

## 1. NAME OF THE MEDICINAL PRODUCT

XOLAIR® 150 mg powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (reconstituted) contains 150mg of omalizumab whereas one vial (before reconstitution) contains 202.5mg of omalizumab. Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line. After reconstitution the vial contains 125 mg/ml of omalizumab (150 mg in 1.2 ml).

For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: white to off-white lyophilizate in a glass vial.

Solvent: clear and colorless solution in a glass ampoule

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Allergic Asthma

Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) 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. Xolair treatment should only be considered for patients with convincing IgE mediated asthma (see section 4.2).

#### 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

#### Dosage regimen for Allergic Asthma

##### Use in adolescents and adults (12 years of age and older)

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

The appropriate dose and dosing frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements 75–600 mg of Xolair in 1 to 4 injections may be needed for each administration.

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that patients with IgE below 76 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 dosing table should not be given Xolair.

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

Method of administration

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

Doses of more than 150 mg should be divided across two or more injection sites.

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

There is limited experience with self-administration of Xolair powder and solvent for solution for injection. Therefore treatment with this formulation is intended to be administered by a healthcare professional only.

Full information for use are provided in section 6.6.

**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
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. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 weeks**

Baseline IgE (IU/mL)	Body weight (kg)									
	≥20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30–100	75	75	75	150	150	150	150	150	300	300
>100–200	150	150	150	300	300	300	300	300	450	600
>200–300	150	150	225	300	300	450	450	450	600	
>300–400	225	225	300	450	450	450	600	600		
>400–500	225	300	450	450	600	600				
>500–600	300	300	450	600	600	ADMINISTRATION EVERY 2 WEEKS				
>600–700	300		450	600		SEE TABLE 3				

**Table 3: ADMINISTRATION EVERY 2 WEEKS. Xolair 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 ABOVE									
> 200-300										375
> 300-400									450	525
> 400-500							375	375	525	600
> 500-600						375	450	450	600	
> 600-700		225			375	450	450	525		
> 700-800	225	225	300	375	450	450	525	600		
> 800-900	225	225	300	375	450	525	600			
> 900-1000	225	300	375	450	525	600				
> 1000-1100	225	300	375	450	600	Insufficient data to Recommend a Dose				
> 1100-1200	300	300	450	525	600					
> 1200-1300	300	375	450	525						
> 1300-1500	300	375	525	600						

Treatment duration, monitoring and dose adjustments

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

At 16 weeks after commencing Xolair therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue Xolair should be based on whether a marked improvement in overall asthma control is seen (see section 5.1; Physician’s overall assessment of treatment effectiveness).

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

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

**Dosage regimen for Chronic Spontaneous Urticaria (CSU)**

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

Prescribers are advised to periodically reassess the need for continued therapy. Clinical trial experience of long-term treatment beyond 6 months in this indication is limited.

**Special populations**

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 IgG clearance process, including degradation in the reticular endothelial system (RES) it is unlikely to be altered by renal or hepatic impairment. While no particular dose adjustment is recommended, Xolair should be administered with caution in these patients (see section 4.4).

#### Geriatric patients (65 years or above)

There are limited data available on the use of Xolair in patients 65 years and older but there is no evidence that elderly patients require a different dosage from younger adult patients.

#### Children (age below 12 years)

Safety and efficacy in pediatric patients below the age of 12 years have not been established and use of Xolair in such patients is therefore not recommended.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

### **4.4 Special warnings and special precautions for use**

#### General

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

Xolair has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment. Caution should be exercised when administering Xolair in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of Xolair therapy is not recommended. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

#### Immune system disorders

- Allergic reactions

As with any protein, local or systemic allergic reactions, including anaphylaxis, may occur when taking omalizumab. Therefore medications for the treatment of anaphylactic reactions should be available for immediate use following administration of Xolair. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. Anaphylactic reactions were rare in clinical trials (see section 4.8). In post-marketing experience, anaphylaxis and anaphylactoid reactions have been reported following the first or subsequent administrations of Xolair. Most of these reactions occurred within 2 hours.

As with all recombinant DNA derived humanised monoclonal antibodies, patients may in rare cases develop antibodies to omalizumab.

- Serum sickness

Serum sickness and serum-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanized-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 to 5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgia, rash (urticarial 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.

#### Malignancies

For further information please see section 4.8.

#### Arterial Thromboembolic Events (ATE)

For further information please see section 4.8.

