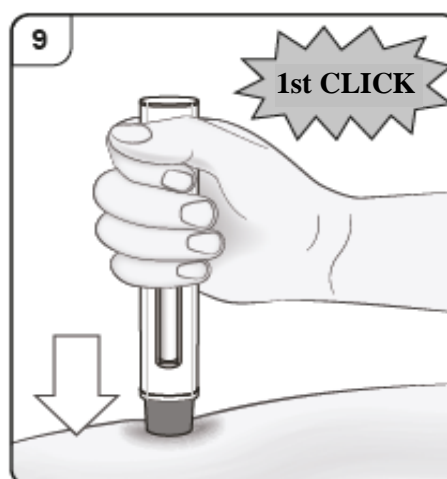
Hold the pen comfortably **with the needle guard directly against the skin**.

The pen should be at a 90° angle to the skin as shown.



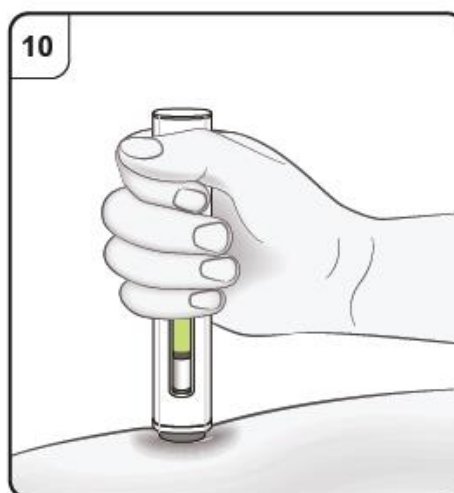
### Step 9. Start injection

Push and hold the pen firmly against the skin. Listen for the **1st click** which indicates that the injection has started.



### Step 10. Monitor injection

Keep holding the pen firmly down against the skin. The green indicator shows the progress of the injection.

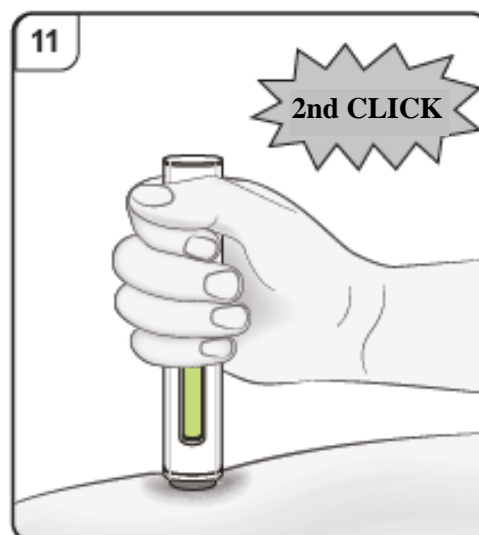




### Step 11. Complete injection

Listen for the **2nd click**. This indicates the injection is **almost** complete.

**Keep holding the pen in position until the green indicator has stopped moving to make sure the injection is complete.** Remove the pen from the skin. The needle is automatically covered by the needle guard. The injection is now complete.



### After the injection

#### Step 12. Check green indicator

If the green indicator has not completely filled the viewing window, contact your doctor or nurse.

There may be a small amount of blood at the injection site.

You can press a cotton ball or gauze pad over the injection site until any bleeding stops.

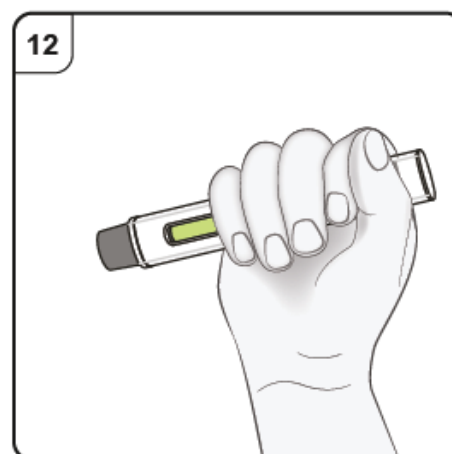
**Do not** rub the injection site. If needed, cover your injection site with a small adhesive plaster.

Note: If you need more than one pen to deliver your full dose, throw away the used pen as described in Step 13.

Repeat Step 2 to Step 13 again for all the pens needed to deliver your full dose.

Carry out the injections immediately one after another.

Make sure the injections are at least 2 cm apart.



**Step 13. Dispose of the pen**

Put the used pen in a sharps disposal container (i.e. a puncture-resistant closable container, or similar) right away after use.

Talk to your doctor or pharmacist about proper disposal of the sharps disposal container. There may be local regulations for disposal.

## **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
2. What you need to know before you are given Xolair
3. How Xolair is given
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

Xolair contains the active substance 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 is used for the treatment of:

- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps

##### Allergic asthma

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

##### Chronic rhinosinusitis with nasal polyps

This medicine is used to treat chronic rhinosinusitis with nasal polyps in adults (18 years of age and older) who are already receiving intranasal corticosteroids (corticosteroid nasal spray), but whose symptoms are not well controlled by these medicines. Nasal polyps are small growths on the lining of the nose. Xolair helps to reduce the size of the polyps and improves symptoms including nasal congestion, loss of sense of smell, mucus in the back of the throat and runny nose.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE contributes to a type of inflammation that plays a key role in causing allergic asthma and chronic rhinosinusitis with nasal polyps.

