NOVARTIS

XOLAIR®

(omalizumab)

75 mg/0,5 ml, 150 mg/1,0 ml solution for injection in pre-filled syringe

Professional Information

Document status: Final

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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

XOLAIR® 75 mg/0,5 ml solution for injection in pre-filled syringe

XOLAIR® 150 mg/1,0 ml Solution for injection in pre-filled syringe

WARNING

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of XOLAIR. Anaphylaxis has occurred as early as after the first dose of XOLAIR, but has also occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after XOLAIR administration, and health care providers administering XOLAIR should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur (see *section 4.4*.)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Solution for injection in pre-filled syringe

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

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

Each pre-filled syringe of 1,0 mL contains 150 mg of omalizumab.

Sugar free

Full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe:

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergic Asthma:

Adults and adolescents (12 years of age and older)

XOLAIR is indicated for the prevention of asthma exacerbations and control of asthma symptoms, when given as add-on therapy for 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 $beta_2$-agonist.

Children (6 to < 12 years of age)

XOLAIR is indicated as add-on therapy to reduce the dose of inhaled corticosteroids 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.

XOLAIR treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma.

Safety and efficacy have not been established in other allergic conditions.

Chronic Spontaneous Urticaria (CSU):

XOLAIR (omalizumab) is indicated for adults and adolescents (12 years of age and above) with chronic spontaneous urticaria refractory to standard of care.

Nasal Polyps:

XOLAIR (omalizumab) is indicated for adults (18 years of age and above) for the treatment of nasal polyps with inadequate response to intranasal corticosteroids.

4.2 Posology and method of administration

Posology

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

Dosage for Allergic Asthma and Nasal Polyps:

Dosing for asthma and nasal polyps follows the same dosing principles.

The appropriate dose and dosing frequency of XOLAIR for these conditions 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. 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 4-1 and 4-2 for a conversion chart and Tables 5 and 6 for the dose determination charts in children (6 years to less than 12 years of age) and in adults and adolescents (12 years of age and older).

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

Table 4-1: 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)
	150 mg [a]		
150	1	1	1.2
225	1	2	1.8
300	2	2	2.4
375	2	3	3.0
450	3	3	3.6
525	3	4	4.2
600	4	4	4.8

[a] 1,2 mL = maximum delivered volume per vial (XOLAIR 150 mg)

Table 4-2: Conversion from dose to number of pre-filled syringes, number of injections and total injection volume for each administration

Dose (mg)	Number of syringes		Number of injections	Total injection volume (mL)
	75 mg	150 mg		
75	1	0	1	0.5
150	0	1	1	1.0
225	1	1	2	1.5
300	0	2	2	2.0
375	1	2	3	2.5
450	0	3	3	3.0
525	1	3	4	3.5
600	0	4	4	4.0

Table 5: ADMINISTRATION EVERY 4 WEEKS - Allergic Asthma and Nasal Polyps

XOLAIR doses (milligrams per dose) administered by subcutaneous injection every 4 weeks

	Body weight (kg)									
Baseline IgE (IU/mL)	> 20 - 25	> 25 - 30*	> 30 - 40	> 40 - 50	> 50 - 60	> 60 - 70	> 70 - 80	> 80 - 90	> 90 - 125	> 125 - 150
≥ 30 – 100	75	75	75	150	150	150	150	150	300	300

	Body weight (kg)									
> 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	ADMINISTRATION EVERY 2 WEEKS SEE TABLE 6					

*Body weights below 30 kg were not studied in the pivotal trials for nasal polyps

Table 6: ADMINSTRATION EVERY 2 WEEKS- Allergic Asthma and Nasal Polyps

XOLAIR doses (milligrams per dose) administered by subcutaneous injection every 2 weeks

	Body weight (kg)										
Baseline IgE (IU/mL)	≥ 20 - 25*	> 25 - 30*	> 30 - 40	> 40 - 50	> 50 - 60	> 60 - 70	> 70 - 80	> 80 - 90	> 90 - 125	> 125 - 150	> 150 - 200*
≥ 30 - 100	ADMINISTRATION EVERY 4 WEEKS SEE ABOVE										225
> 100 - 200											375
> 200 - 300										375	525

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

*Body weights below 30 kg and above 150 kg were not studied in the pivotal trials for nasal polyps

Administration

For information on reconstitution of XOLAIR, see Instructions for use and handling, and disposal.

Treatment duration, monitoring and dose adjustments

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.

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

XOLAIR is intended for long-term treatment.

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 5, 6).

Dosage 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.

Dosing of XOLAIR in CSU patients is not dependent on serum total IgE (IU/mL) or body weight (kg).

Elderly (65 years of age and older)

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

Children (below 6 years of age)

In allergic asthma, XOLAIR is not recommended for use in children below age 6 due to insufficient data on safety and efficacy.

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

Special populations

Paediatric population

In nasal polyps, safety and efficacy in patients below the age of 18 years have not been established.

Method of administration

Pre-filled syringe:

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.

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 *section 4.2*.

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Anaphylaxis

Anaphylaxis has been reported to occur after administration of XOLAIR in pre-marketing clinical trials and in post-marketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In pre-marketing clinical trials the frequency of anaphylaxis attributed to XOLAIR use was estimated to be 0,1 %. In post-marketing spontaneous reports, the frequency of anaphylaxis attributed to XOLAIR use was estimated to be at least 0,2 % of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of XOLAIR, but has also occurred beyond one year after beginning regularly scheduled treatment.
XOLAIR should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Patients should be closely observed for an appropriate period of time after administration of XOLAIR, taking into account the time to

onset of anaphylaxis seen in pre-marketing clinical trials and post-marketing spontaneous reports (see *section 4.4*). Patients should be informed of the signs and symptoms of anaphylaxis, and instructed to seek immediate medical care should signs or symptoms occur. XOLAIR should be discontinued in patients who experience a severe hypersensitivity reaction (see *section 4.3*).

Special precautions

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 hyper immunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy. XOLAIR is not intended for the treatment of these conditions.

XOLAIR has not been adequately studied in atopic dermatitis or allergic rhinitis.

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

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

Immune system disorders

Allergic reactions type I

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

Patients may in rare cases develop antibodies to omalizumab.

Serum Sickness

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have rarely been seen in patients treated with humanized monoclonal antibodies including omalizumab. The 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/arthralgia's, 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 with systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids.

Patients on therapy with anti-asthma agents, including XOLAIR, 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 XOLAIR 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 program, which was not designed to detect such infections, was less than 1 in 1,000 patients. However, caution may be warranted in patients at high risk of helminth infection, in particular when traveling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of XOLAIR should be considered.

Pre-filled syringe, latex-sensitive individuals

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

4.5 Interaction with other medicines and other forms of interactions

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

Allergic Asthma:

In clinical studies XOLAIR was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of XOLAIR was altered with these other commonly used asthma medications. Limited data are available on the use of XOLAIR in combination with specific immunotherapy (hypo-sensitisation therapy).

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). In the phase III studies Q4881g and Q4882g all patients received H1 antihistamines in addition to XOLAIR or placebo. In the phase III study Q4883g, all patients received one or more H1 antihistamine(s), and/or H2 antihistamines and/or LTRAs in addition to XOLAIR or placebo. There was no evidence that

the safety of omalizumab was altered when used with these medicinal products relative to its known safety profile in allergic asthma. In addition, a population pharmacokinetic analysis showed no relevant effect of H2 antihistamines and LTRAs on omalizumab pharmacokinetics *(see section 5.2).*

Usage of XOLAIR in combination with immunosuppressive therapies has not been studied.

Nasal Polyps

In clinical studies XOLAIR was used in conjunction with intranasal mometasone spray per protocol.

Other commonly used concomitant medications included other intranasal corticosteroids, bronchodilators, antihistamines, leukotriene receptor antagonists, adrenergics/sympathomimetics, and local nasal anaesthetics.

There was no indication that the safety of XOLAIR was altered with these other commonly used nasal polyps medications.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

There are no special recommendations for women of childbearing potential.

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Safety with lactation has not been established.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients receiving XOLAIR should be warned that if they experience dizziness, fatigue, faintness or drowsiness, they should not drive or use machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Allergic Asthma:

Over 4,400 allergic asthma patients were randomised in controlled efficacy trials with XOLAIR. During clinical trials with adults 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 with patients 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.

Table 7 lists the adverse reactions recorded in clinical studies in the total allergic asthma safety population treated with XOLAIR by system organ class and by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: Very common (≥ 1/10), common (≥ 1/100; < 1/10), uncommon (≥ 1/1000; < 1/100), rare (< 1/1000), very rare (< 1/10,000).