#### 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 asthma 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 the recommended anti-helminth treatment, discontinuation of Xolair should be considered.

### **4.5 Interaction with other medicinal products and other forms of interaction**

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

#### **Allergic Asthma**

In clinical studies Xolair was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used asthma medications. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitization therapy). Efficacy of Xolair treatment in combination with specific immunotherapy has not been established.

#### **Chronic Spontaneous Urticaria (CSU)**

In clinical studies in CSU Xolair was used in conjunction with antihistamines (anti-H1, anti-H2) and leukotriene receptor antagonists (LTRAs). There was no evidence that the safety of omalizumab was altered when used with these medicinal products relative to its known safety profile in allergic asthma. In

addition, a population pharmacokinetic analysis showed no relevant effect of H2 antihistamines and LTRAs on omalizumab pharmacokinetics (see Section 5).

#### **4.6 Pregnancy, lactation, females and males of reproductive potential**

##### Pregnancy

##### Risk Summary

There are no well controlled clinical studies of Xolair in pregnant women. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to Xolair showed the prevalence of major congenital anomalies was similar (8.1% vs 8.9%) between EXPECT and disease matched (moderate and severe asthma) patients. This study cannot definitively establish the absence of any risk, however, because of methodological limitations, including a nonrandomized study design and potential differences between the registry population and the comparator group (see Human Data). IgG molecules are known to cross the placental barrier. Clinical considerations

Disease-associated maternal and/or embryo/fetal risk:

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

##### Data

##### Human data

A prospective pregnancy registry study (EXPECT) conducted in the US from 2006 to 2018, included 250 pregnant women with asthma treated with Xolair. 246 of the women were exposed to Xolair in the first trimester of pregnancy, and 78.4% (196/250) of the women were exposed to Xolair at least once during all 3 trimesters of pregnancy with an overall median exposure duration of 8.7 months. The EXPECT findings for relevant mother and infant subgroups were compared to age-adjusted frequencies in a disease matched external cohort of 1,153 pregnant women with asthma (without exposure to Xolair) identified from healthcare databases of residents in the Canadian province of Quebec, and termed the Quebec External Comparator Cohort (QECC).

Among EXPECT infants used for comparison to QECC (n=223), the prevalence of major congenital anomalies (8.1%) was similar to that for QECC infants (8.9%). Among EXPECT pregnancies used for comparison to QECC (n=230), 99.1% led to live births, similar to 99.3% for QECC pregnancies.

A sub-study in EXPECT examined platelet levels in 51 infants born to Xolair exposed women, all of them were in the normal range.

##### Animal data

Doses of omalizumab in excess of the clinical dose have been associated with age-dependent decreases in blood platelets in nonhuman primates, with a greater relative sensitivity in juvenile animals (see section 5.3).

##### Lactation

##### Risk summary

While omalizumab presence in human milk after administration of Xolair has not been studied, IgGs are present in human milk and therefore it is expected that omalizumab will be present in human milk. The frequency of infant infections identified in EXPECT was evaluated as an indirect measure of immune system development after exposure during pregnancy or through breast-feeding. The majority of infants in the

primary analytic population (77.5%, 186/240) were breastfed. Serious adverse events (SAEs) categorized as “infections and infestations” were observed in 11.4% (5/44) of infants who were not breastfed, 10.4% (16/154) of infants who were exposed to Xolair through breast-feeding, and 12.5% (4/32) of infants who were breast-fed without exposure to Xolair through breast-feeding. The study has methodological limitations, including a nonrandomized study design.

The developmental and health benefits of breast-feeding should be considered along with the mother’s clinical need for Xolair and any potential adverse effects on the breast-fed child from omalizumab or from the underlying maternal condition

#### Females and males of reproductive potential

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

#### Infertility

There are no human fertility data for omalizumab. In specifically-designed non clinical fertility studies in adult cynomolgus monkeys including mating studies, no impairment of male or female fertility was observed following repeated subcutaneous dosing with omalizumab at dose levels up to 75 mg/kg/week.

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

No adverse effects on the ability to drive and use machines have been reported, but patients receiving Xolair should be warned that if they experience dizziness, fatigue, faintness or drowsiness they should not drive or use machinery.

#### **4.8 Adverse drug reactions**

##### **Allergic Asthma**

##### **Summary of the safety profile**

During clinical studies the most commonly reported adverse drug reactions were headaches and injection site reactions, including injection site pain, swelling, erythema and pruritus. Most of the reactions were mild or moderate in severity.