#### **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**

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 are travelling to a region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis) for example resulting from a medicine, an insect bite or food.

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.

## **Look out for signs of allergic reactions and other serious side effects**

Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a possible serious side effect. Such signs are listed under “Serious side effects” in section 4. The majority of severe allergic reactions occur within the first 3 doses of Xolair.

## **Children and adolescents**

### Allergic asthma

Xolair is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

### Chronic rhinosinusitis with nasal polyps

Xolair is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age 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**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. 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.

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

## **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**

Your doctor will decide 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.

Keep taking your current asthma and/or nasal polyps medicine during Xolair treatment. Do not stop taking any asthma and/or nasal polyps medicine without talking to your doctor.

You may not see an immediate improvement after beginning Xolair therapy. In patients with nasal polyps effects have been seen 4 weeks after the start of the treatment. In asthma patients it usually takes between 12 and 16 weeks to have the full effect.

#### **Use in children and adolescents**

##### Allergic asthma

Xolair can be given to children and adolescents aged 6 years and older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers and 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 rhinosinusitis with nasal polyps

Xolair should not be given to children and adolescents under 18 years of age.

#### **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 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.

#### Serious side effects:

Seek medical attention immediately if you notice any signs of the following side effects:

Rare (may affect up to 1 in 1 000 people)

- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

Other side effects include:

Very common (may affect more than 1 in 10 people)

- fever (in children)

Common (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
- headache (very common in children)
- feeling dizzy
- pain in joints (arthralgia)

Uncommon (may affect up to 1 in 100 people)

- feeling 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 (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 after EXP. 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, histidine, 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, the lower abdomen (but not the area 5 centimetres around the navel) 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
2. What you need to know before you are given Xolair
3. How Xolair is given
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

Xolair contains the active substance 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 is used for the treatment of:

- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps
- chronic spontaneous urticaria (CSU)

##### Allergic asthma

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

##### Chronic rhinosinusitis with nasal polyps

This medicine is used to treat chronic rhinosinusitis with nasal polyps in adults (18 years of age and older) who are already receiving intranasal corticosteroids (corticosteroid nasal spray), but whose symptoms are not well controlled by these medicines. Nasal polyps are small growths on the lining of the nose. Xolair helps to reduce the size of the polyps and improves symptoms including nasal congestion, loss of sense of smell, mucus in the back of the throat and runny nose.

##### Chronic spontaneous urticaria (CSU)

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

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE contributes to a type of inflammation that plays a key role in causing allergic asthma, chronic rhinosinusitis with nasal polyps and CSU.

## **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**

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 are travelling to a region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis) for example resulting from a medicine, an insect bite or food.

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.

### **Look out for signs of allergic reactions and other serious side effects**

Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a possible serious side effect. Such signs are listed under “Serious side effects” in section 4. The majority of severe allergic reactions occur within the first 3 doses of Xolair.

### **Children and adolescents**

#### Allergic asthma

Xolair is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

#### Chronic rhinosinusitis with nasal polyps

Xolair is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age has not been studied.

#### Chronic spontaneous urticaria (CSU)

Xolair is not recommended for children under 12 years of age. Its use in children under 12 years of age 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**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. 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.

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

**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 and chronic rhinosinusitis with nasal polyps

Your doctor will decide 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.

Keep taking your current asthma and/or nasal polyps medicine during Xolair treatment. Do not stop taking any asthma and/or nasal polyps medicine without talking to your doctor.

You may not see an immediate improvement after beginning Xolair therapy. In patients with nasal polyps effects have been seen 4 weeks after the start of the treatment. In asthma patients 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.

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

**Use in children and adolescents**Allergic asthma

Xolair can be given to children and adolescents aged 6 years and older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers and 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 rhinosinusitis with nasal polyps

Xolair should not be given to children and adolescents under 18 years of age.

### Chronic spontaneous urticaria (CSU)

Xolair can be given to adolescents aged 12 years and older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines. The dose for adolescents aged 12 years and above is the same as for adults.

### **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 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:

Seek medical attention immediately if you notice any signs of the following side effects:

Rare (may affect up to 1 in 1 000 people)

- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

### Other side effects include:

Very common (may affect more than 1 in 10 people)

- fever (in children)

Common (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
- 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)
- feeling dizzy

Uncommon (may affect up to 1 in 100 people)

- feeling, 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 (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 after EXP. 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, histidine, 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 1 vial of powder and 1 ampoule of water for injections, and in multipacks containing 4 (4 x 1) vials of powder and 4 (4 x 1) ampoules of water for injections or 10 (10 x 1) vials of powder and 10 (10 x 1) ampoules of water for injections.

Not all pack sizes may be marketed.

Xolair is also available in vials with 75 mg omalizumab.

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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:

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, the lower abdomen (but not the area 5 centimetres around the navel) or the thigh.