Table 7: Adverse reactions from the clinical studies

Infections and infestations	
Uncommon Rare	Pharyngitis Parasitic infections
Immune system disorders	
Rare	Anaphylactic reaction and other serious allergic conditions, antitherapeutic antibody development
Nervous system disorders	
Common	Headache**
Uncommon	Syncope, paraesthesia, somnolence, dizziness
Vascular disorders	
Uncommon	Postural hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	Allergic bronchospasm, pharyngitis, coughing
Rare	Laryngoedema
Gastrointestinal disorders	
Common	Abdominal pain upper*
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
Skin and subcutaneous tissue disorders	
Uncommon	Photosensitivity, urticaria, rash, pruritus
Rare	Angioedema
General disorders and administration site conditions	
Very common	Pyrexia*
Common	Injection site reactions such as swelling, erythema, pain, pruritus

Uncommon	Influenza-like illness, swelling arms, weight increase, fatigue
** Very common in children 6 to < 12 years of age * In children 6 to < 12 year of age.	
Events reported in the post-marketing setting are listed with frequency not known (cannot be estimated from the available data):	
Blood and the lymphatic system disorders	
Not known	Idiopathic severe thrombocytopenia
Immune system disorders	
Not known	Serum sickness, may include fever and lymphadenopathy Anaphylaxis and anaphylactoid reactions have been reported following the first or subsequent administrations, serum sickness
Respiratory, thoracic and mediastinal disorders	
Not known	Allergic granulomatous vasculitis (i.e. Churg Strauss syndrome)
Skin and subcutaneous tissue disorders	
Not known	Alopecia
Musculoskeletal and connective tissue disorders	
Not known	Arthralgia, myalgia, joint swelling
Blood (platelets)	
Not known	Cases of idiopathic thrombocytopenia
Parasitic infections	
Not known	Increase in the infection rate in patients at chronic high risk of helminth infection

Nasal Polyps

Summary of the safety profile

The data described below reflect data from two placebo-controlled studies in patients ≥ 18 years of age. In these studies, patients received either XOLAIR 150 to 600 mg every 2 or 4 weeks or placebo. All patients received background intranasal mometasone therapy. The safety profile in patients with nasal polyps was consistent with that in allergic asthma and CSU. The most frequently (> 3 %) reported adverse drug reactions, which were higher in frequency in comparison to placebo are shown in Table 7-2.

Tabulated summary of adverse drug reactions from the clinical studies

Table 7-2 lists the adverse drug reactions recorded in clinical studies in the total nasal polyp safety population treated with XOLAIR by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 7-2 Adverse drug reactions from the clinical studies in Nasal Polyps

Adverse drug reactions (by MedDRA preferred term)	**Omalizumab Nasal Polyp Study1 and Study 2 Pooled**		**Frequency category**
	Placebo N = 130	Omalizumab N = 135	
Nervous system disorders			
Headache	7 (5.4 %)	11 (8.1 %)	Common
Dizziness	1 (0.8 %)	4 (3.0 %)	Common
Musculoskeletal and connective tissue disorders			

Adverse drug reactions (by MedDRA preferred term)	**Omalizumab Nasal Polyp Study1 and Study 2 Pooled**		**Frequency category**
	Placebo N = 130	Omalizumab N = 135	
Arthralgia	2 (1.5 %)	4 (3.0 %)	Common
Gastrointestinal disorder			
Abdominal pain upper	1 (0.8 %)	4 (3.0 %)	Common
General disorders and administration site conditions			
Injection site reactions (Injection site reactions, Injection related reaction, injection site pain)	2 (1.5 %)	7 (5.2 %)	Common

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 reactions observed were headache and nasopharyngitis.

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

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

Table 8: Adverse reactions from the pooled CSU safety database (Day 1 to week 12) at the recommended doses:

Adverse reactions (by MedDRA preferred term)	**Omalizumab Studies Q4881g, Q4882g and Q4883g Pooled**			**Frequency category**
	Placebo N = 242	**150 mg N = 175**	**300 mg N = 412**	
Infections and infestations				
Nasopharyngitis	17 (7,0 %)	16 (9,1 %)	27 (6,6 %)	Common
Sinusitis	5 (2,1 %)	2 (1,1 %)	20 (4,9 %)	Common

Viral upper respiratory tract infection	0	4 (2,3 %)	2 (0,5 %)	Common
Nervous system disorders				
Headache	7 (2,9 %)	21 (12,0 %)	25 (6,1 %)	Very common
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (0,4 %)	5 (2,9 %)	12 (2,9 %)	Common

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

Infections and infestations: upper respiratory tract infections (placebo 3,1 %, 150 mg 3,4 %, 300 mg 5,7 %), urinary tract infection (placebo 1,8 %, 150 mg 4,6 %, 300 mg 2,4 %).
Nervous system disorders: sinus headache (placebo 0 %, 150 mg 2,3 %, 300 mg 0,3 %).
Musculoskeletal and connective tissue disorders: myalgia (placebo 0 %, 150 mg 2,3 %, 300 mg 0,9 %), pain in extremity (placebo 0 %, 150 mg 3,4 %, 300 mg 0,9 %), musculoskeletal pain (placebo 0 %, 150 mg 2,3 %, 300 mg 0,9 %).
General disorders and administration site conditions: pyrexia (placebo 1,2 %, 150 mg 3,4 %, 300 mg 0,9 %).

Injection site reactions: Injection site reactions occurred during the studies in more omalizumab-treated patients than placebo patients (2,7 % at 300 mg, 0,6 % at 150 mg, 0,8 % with placebo). They included: swelling, erythema, pain, bruising, itching, bleeding and urticaria.

In a 48-week study, 81 CSU patients received omalizumab 300 mg every 4 weeks (see section 12 Clinical studies - CSU). The safety profile of long-term use was similar to the safety profile observed in CSU studies up to 24 weeks.

Description of safety aspects of special interest pertinent to allergic asthma and CSU indications:

No relevant data was obtained in clinical studies in CSU that would require a modification of the sections below.

Anaphylaxis

In post-marketing reports, the frequency of anaphylaxis in patients exposed to XOLAIR use was estimated to be 0,2 % based on a total number of anaphylactic reactions observed from an estimated exposure of over 500,000 patient years.

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

Malignancies

During initial clinical trials in adults and adolescents 12 years of age and older, there was a numerical imbalance in cancers arising in the active treatment group, compared with the control group. The number of observed cases was uncommon (< 1/100) in both the active and the control group. In a subsequent observational study comparing 5007 XOLAIR-treated and 2829 non-XOLAIR-treated patients followed for up to 5 years, the incidence rates of primary malignancies per 1000 patient years were 16,01 (295/18426 patient years) and 19,07 (190/9963 patient years), respectively, which does not indicate an increased malignancy risk (rate ratio 0,84, 95 % confidence interval, 0,62 - 1,13). In a further analysis of randomized,

double-blind, placebo-controlled clinical trials including 4254 patients on XOLAIR and 3178 patients on placebo, XOLAIR treatment was not associated with an increased malignancy risk based on incidence rates per 1000 patient years of 4,14 (14/3382 patient years) for XOLAIR treated patients and 4,45 (11/2474 patient years) for placebo patients (rate ratio 0,93, 95 % confidence interval 0,39 - 2,27). The overall observed incidence rate of malignancy in the XOLAIR clinical trial program was comparable to that reported in the general population.

There were no cases of malignancy with XOLAIR in the clinical trials in children 6 to < 12 years of age; there was a single case of malignancy in the control group. The paediatric program was not designed to detect the differences in malignancy rates.

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 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 1000 patient years was 7,52 (115/15286 patients years) for XOLAIR-treated patients and 5,12 (51/9963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1,32 (95 % confidence interval 0,91 to 1,91). In a new analysis of pooled clinical trials including all randomized double-blind, placebo-controlled clinical trials of 8 or more weeks duration, the rate of ATE per 1000 patient years was 2,69 (5/1856 patients years) for XOLAIR-treated patients and 2,38 (4/1680 patient years) for placebo patients (rate ratio 1,13; 95 % confidence interval 0,24 to 5,71).

Platelets

In clinical trials few patients experienced platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in haemoglobin. No pattern of persistent decrease in platelet counts, as observed in non-human primates, has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia 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 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*).

Other laboratory data

There was no evidence of clinically relevant changes in laboratory safety tests during clinical trials.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

Maximum tolerated dose of XOLAIR has not been determined. Single intravenous doses up to 4000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period and this dose did not result in any untoward acute effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A 34. Other

Pharmacotherapeutic group and ATC code:

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

General characteristics:

Omalizumab is a recombinant DNA-derived humanized 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 and Nasal Polyps:

Omalizumab binds to IgE and prevents binding of IgE to the high-affinity FcεRI receptor, thereby reducing the amount of free IgE that is available to trigger the allergic cascade.

Treatment with XOLAIR 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.

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 signalling 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.

Patients with Allergic Asthma:

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 pre-dose 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.