##### **Tabulated summary of adverse drug reactions from the clinical studies**

Table 4 lists the adverse drug reactions recorded in clinical studies in the total allergic asthma safety population treated with Xolair by system organ class and by frequency. Frequencies are defined as: Very common ( $\geq 1/10$ ), common ( $> 1/100$ ;  $< 1/10$ ), uncommon ( $> 1/1,000$ ;  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ).

##### **Table 4: Adverse drug reactions from the clinical studies**

<b>Infections and infestations</b> Rare	Parasitic infection
<b>Immune system disorders</b> Rare	Anaphylactic reaction, other serious allergic conditions, anti-therapeutic antibody development
<b>Nervous system disorders</b> Common Uncommon	Headache Dizziness, somnolence, paraesthesia, syncope
<b>Vascular disorders</b> Uncommon	Postural hypotension, flushing
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon Rare	Pharyngitis, coughing, allergic bronchospasm Laryngoedema
<b>Gastrointestinal disorders</b> Uncommon	Nausea, diarrhoea, dyspeptic signs and symptoms
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon Rare	Urticaria, rash, pruritus, photosensitivity Angioedema
<b>General disorders and administration site conditions</b>	
Common Uncommon	Injection site reactions such as pain, erythema, pruritus, swelling Weight increase, fatigue, swelling arms, influenza-like illness

#### **Adverse drug reactions from spontaneous reports (frequency not known)**

The following adverse drug reactions have been identified from post-marketing experience with Xolair via spontaneous reporting. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness:

Immune system disorders (see section 4.4): Anaphylaxis and anaphylactoid reactions have been reported following the first or subsequent administrations; serum sickness.

Skin and subcutaneous tissue disorders: Alopecia.

Blood and lymphatic system disorders: Idiopathic severe thrombocytopenia.

Respiratory, thoracic and mediastinal disorders: Churg Strauss syndrome (i.e., Eosinophilic Granulomatosis with Polyangiitis)

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

#### **Chronic Spontaneous Urticaria (CSU)**

##### **Summary of the safety profile**

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

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

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

Adverse drug reactions (events occurring in  $\geq 1\%$  of patients in any treatment group and  $\geq 2\%$  more frequently in any omalizumab treatment group than in the placebo group after medical review) reported at the recommended doses (150mg and 300mg) in the three pooled Phase III studies are listed by MedDRA system organ class (Table 5). Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions listed first. The corresponding frequency category for each adverse reaction is based on the following convention (CIOMS III): very common ( $\geq 1/10$ ); 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 ( $< 1/10,000$ ).

**Table 5 Adverse drug reactions from the pooled CSU safety database (day 1 to week 12) at the recommended doses**

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

Additional events reported anytime during the day 1 to week 24 treatment period (studies Q4881g and Q4883g) that met the criteria of adverse drug reactions:

Infections and infestations: upper respiratory tract infections (placebo 3.1%, 150 mg 3.4%, 300 mg 5.7%), urinary tract infection (placebo 1.8%, 150 mg 4.6%, 300 mg 2.4%).

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

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

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

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

**Description of adverse drug reactions of special interest pertinent to allergic asthma and CSU indications**

Anaphylaxis

In post-marketing reports, the frequency of anaphylaxis in patients exposed to Xolair use was estimated to be 0.2% based on a total number of anaphylactic reactions observed from an estimated exposure of over 500,000 patient years.

A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

### Thrombocytopenia

In clinical trials few patients experienced platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in hemoglobin. No pattern of persistent decrease in platelet counts has been reported in humans as was observed in non-human primates (see Section 5.3). Thrombocytopenia has been reported in post-marketing experience.

### Parasitic infections

In allergic asthma 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).

### Malignancies

During initial clinical trials in adults and adolescents 12 years of age and older, there was a numerical imbalance in cancers arising in the active treatment group, compared with the control group. The number of observed cases was uncommon (<1/100) in both the active and the control group. In a subsequent observational study comparing 5,007 Xolair-treated and 2,829 non-Xolair-treated patients followed for up to 5 years, the incidence rates of primary malignancies per 1,000 patient years were 16.01 (295/18,426 patient years) and 19.07 (190/9,963 patients years), respectively, which does not indicate an increased malignancy risk (rate ratio 0.84, 95% confidence interval, 0.62 to 1.13). However, study limitations preclude definitively ruling out a malignancy risk with Xolair. Study limitations include: the observational study design, the bias introduced by allowing enrollment of patients previously exposed to Xolair (88%), enrollment of patients (56%) while a history of cancer or a premalignant condition were study exclusion criteria, and the high study discontinuation rate (44%).

In a further analysis of randomized, double-blind, placebo-controlled clinical trials including 4,254 patients on Xolair and 3,178 patients on placebo, Xolair treatment was not associated with an increased malignancy risk based on incidence rates per 1,000 patient years of 4.14 (14/3,382 patient years) for Xolair treated patients and 4.45 (11/2,474 patient years) for placebo patients (rate ratio 0.93, 95% confidence interval 0.39-2.27). The overall observed incidence rate of malignancy in the Xolair clinical trial program was comparable to that reported in the general population.

### Arterial Thromboembolic Events (ATE)

In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATEs was observed. ATE included stroke, transient ischemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patients years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% confidence interval 0.91 to 1.91). In a separate analysis of pooled clinical trials including all randomized double-blind, placebo-controlled clinical trials of 8 or more weeks duration, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patients years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24 to 5.71).

## **4.9 Overdosage**

No case of overdose has been reported. A 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.

## **5. PHARMACOLOGICAL PROPERTIES**

## 5.1 Pharmacodynamic properties

### General characteristics

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

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

### Patients with Allergic Asthma

Omalizumab binds to IgE and prevents binding of IgE to FCεRI, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FCεRI receptors. Furthermore, the *in vitro* histamine release from basophils isolated from Xolair-treated subjects was reduced by approximately 90% following stimulation with an allergen compared to pre-treatment values.

In clinical studies in asthma patients, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after drug washout.

### Patients with Chronic Spontaneous Urticaria (CSU)

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

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

In clinical studies in CSU patients, omalizumab treatment led to a dose-dependent reduction of free IgE and an increase of total IgE levels in serum, similar to the observations in allergic asthma patients. Maximum suppression of free IgE was observed 3 days after the first subcutaneous dose. After repeated dosing once every 4 weeks, pre-dose serum free IgE levels remained stable between 12 and

24 weeks of treatment. Total IgE levels in serum increased after the first dose due to the formation of omalizumab: IgE complexes which have a slower elimination rate compared with free IgE. After repeated dosing once every 4 weeks at 75 mg to 300 mg, average predose serum total IgE levels at week 12 were two-to three-fold higher compared with pre-treatment levels, and remained stable between 12 and 24 weeks of treatment. After discontinuation of Xolair, free IgE levels increased and total IgE levels decreased towards pre-treatment levels over a 16-week treatment-free follow-up period.

### Clinical studies

#### Allergic Asthma

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

In identical 16-week studies 1 and 2 the safety and efficacy of omalizumab as add-on therapy were

demonstrated in 1,071 allergic asthmatics, who were symptomatic despite treatment with inhaled corticosteroids (beclomethasone dipropionate 500 to 1,200 micrograms/day).

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

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

In Studies 1 and 2, clinically meaningful improvement in asthma-related quality of life, measured by the validated Juniper's Asthma Quality of Life Questionnaire, was demonstrated in the Xolair group at the end of the 28-week core trial compared to that observed in the placebo treated group (difference from placebo  $p \leq 0.001$  in Studies 1 and 2).

In study 3 the safety and corticosteroid-sparing effect of omalizumab was demonstrated in 246 patients with severe allergic asthma requiring daily treatment with high-dose inhaled corticosteroids (fluticasone  $\geq 1,000$  micrograms/day) and in whom long-acting beta2-agonists were allowed. The study included a 16-week steroid stable phase with study medication added, followed by a 16-week steroid reduction phase. The percent reduction in inhaled corticosteroid dose at the end of the treatment phase was significantly greater in omalizumab-treated patients versus placebo patients (median 60% vs. 50%,  $p=0.003$ ). The proportion of omalizumab patients who were able to reduce their fluticasone dose to  $\leq 500$  micrograms/day was 60.3% versus 45.8% in the placebo group.

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

The co-primary endpoints for study 4 were the incidence of asthma exacerbations (worsening of asthma requiring systemic corticosteroids or a doubling of the patient's baseline budesonide dose) and the proportion of patients in each treatment group with a  $\geq 1.0$  improvement from baseline at the end of the treatment phase in both asthma and rhinitis specific quality of life assessments (Juniper Quality of Life Assessment).