Patients with Nasal Polyps:

In clinical studies in patients with nasal polyps, XOLAIR treatment led to a reduction in serum free IgE and an increase in serum total IgE levels, similar to the observations in patients with allergic asthma. After repeated dosing every 2 or 4 weeks, with dosage and frequency according to Tables 4-3 and 4-4 *(see section 4.2*), mean pre-dose serum free IgE levels decreased by approximately 95 % and remained stable between 16 and 24 weeks of treatment. Total IgE levels in serum increased due to the formation of omalizumab-IgE complexes, which have a slower elimination rate compared with free IgE. After repeated dosing every 2 or 4 weeks, with dosage and frequency according to Tables 4-3 and 4-4 *(see section 4.2*), mean pre-dose serum total IgE levels at Week 16 were 3- to 4- fold higher compared with pre-treatment levels, and remained stable between 16 and 24 weeks of treatment.

5.2 Pharmacokinetic properties

General characteristics:

Absorption:

After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62 %. The pharmacokinetics of omalizumab is 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. Tissue distribution studies in cynomolgus monkeys showed no specific uptake of ^{125}I-omalizumab by any organ or tissue.

Elimination:

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

Patients with Allergic Asthma:

Absorption:

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

Distribution:

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

Elimination:

In asthma patients omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2,4 ± 1,1 mL/kg/day. In addition, doubling of body weight approximately doubled apparent clearance.

Patients with Nasal Polyps

The population pharmacokinetics analyses of omalizumab suggested that pharmacokinetics of omalizumab in nasal polyps were consistent with that in asthma. Graphical covariate analyses were performed to evaluate the effects of demographic characteristics and other factors on omalizumab exposure and clinical responses. These analyses demonstrate that no dose adjustments are necessary for age (18 to 75 years) or gender. Race and ethnicity data are too limited in nasal polyps to inform dose adjustment.

The safety and efficacy of XOLAIR were evaluated in two randomized, multicentre, double-blind, placebo-controlled clinical trials that enrolled patients with chronic rhinosinusitis with nasal polyps (study 1, N = 138; study 2, N = 127). Patients received XOLAIR or placebo subcutaneously every 2 or 4 weeks, with dosage and frequency according to Tables 4-3 and 4-4 *(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 XOLAIR or placebo for 24 weeks followed by a 4-week follow-up period. Demographics and baseline characteristics, including allergic comorbidities, are described in Table 9-1.

Table 9-1 Demographics and baseline characteristics of Nasal Polyps Studies

Parameter	**Nasal Polyp Study 1** **N = 138**	**Nasal Polyp Study 2** **N = 127**

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
Mean bilateral endoscopic NPS* (SD), range 0 - 8	6.2 (1.0)	6.3 (0.9)
Mean nasal congestion (NC) score* (SD), range 0 - 3	2.4 (0.6)	2.3 (0.7)
Mean sense of smell score* (SD) range 0 - 3	2.7 (0.7)	2.7 (0.7)
Mean SNOT-22 total score* (SD) range 0 - 110	60.1 (17.7)	59.5 (19.3)
Mean blood eosinophils (cells/µl) (SD)	346.1 (284.1)	334.6 (187.6)
Mean total IgE IU/mL (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; NPS = nasal polyp score; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; IgE = Immunoglobulin E; IU = international units. For NPS, NCS, sense of smell,

postnasal drip, runny nose, and SNOT-22 scores higher scores indicate greater disease severity.

The co-primary endpoints were bilateral nasal polyp score (NPS) and average daily nasal congestion score (NCS) at Week 24. NPS was measured via endoscopy at baseline and pre-specified time points and scored (range 0-4 per nostril) for a total NPS (range 0/best-8/worst). Nasal congestion was measured by a daily NCS (range 0/best-3/worst). Patients were required to have NPS ≥ 5 and weekly average of NCS > 1 prior to randomization, despite use of intranasal mometasone. The mean NPS at baseline was balanced between the two treatment groups in both studies.

In both nasal polyps studies 1 and 2, patients who received XOLAIR had a statistically significant greater improvement from baseline at Week 24 in NPS and weekly average NCS than patients who received placebo. Results from Nasal Polyps Study 1 and 2 are shown in Table 9-2.

The greater improvements in NPS and NCS in the XOLAIR group compared to the placebo group were observed as early as the first assessment at Week 4 in both studies as seen in Figure 9-1. The LS mean difference in change from baseline at Week 4 in NPS in XOLAIR compared to placebo was -0.92 (95 % CI: -1.37, -0.48) in study 1 and -0.52 (95 % CI: -0.94, -0.11) in study 2. The LS mean difference in change from baseline at Week 4 in NCS in XOLAIR compared to placebo was -0.25 (95 % CI: -0.46, -0.04) in study 1 and -0.26 (95 % CI: -0.45, -0.07) in study 2. However, statistical tests at this time point were not pre-specified.

Table 9-2 Demographics and baseline characteristics of Nasal Polyps Studies

Parameter	Nasal Polyp Study 1	Nasal Polyp Study 2

	N = 138	**N = 127**
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
Mean bilateral endoscopic NPS* (SD), range 0-8	6.2 (1.0)	6.3 (0.9)
Mean nasal congestion (NC) score* (SD), range 0-3	2.4 (0.6)	2.3 (0.7)
Mean sense of smell score* (SD) range 0-3	2.7 (0.7)	2.7 (0.7)
Mean SNOT-22 total score* (SD) range 0-110	60.1 (17.7)	59.5 (19.3)
Mean blood eosinophils (cells/µl) (SD)	346.1 (284.1)	334.6 (187.6)
Mean total IgE IU/mL (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; NPS = nasal polyp score; SNOT-22 = Sino-Nasal Outcome Test 22 Questionnaire; IgE = Immunoglobulin E; IU=international units. For NPS, NCS, sense of smell,

postnasal drip, runny nose, and SNOT-22 scores higher scores indicate greater disease severity.

The co-primary endpoints were bilateral nasal polyp score (NPS) and average daily nasal congestion score (NCS) at Week 24. NPS was measured via endoscopy at baseline and pre-specified time points and scored (range 0 - 4 per nostril) for a total NPS (range 0/best-8/worst). Nasal congestion was measured by a daily NCS (range 0/best-3/worst). Patients were required to have NPS ≥ 5 and weekly average of NCS > 1 prior to randomization, despite use of intranasal mometasone. The mean NPS at baseline was balanced between the two treatment groups in both studies.

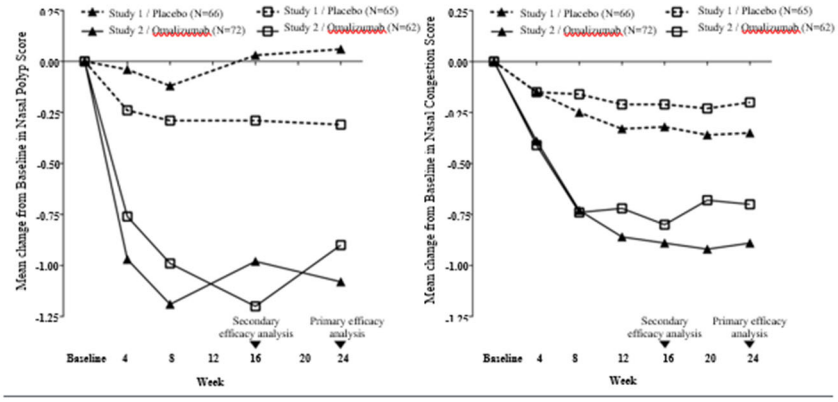
In both nasal polyps studies 1 and 2, patients who received XOLAIR had a statistically significant greater improvement from baseline at Week 24 in NPS and weekly average NCS than patients who received placebo. Results from Nasal Polyps Study 1 and 2 are shown in Table 9-2.

The greater improvements in NPS and NCS in the XOLAIR group compared to the placebo group were observed as early as the first assessment at Week 4 in both studies as seen in Figure 9-1. The LS mean difference in change from baseline at Week 4 in NPS in XOLAIR compared to placebo was -0.92 (95 % CI: -1.37, -0.48) in study 1 and -0.52 (95 % CI: -0.94, -0.11) in study 2. The LS mean difference in change from baseline at Week 4 in NCS in XOLAIR compared to placebo was -0.25 (95 % CI: -0.46, -0.04) in study 1 and -0.26 (95 % CI: -0.45, -0.07) in study 2. However, statistical tests at this time point were not pre-specified.