Patients treated with omalizumab had a significantly lower incidence of asthma exacerbations than patients receiving placebo (20.6% omalizumab vs 30.1% placebo,  $p=0.02$ ) and there was a significantly higher proportion of omalizumab-treated than placebo patients that improved by  $\geq 1.0$  points in both asthma and rhinitis specific quality of life assessments (57.7% omalizumab vs 40.6% placebo,  $p < 0.0001$ ).

The reduction in exacerbations and improvements of quality of life in omalizumab-treated patients were seen in the context of statistically significant improvements in both rhinitis and asthma symptoms, and lung function, compared to placebo.

In study 5 the efficacy and safety of Xolair were demonstrated in a 28-week study involving 419 severe allergic asthmatics, ages 12 to 79 years, who had reduced lung function (FEV1 40 to 80% predicted) and poor asthma symptom control despite receiving  $>1,000$  micrograms of beclomethasone dipropionate (or equivalent) plus long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to  $>1,000$  micrograms beclomethasone dipropionate (or equivalent) plus long-acting beta2-agonist. Oral corticosteroid (22%), theophylline (27%) and anti-

leukotriene (35%) maintenance therapies were allowed. In the treatment phase concomitant asthma therapy was not changed.

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

### Chronic Spontaneous Urticaria (CSU)

The efficacy and safety of Xolair were demonstrated in two randomised, placebo-controlled phase III studies (study 1 and 2) in patients with CSU who remained symptomatic despite H1 antihistamine therapy at the approved dose. A third study (study 3) primarily evaluated the safety of Xolair in patients with CSU who remained symptomatic despite treatment with H1 antihistamines at up to four times the approved dose and H2 antihistamine and/or LTRA treatment. The three studies enrolled 975 patients aged between 12 and 75 years (mean age 42.3 years; 39 patients 12-17 years, 54 patients  $\geq 65$  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 medications (including H1 antihistamines) for CSU symptoms prior to study enrollment. Patients received Xolair at 75 mg, 150 mg or 300 mg or placebo by subcutaneous injection every 4 weeks for 24 and 12 weeks in studies 1 and 2, respectively, and 300 mg or placebo by subcutaneous injection every 4 weeks for 24 weeks in study 3. All studies had a 16-week treatment-free follow-up period.

The primary endpoint was the change from baseline to week 12 in weekly itch severity score.

Omalizumab at 300 mg reduced the weekly itch severity score by 8.55 to 9.77 ( $p < 0.0001$ ) compared to a reduction of 3.63 to 5.14 for placebo (see Table 6). The responder rates for  $UAS7 \leq 6$  (at week 12) ranging from 52-66% (300 mg dose), all were statistically significantly higher compared to 11-19% in the placebo group ( $p < 0.0001$ ). Complete response ( $UAS7 = 0$ ) at week 12, 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%) compared to the placebo groups (88.1-89.2%; all  $p < 0.001$ ). Mean change from baseline to week 12 in the overall DLQI for the 300 mg treatment groups was statistically significantly greater 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 (all  $p < 0.001$ ).

**Table 6: 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. placebo1	-	-4.81
95% CI for difference	-	-6.49,-3.13
P-value vs. placebo2	-	<0.0001
<b>Study 3</b>		
N	83	252
Mean (SD)	-4.01 (5.87)	-8.55 (6.01)
Difference in LS means vs. placebo1	-	-4.52
95% CI for difference	-	-5.97,-3.08
P-value vs. placebo2	-	<0.0001

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

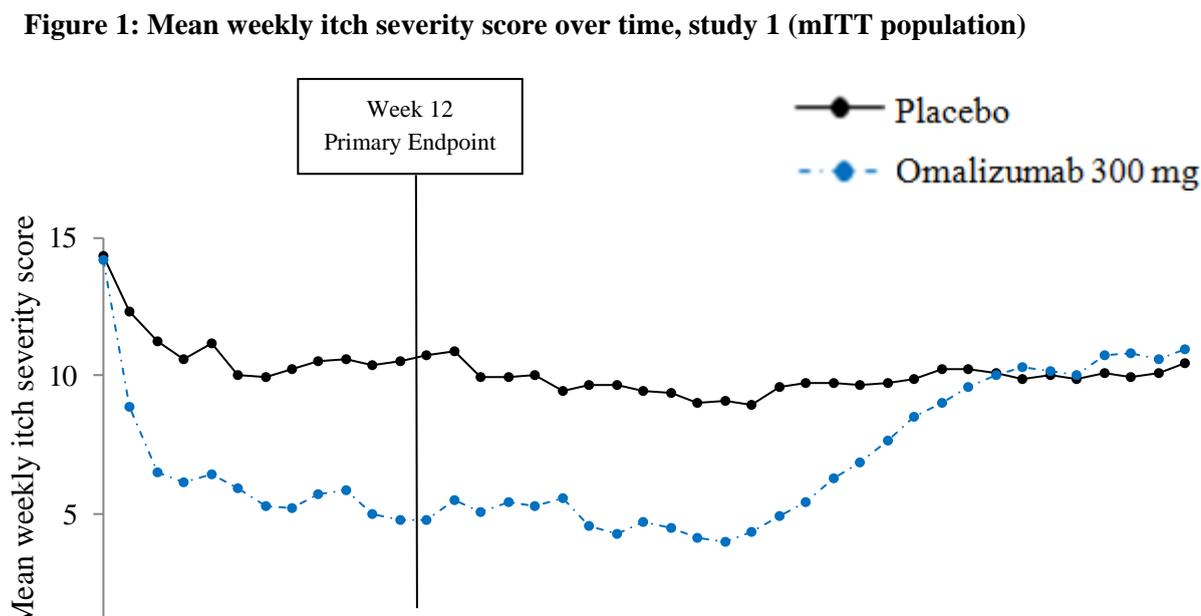
BOCF (Baseline Observation Carried Forward) was used to impute missing data.

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

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

Figure 1 shows the mean weekly itch severity score over time in study 1. The mean weekly itch severity scores significantly decreased with a maximum effect around week 12 that was sustained over the 24-week treatment period. The results were similar in study 3.

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



Omalizumab or placebo administered

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

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

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

## 5.2 Pharmacokinetic properties

### General characteristics

#### Absorption

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

#### 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*.

#### 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.

### Patients with Allergic Asthma

#### **Absorption**

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

#### **Distribution**

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

#### **Elimination**

In asthma patients 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.

## **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 in asthma patients for age (12 to 76 years), race, ethnicity or gender or body mass index.

## **Patients with Chronic Spontaneous Urticaria (CSU)**

### **Absorption**

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

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

### **Distribution**

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

### **Elimination**

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

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

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

## **Patients with renal or hepatic impairment**

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

## **5.3 Non-clinical 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-fold the highest recommended clinical dose in mg/kg) was well tolerated in non-human primates, 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 (about 12-fold exposure ratio based on 28-day AUC values at 75 mg/kg versus the clinical maximum dose) 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 milk in cynomolgus monkeys. Milk levels of omalizumab were 1.5% of the maternal blood concentration.

Reproduction, milk excretion and fertility studies in animals are described in section 4.6.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Powder:

Sucrose

Histidine

Histidine hydrochloride monohydrate

Polysorbate 20

Solvent:

Water for injection

### **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 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 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 should 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 to 8°C).

Do not freeze.

In order to protect from light, store in the original package.

### **6.5 Nature and contents of container**

Xolair 150mg:

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 injection.

Package of one vial of powder for solution for injection and one ampoule of water for injection.

### **6.6 Instructions for use, handling and disposal**

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

Xolair 150 mg powder for solution for injection are supplied in a single-use vial and contain no antibacterial preservatives. Chemical and physical stability of the reconstituted product has been demonstrated for 8 hours at 2°C to 8°C and for 4 hours at 30°C. From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 8 hours at 2°C to 8°C or 2 hours at 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

The lyophilised product takes 15 to 20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted product will appear clear to slightly opalescent, colorless 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 product care must be taken to **WITHDRAW ALL OF THE PRODUCT** from the vial before expelling any air or excess solution from the syringe in order to obtain the 1.2 ml (150mg).

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 to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

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

When the product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted product will appear clear or slightly opaque. 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 to 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 arm, thigh, or lower abdomen (but not the area of 5 centimeters around the navel). Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. If you need to give more than one injection for the full dose, choose a different injection site each time you inject.

### **Special precautions for disposal - Xolair powder and solvent for solution for injection**

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

#### **7. PRODUCT OWNER**

Novartis Pharma AG  
CH 4056, Basel  
Switzerland

#### **8. DATE OF REVISION OF THE TEXT**

December 2018.SINv1