Table 9-3 Change from baseline at Week 24 in nasal polyp score and 7-day average of daily nasal congestion score in Nasal Polyp Study 1 and Nasal Polyp Study 2

	Nasal Polyp Study 1		**Nasal Polyp Study 2**	
	Placebo	**XOLAIR**	**Placebo**	**XOLAIR**
N	66	72	65	62
Nasal polyp score				
Baseline mean	6.32	6.19	6.09	6.44
LS mean change at Week 24	0.06	-1.08	-0.31	-0.90
Difference in LS means vs. placebo	-1.14		-0.59	
95 % CI for difference	-1.59, -0.69		-1.05, -0.12	
p-value	< 0.0001		0.0140	
7-day average of daily nasal congestion score				
Baseline mean	2.46	2.40	2.29	2.26
LS mean change at week 24	-0.35	-0.89	-0.20	-0.70
Difference in LS means vs. placebo	-0.55		-0.50	
95% CI for difference	-0.84, -0.25		-0.80, -0.19	
p-value	0.0004		0.0017	

Figure 9-1 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 Nasal Polyp Study 2



A key secondary endpoint was the assessment of the change from baseline at Week 24 of the total nasal symptom score (TNSS). Patient-reported TNSS was the sum of four equally weighted individual daily symptom scores: NCS, sense of smell score, posterior rhinorrhea score, and anterior rhinorrhea score. The TNSS ranged from 0/best-12/worst. XOLAIR significantly improved the average daily TNSS compared to placebo. The LS mean difference for change from baseline to Week 24 was -1.91 points (95 % CI: -2.85, -0.96; p = 0.0001) in study 1 and -2.09 points (95 % CI: -3.00, -1.18; p < 0.0001) in study 2.

XOLAIR significantly improved SNOT-22 (Sino-Nasal Outcome Test), which combines measures of sino-nasal symptoms with psychological and sleep dysfunction measures. The SNOT-22, ranged from 0 to 110 (0/best-110/worst). The LS mean difference for change from baseline to Week 24 in SNOT-22 in XOLAIR compared to placebo was -16.12 (95 % CI: -21.86, -10.38; p < 0.0001) in study 1 and -15.04 (95 % CI: -21.26, -8.82; p < 0.0001) in study 2.

XOLAIR also significantly improved the average daily UPSIT (University of Pennsylvania Sell Identification Test) compared to placebo. The UPSIT ranged from 0 to 40 (0/worst-40/best). The LS mean difference for change from baseline to Week 24 in XOLAIR compared to placebo

was 3.81 points (95 % CI: 1.38, 6.24; p = 0.0024) in study 1 and 3.86 points (95 % CI: 1.57, 6.15; p = 0.0011) in study 2.

The effect on TNSS and SNOT-22 was observed as early as the first assessment at week 4 in both studies. Additionally, the effect on UPSIT was observed at the first assessment at week 8 in both studies. The LS mean difference for change from baseline at Week 4 in TNSS in XOLAIR compared to placebo was -0.97 (95 %: -1.61, -0.33) in study 1 and -1.18 (95 % CI: -1.76, -0.59) in study 2. The LS mean difference in change from baseline at Week 4 in SNOT-22 in XOLAIR compared to placebo was -10.43 (95 % CI: -15.08, -5.79) in study 1 and -8.84 (95 % CI: -13.84, -3.84) in study 2. The LS mean difference in change from baseline at Week 8 in UPSIT in XOLAIR compared to placebo was 3.72 (95 % CI: 1.54, 5.90) in study 1 and 5.12 (95 % CI: 2.57, 7.67) in study 2. These analyses were not pre-specified.

Additional secondary endpoint analyses included Week 16 assessments of NPS and NCS. XOLAIR significantly improved the NPS at week 16, (range 0/best-8/worst) compared to placebo. The LS mean difference for change from baseline to Week 16 in XOLAIR compared to placebo was -1.01 (95 % CI: -1.43, -0.60; p < 0.0001) in study 1 and -0.91 (95 % CI: -1.39, -0.44; p = 0.0002) in study 2. XOLAIR significantly improved the NCS at week 16, (range 0/best-3/worst) compared to placebo. The LS mean difference for change from baseline to Week 16 in average daily NCS in XOLAIR compared to placebo was -0.57 (95 % CI: -0.83, -0.31; p < 0.0001) in study 1 and of -0.59 (95 % CI: -0.87, -0.30; p < 0.0001) in study 2.

In a pre-specified pooled analysis of rescue treatment (systemic corticosteroids for ≥ 3 consecutive days or nasal polypectomy) during the 24-week treatment period, the proportion of patients requiring rescue treatment was lower in XOLAIR compared to placebo

(2.3 % versus 6.2 %, respectively). The odds-ratio of having taken rescue treatment in XOLAIR compared to placebo was 0.38 (95 % CI: 0.10, 1.49). There were no sino-nasal surgeries reported in either study.

Characteristics in patient populations:

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

The population pharmacokinetics of XOLAIR were analysed to evaluate the effects of demographic characteristics. Analyses of this data suggest that no dose adjustments are necessary for age (6 – 76 years), race, ethnicity, 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 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 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).

Renal and hepatic impairment:

There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment in allergic asthma and CSU patients. Caution should be exercised when administering XOLAIR in these patient populations.

Chronic Spontaneous Urticaria (CSU):

The clinical Phase III development program for CSU included three randomized, double-blind, placebo controlled, parallel-group, multi-centre studies: Q4881g, Q4882g and Q4883g. Studies Q4881g and Q4882g evaluated efficacy and safety of administration of 75 mg, 150 mg, or 300 mg XOLAIR every 4 weeks for 24 and 12 weeks respectively, with a 16-week

treatment-free follow-up period in patients (12 to 75 years) with refractory CSU despite H1 antihistamine treatment.

Study Q4883g evaluated safety and efficacy of 300 mg XOLAIR administered every 4 weeks for 24 weeks, with a 16-week treatment-free follow-up period in patients (12 to 75 years) with refractory CSU despite H1 and/or H2 antihistamine and/or leukotriene receptor antagonist (LTRA) treatment.

Table 1: Efficacy endpoints

Change from baseline to week 12 in weekly Itch Severity Score (ISS, range 0 - 21)	Primary endpoint in studies Q4881g and Q4882g Secondary endpoint in safety study Q4883g
Time to MID [a] response (decrease from baseline of ≥ 5 points) in weekly ISS up to week 12	Secondary endpoints in all three studies Q4881g, Q4882g and Q4883g
Change from Baseline to week 12 in Urticaria Activity score during a 7 day period (UAS7 [b], range 0 - 42)	
Proportion of patients with Urticaria Activity Score during a 7-Day Period ≤ 6 (UAS7 [b] ≤ 6) at week 12	

Proportion of patients with Urticaria Activity Score during a 7-Day Period = 0 (UAS7 [b] = 0) at week 12 [c]	
Changes from baseline in the weekly number of hives score at week 12	
Change from baseline to week 12 in overall Dermatology Life Quality Index (DLQI)	
Proportion of patients with angioedema-free days from week 4 to week 12 [d]	

[a] MID: Minimally Important Difference

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

[c] Post hoc analysis for study Q4882g

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

In studies Q4881g and Q4882g the 75 mg dose did not consistently meet either the primary efficacy endpoint (change from baseline to week 12 in weekly itch severity score) or a number of secondary endpoints. It was deemed not efficacious and therefore not further presented.

Change from baseline to week 12 in weekly itch severity score

The primary efficacy endpoint, change from baseline to week 12 in weekly itch severity score was met by both the 150 mg and 300 mg doses in studies Q4881g and Q4882g and by the 300 mg dose in Q4883g (see Table 2).

Table 2: Change from baseline to week 12 in weekly itch severity score, Studies Q4881g, Q4882g and Q4883g (mITT population*)

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

	Placebo	Omalizumab 150mg	Omalizumab 300mg
Difference in LS means vs. placebo[1]	-	-	-4.52
95 % CI for difference	-	-	−5.97, −3.08
P-value vs. placebo[2]	-	-	<0.0001

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

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

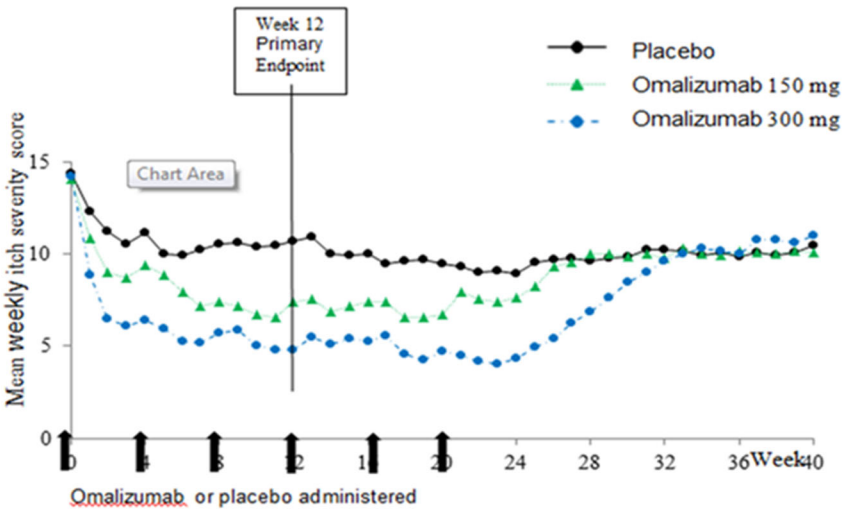
[1] The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (< 13 vs. ≥ 13) and baseline weight (< 80 kg vs. ≥ 80 kg).

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

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

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

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



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

Time to Minimal Important Difference (MID) response of 5 points in weekly ISS up to week 12

In studies Q4881g and Q4882g the times to attain MID of 5 points on the weekly itch severity score were statistically significantly shorter for patients in the 300 mg treatment groups, compared to the placebo groups with p-value < 0,0001. A shorter time was also observed for the 150 mg treatment groups compared to placebo with p = 0,0301 in study Q4881g and p = 0,0101 in study Q4882g. The median times for attaining MID response were 1 week in the 300 mg treatment group, 2 weeks in the 150 mg groups and 4 weeks for placebo. Similar results were observed in study Q4883g with p < 0,0001 (median time to MID response was 2 weeks in the 300 mg treatment group and 5 weeks in the placebo group.

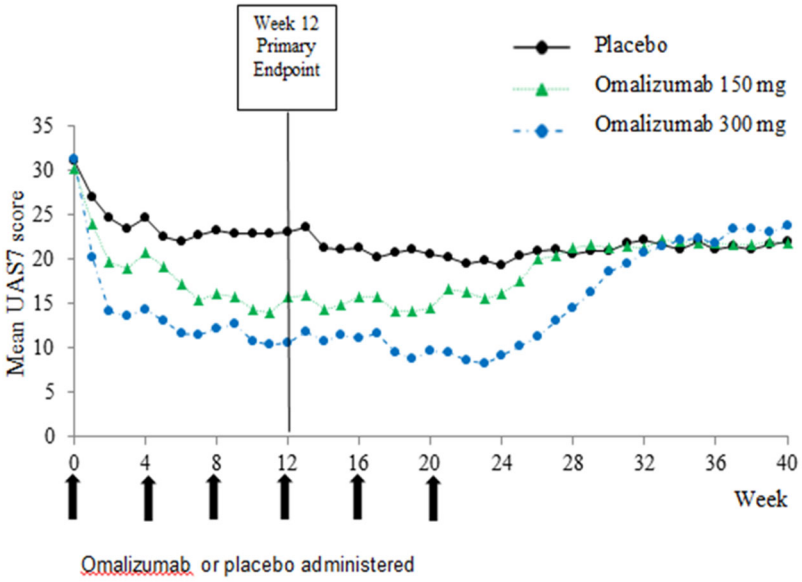
Change from baseline to week 12 in UAS7

In the phase III studies the omalizumab 150 mg and 300 mg treatment groups showed a statistically significant difference from placebo in mean change from baseline to week 12 in UAS7 (Figure 2 for study Q4881g). Statistical significance ($p < 0,0001$) was achieved in all three studies for the 300 mg treatment group, and in studies Q4881g ($p = 0,0008$) and Q4882g ($p = 0,0001$) for the 150 mg treatment group.

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

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

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



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

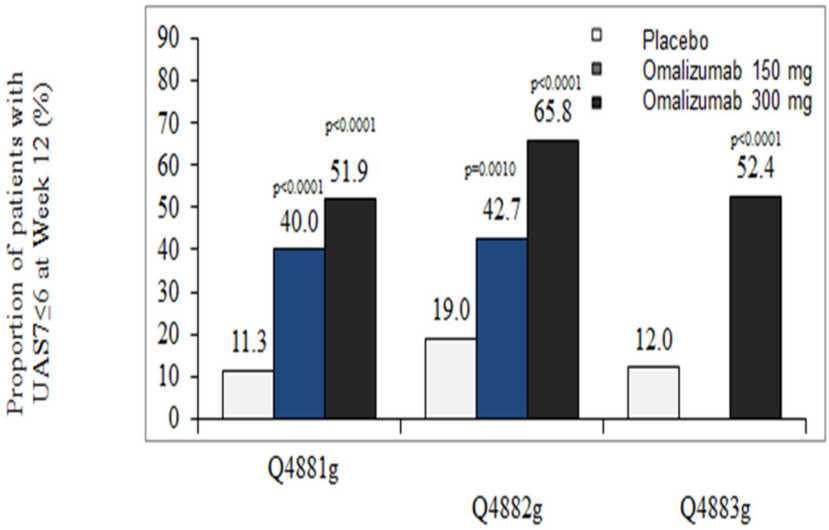
Proportion of patients with UAS7 ≤ 6 at week 12

The response rates for UAS7 ≤ 6 at week 12, ranging from 52 - 66 % for the 300 mg treatment group (51,9 % in Q4881g, 65,8 % in Q4882g and 52,4 % in Q4883g; were all statistically significantly higher compared to 11 - 19 % for the placebo groups (11,3 % in Q4881g, 19,0 % in Q4882g and 12,0 % in Q4883g). In the 150 mg treatment groups, the proportion of patients with UAS7 ≤ 6 at week 12 ranging from 40 – 43 % (40,0 % in Q4881g, 42,7 % in Q4882g) showed a clinically notable difference to the placebo groups (11,3 % and 19,0 %; p < 0,0001 and p = 0,0010, respectively).

The proportions of patients with a UAS7 ≤ 6 at week 12 are shown in Figure 3. The response rates ranged from 52 - 66 % (300 mg dose; all were statistically significantly higher compared to 11 to 19 % in the placebo group (p < 0,0001).

The response rates for the 150 mg dose show a notable difference (40-43 %; p ≤ 0,001) compared to placebo.

Figure 3: Proportion of patients with UAS7 ≤ 6 at week 12, Studies Q4881g, Q4882g and Q4883g



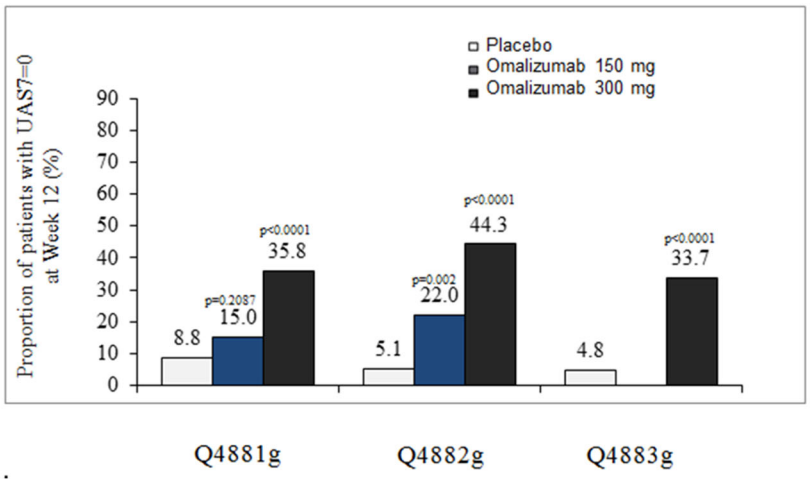
p-values are omalizumab vs placebo group

Proportion of patients with UAS7 = 0 at week 12

The proportion of patients with a complete response, defined by a UAS7 = 0 at week 12, was statistically significant for the 300 mg treatment groups compared to placebo, ranging from 34 to 44 % (35,8 % in Q4881g, 44,3 % in Q4882g, and 33,7 % in Q4883g, versus 8,8 % in Q4881g, 5,1 % in Q4882g and 4,8 % in Q4883g with placebo; all p < 0,0001). It was numerically better for the 150 mg treatment groups, with 15,0 % in Q4881g and 22,0 % in Q4882g compared placebo.

The proportion of patients with a complete response shown by a UAS7 = 0 at week 12 ranged from 34 to 44 % (300 mg dose, statistically significant, all p < 0,0001) compared to 5 to 9 % in the placebo groups. In the 150 mg treatment groups, a clinically notable difference compared to placebo was observed ranging from 15 – 22 % (Figure 4).

Figure 4: Proportion of patients with UAS7 = 0 at week 12, Studies Q4881g, Q4882g and Q4883g



p-values are omalizumab vs placebo group

Prospective analysis in studies Q4881g and Q4883g, and as post-hoc analysis in study Q4882g

Changes from baseline in the weekly number of hives score at week 12

In all three phase III studies, the difference from placebo in mean changes from baseline in the weekly number of hives score at week 12 for the 300 mg treatment groups was statistically significant displaying a decrease number of hives score compared to placebo (-11,35 in Q4881g, -11,97 in Q4882g and -10,46 in Q4883g versus -4,37, -5,22 and -4,49 for the

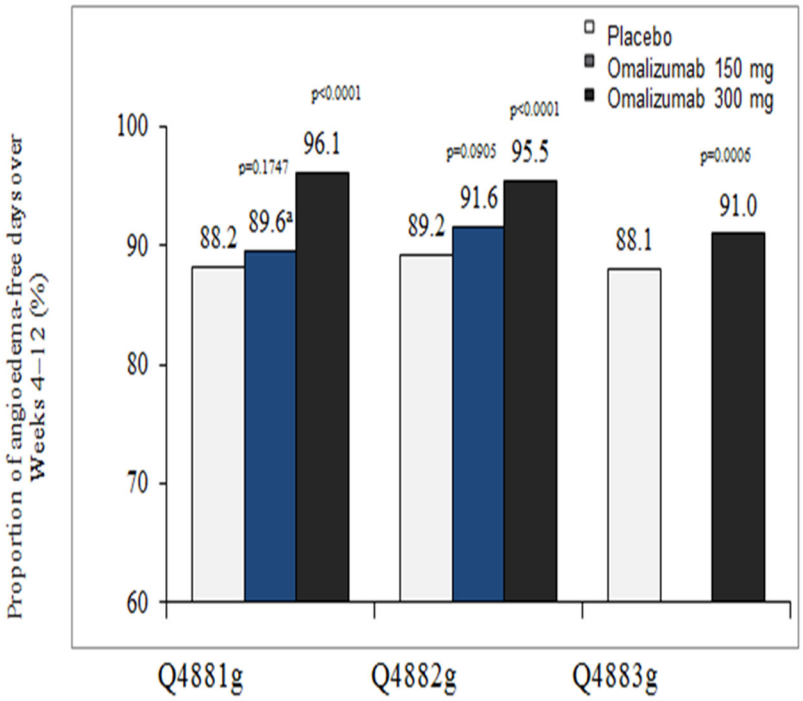
corresponding placebo groups. For the 150 mg treatment groups, the mean changes were -7,78 (p = 0,0017) in Q4881g and -9,75 (p < 0,001) in Q4882g.

Proportion of angioedema-free days from week 4 to week 12

In all three phase III studies the 300 mg treatment groups consistently achieved the highest mean proportion of angioedema-free days from week 4 to week 12 (96,1 % in Q4881 g; 95,5 % in Q4882g; 91 % in Q4883g; compared to the placebo group (88,2 %, 89,2 %, 88,1 %, respectively; all p < 0,001). In the 150 mg treatment groups, the mean proportions of angioedema-free days for the same time period for studies Q4881 g and Q4882 g were 89,6 % and 91,6 % respectively, with no statistically significant difference to placebo.

In all three Phase III studies the 300 mg treatment groups consistently achieved the highest mean proportion of angioedema-free days from week 4 to week 12 (91 to 96 %). The increase in the proportion of angioedema-free days compared to placebo was statistically significant (p < 0,001) (Figure 5). In the 150 mg treatment group, the mean proportions of angioedema-free days for the same time period for studies Q4881g and Q4882 were 89,6 % and 91,6 % respectively. The corresponding placebo values for the same studies were 88,2 % and 89,2 %. In both of these studies, the differences from placebo did not achieve statistical significance for the 150 mg dose.

Figure 5: Proportion of angioedema-free days from week 4 to week 12, Studies Q4881g, Q4882g and Q4883g



p values are omalizumab vs placebo group

[a]Not evaluated for statistical significance in accordance with the type I error control plan.

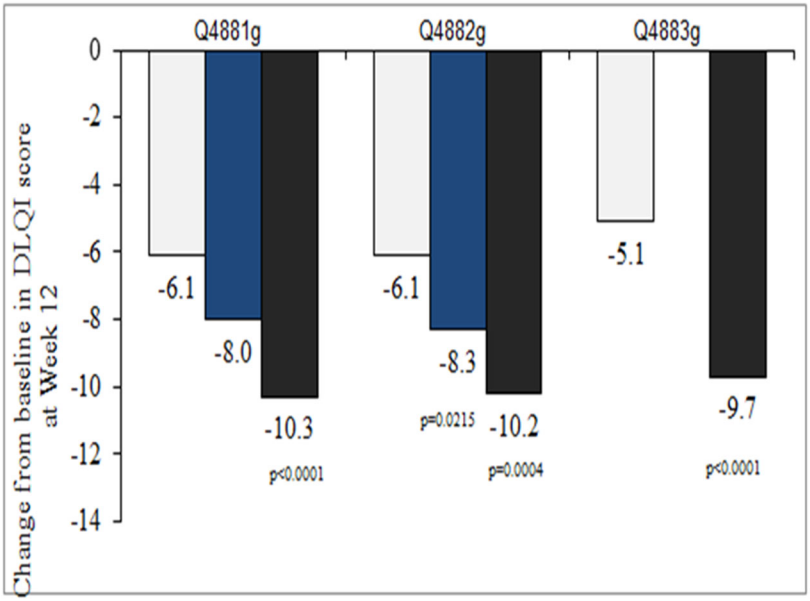
The mean proportion of angioedema-free days from week 4 to week 12 was calculated for the entire study population, including those patients asymptomatic for angioedema.

Change from baseline to week 12 in overall Dermatology Life Quality Index (DLQI)

In all three phase III studies, the mean change from baseline to week 12 in the overall DLQI for the 300 mg treatment groups was statistically significantly greater than placebo showing an improvement of 10,3 points in Q4881g, 10,2 in Q4882 g and 9,7 in Q4883 g versus 6,1; 6,1; and 5,1 for the corresponding placebo groups (all $p < 0,001$). For the 150 mg treatment groups, the mean changes were 8,0 points ($p = 0,2286$) in Q4881g and 8,3 points ($p = 0,0215$) in Q4882g versus 6,1 for each of the corresponding placebo groups.

In all three Phase III studies, the change from baseline to week 12 in the overall DLQI for the 300 mg treatment group was statistically significantly (p < 0,001) greater compared to placebo. The 150 mg omalizumab group showed a clinically notable difference to placebo in study Q4882 g (p = 0,022) (Figure 6).

Figure 6: Change from baseline to week 12 in overall Dermatology Life Quality Index, Studies Q4881g, Q4882g and Q4883g



DLQI = Dermatology Life Quality Index

p values are omalizumab vs placebo groups

Efficacy after 48 weeks of treatment 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 randomized 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 ≥ 12 for at least 2 consecutive weeks post-randomization 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 %).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solution for injection in pre-filled syringe

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

6.2 Incompatibilities

Solution for injection in pre-filled syringe:

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

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Storage of the XOLAIR 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 20 minutes). Leave the syringe in

the box to protect it from light. The time that the syringe is kept at room temperature (25 °C) before use must not exceed 2 days (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.
- Any unused product or waste material should be discarded.
- Store in the original package/container.

6.5 Nature and contents of container

XOLAIR pre-filled syringe:

The primary packaging for XOLAIR 75 mg/0.5 mL and 150 mg/1.0 mL consists of the following components:

- a type I glass syringe barrel with a staked stainless steel needle where the needle is fixed to the syringe barrel with an adhesive,
- a rubber plunger stopper, and
- a rigid needle shield composed of a rubber needle shield covered by a rigid shell, which are assembled with a needle safety device.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 The holder of the certificate of registration

NOVARTIS SOUTH AFRICA (PTY) LTD

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg, South Africa

2090

+27 10 347 6600

8 Registration number(s)

XOLAIR 75 mg, Solution for injection in pre-filled syringe: 55/34/0713

XOLAIR 150 mg, Solution for injection in pre-filled syringe: 55/34/0714

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

XOLAIR 75 mg/0,5 ml and XOLAIR 150 mg/1,0 ml: 25 May 2021

10 DATE OF REVISION OF TEXT

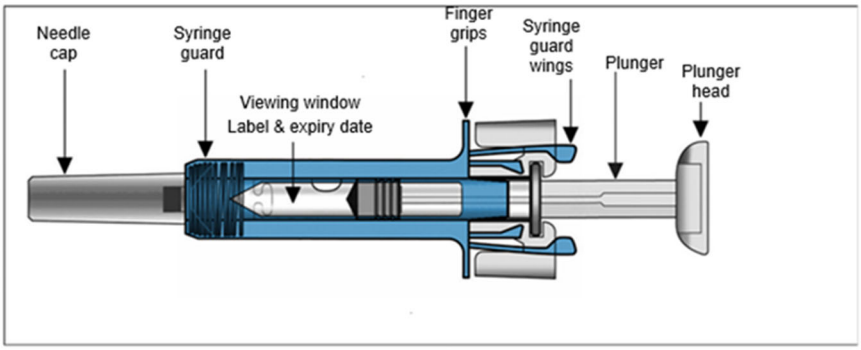
08 April 2025

Instructions for use and handling - XOLAIR solution for injection in 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.

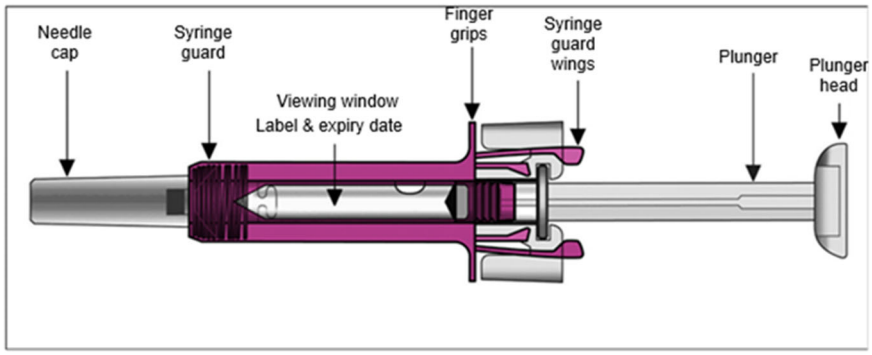
XOLAIR pre-filled syringe is available in two strengths, 75 mg and 150 mg. You may receive one or both strengths from the pharmacy.

Your XOLAIR 75/0 ,5ml mg 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 needle stick injuries.

Your XOLAIR 150 mg/1,0 ml 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 needle stick injuries.

Other items you need for your injection:

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



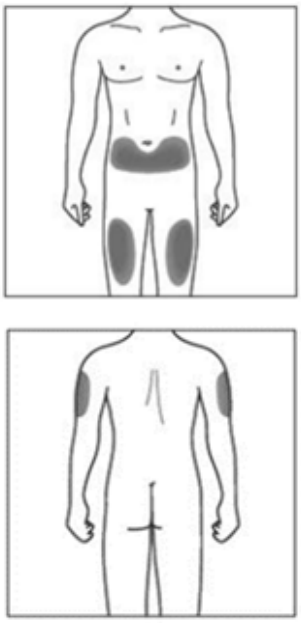
Important safety information

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.

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 centimeters 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.

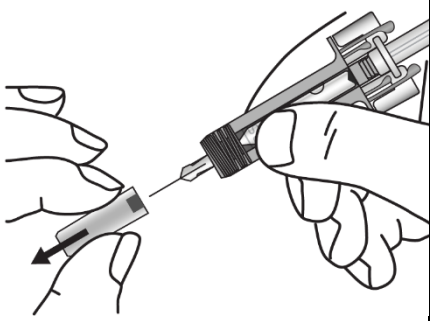
Preparing the XOLAIR pre-filled syringe for use

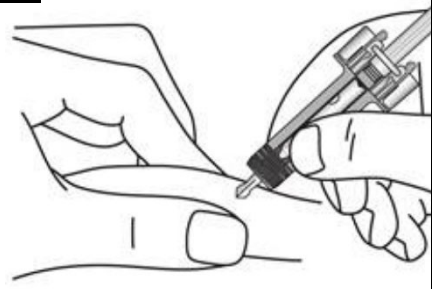
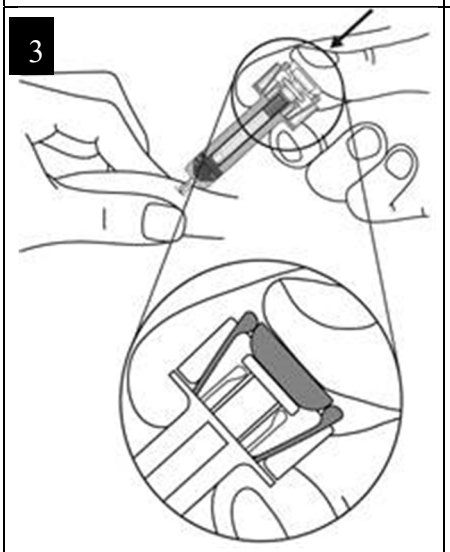
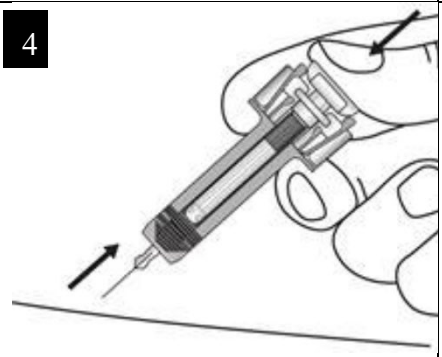
Note: Depending on the dose prescribed to you by your doctor, you may need to prepare one or more pre-filled syringes and inject the contents of them all. The following table gives examples of how many injections of each dose strength you need for a given dose:

Dose	Syringes needed for the dose			
75 mg	1 blue (75 mg)			
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 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 the XOLAIR 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.

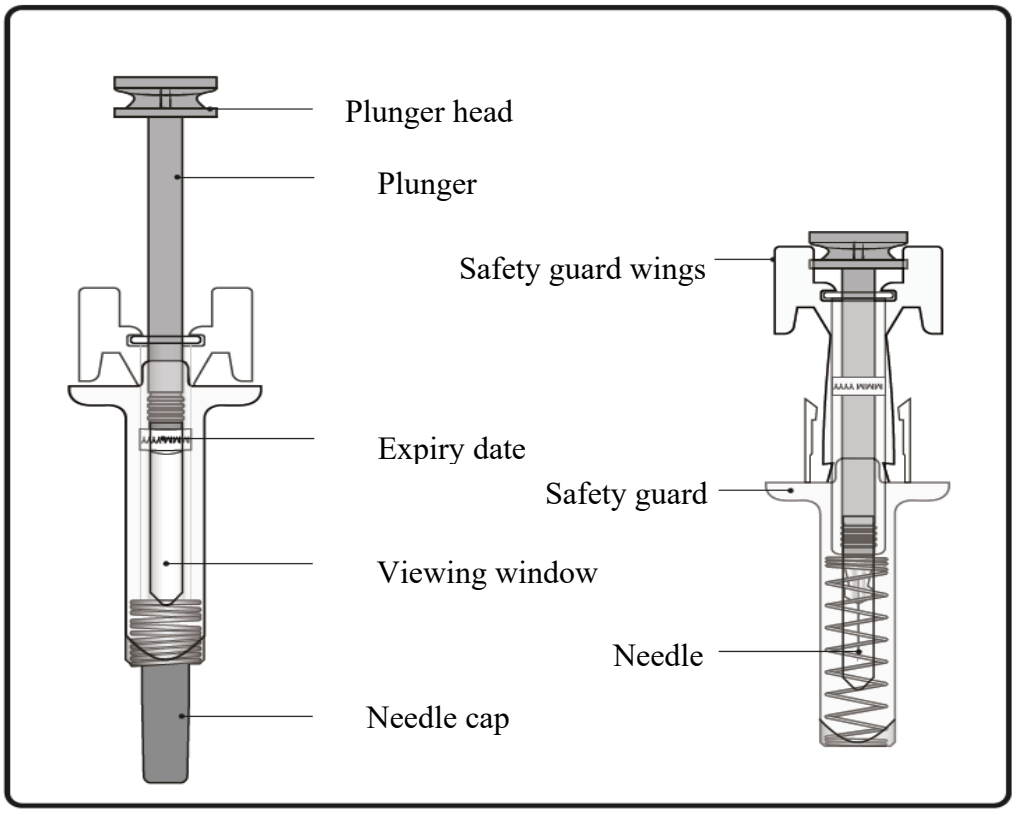
Instructions for use and handling – XOLAIR solution for injection in pre-filled syringe (pre-filled syringe with 27-gauge staked needle)

This “Instructions for Use” contains 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 this “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. It can be placed back in the refrigerator if necessary.
- **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.

Important: 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.

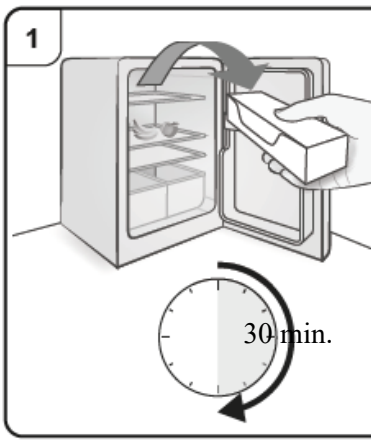
Contact your doctor if you have questions on the Dosing Table.



DOSE	Prefilled syringes needed for dose	Blue 75 mg	Purple 150 mg	Gray 300 mg
75 mg	1 blue	1		
150 mg	1 purple		1	
225 mg	1 blue + 1 purple	1	1	
300 mg (ages 12 and up)	1 gray			1
300 mg (children under age 12)	2 purple		2	
375 mg (ages 12 and up)	1 blue + 1 gray	1		1
375 mg (children under age 12)	1 blue + 2 purple	1	2	
450 mg (ages 12 and up)	1 purple + 1 gray		1	1
450 mg (children under age 12)	3 purple		3	
525 mg (ages 12 and up)	1 blue + 1 purple + 1 gray	1	1	1
525 mg (children under age 12)	1 blue + 3 purple	1	3	
600 mg (ages 12 and up)	2 gray			2
600 mg (children under age 12)	4 purple		4	

Prepare to inject XOLAIR

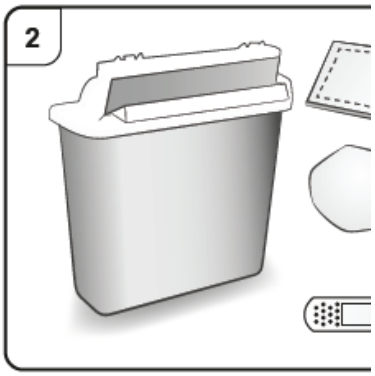
Step 1. Bring to room temperature



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.

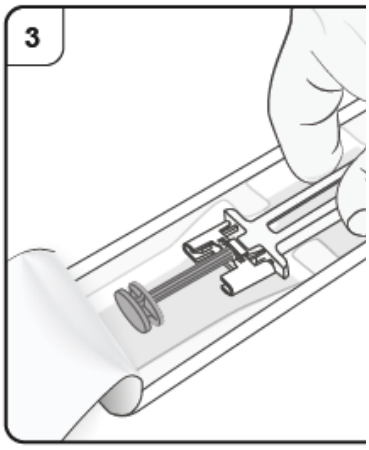
Step 2. Gather supplies



You will need the following supplies (not included in the carton):

- Alcohol wipe
- Cotton ball or gauze pad
- Sharps disposal container
- Adhesive plaster

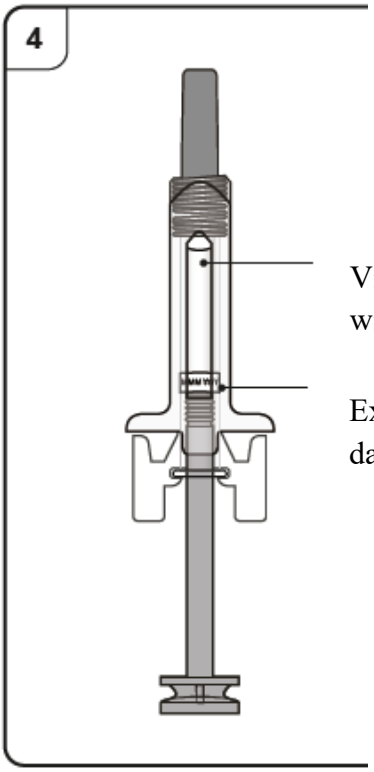
Step 3. Unpack



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 color may vary from colorless 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.

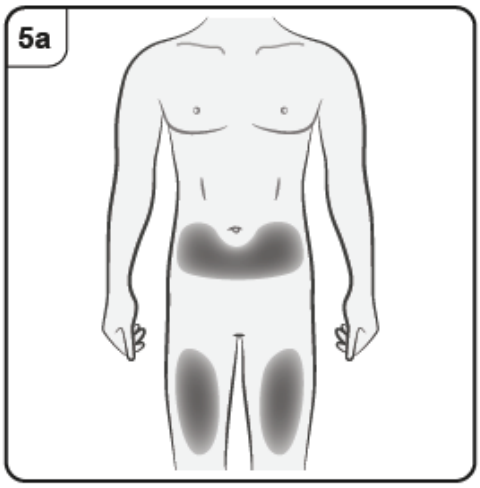
In all of these cases, contact your doctor, nurse or pharmacist.

Step 5. Choose injection site

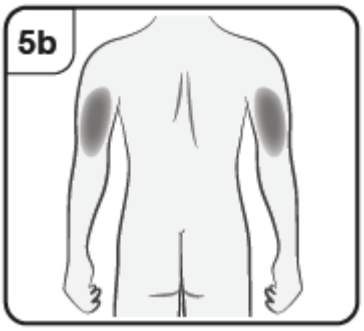
You should inject into the front of the thighs or the lower stomach area but not the area 5 cm around the belly button.

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.

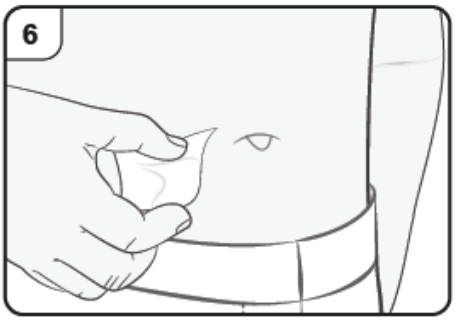


If your caregiver, doctor or nurse is giving you the injection, they may also inject into the outer upper arm.



Inject with XOLAIR

Step 6. Clean injection site

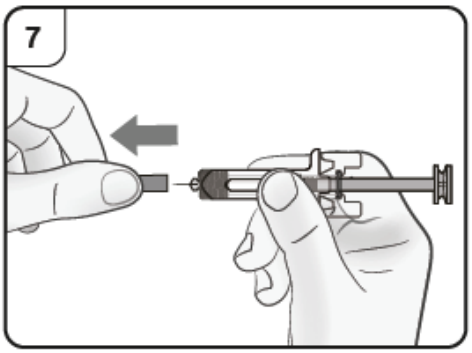


Clean your hands.

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

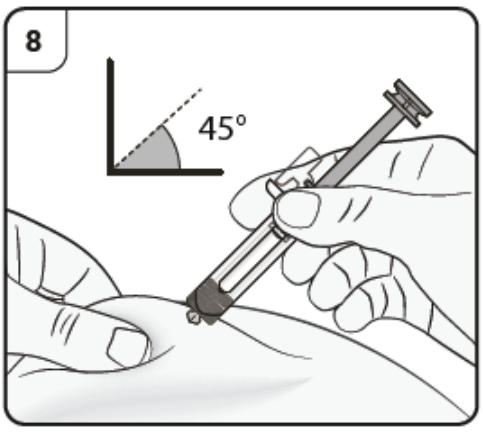


Firmly pull straight to remove the needle cap from the pre-filled syringe. You may see a drop of liquid at the end of the needle. This is normal.

Do not put the needle cap back on.

Throw away the needle cap.

Step 8. Insert needle

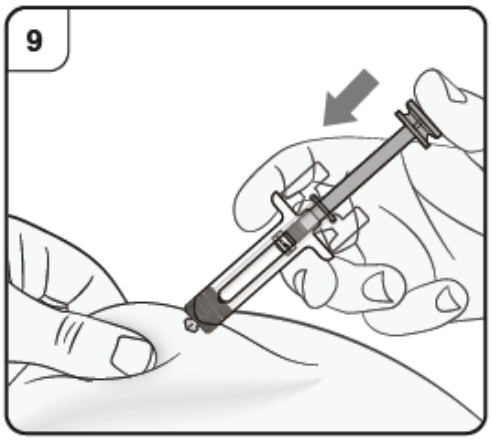


Gently pinch the skin at the injection site and hold the pinch throughout the injection. With the other hand insert the needle into the skin at an angle of approximately 45 degrees as shown.

Do not press the plunger while inserting the needle.

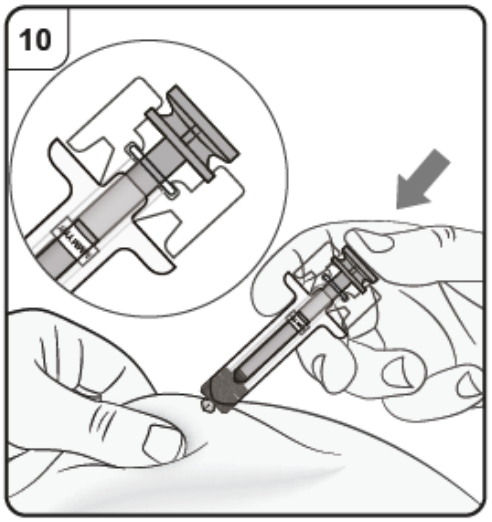
Step 9. Start injection

Continue to pinch the skin. Slowly press the plunger **as far as it will go**. This will ensure that a full dose is injected.

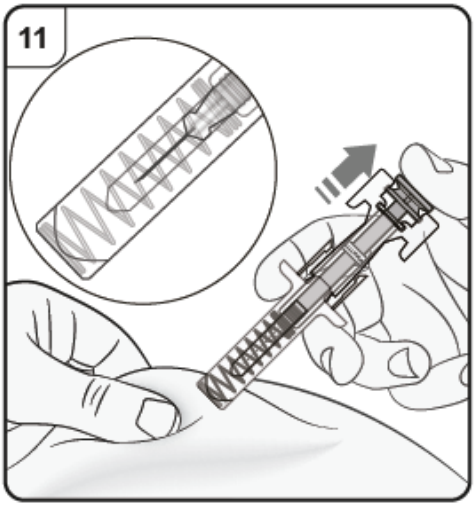


Step 10. Complete injection

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 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.

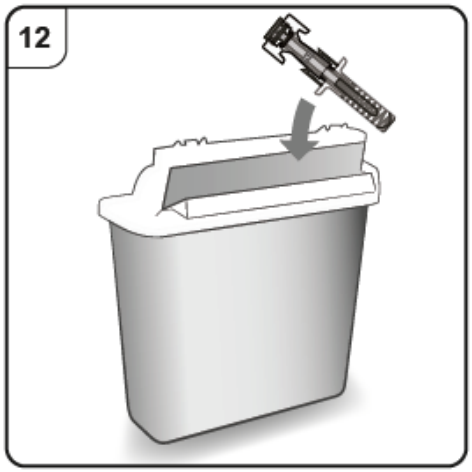
Repeat Step 2 to Step 12 again for all the pre-filled syringes needed to deliver your full dose.

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 throw away the pre-filled syringe into household waste.

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.