ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Omlyclo 75 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergic asthma

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

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

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

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

Chronic rhinosinusitis with nasal polyps (CRSwNP)

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

4.2 Posology and method of administration

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

Posology

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

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

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts.

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

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

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

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

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

	Body weight (kg)									
Baseline IgE (IU/ml)	≥ 20–25*	> 25–30*	> 30–40	> 40–50	> 50–60	> 60–70	> 70–80	> 80–90	> 90–125	> 125–150
≥ 30–100	75	75	75	150	150	150	150	150	300	300
> 100–200	150	150	150	300	300	300	300	300	450	600
> 200–300	150	150	225	300	300	450	450	450	600	
> 300–400	225	225	300	450	450	450	600	600		
> 400–500	225	300	450	450	600	600				
> 500–600	300	300	450	600	600					
> 600–700	300		450	600						
> 700–800	ADMINISTRATION EVERY 2 WEEKS SEE TABLE 3									
> 800–900										
> 900–1,000										
> 1,000–1,100										

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

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

	Body weight (kg)									
Baseline IgE (IU/ml)	≥ 20–25*	> 25–30*	> 30–40	> 40–50	> 50–60	> 60–70	> 70–80	> 80–90	> 90–125	> 125–150
≥ 30–100	ADMINISTRATION EVERY 4 WEEKS SEE TABLE 2									
> 100–200										
> 200–300										375
> 300–400									450	525
> 400–500							375	375	525	600
> 500–600						375	450	450	600	
> 600–700		225			375	450	450	525		
> 700–800	225	225	300	375	450	450	525	600		
> 800–900	225	225	300	375	450	525	600			
> 900–1,000	225	300	375	450	525	600				
> 1,000–1,100	225	300	375	450	600					
> 1,100–1,200	300	300	450	525	600	Insufficient data to recommend a dose				
> 1,200–1,300	300	375	450	525						
> 1,300–1,500	300	375	525	600						

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

Treatment duration, monitoring and dose adjustments

Allergic asthma

Omlyclo is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12 – 16 weeks for omalizumab treatment to show effectiveness. At 16 weeks after commencing Omlyclo therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue treatment following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician's overall assessment of treatment effectiveness).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

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

Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

Discontinuation of treatment generally results in a return to elevated free IgE levels and associated symptoms. Total IgE levels are elevated during treatment and remain elevated for up to one year after

the discontinuation of treatment. Therefore, re-testing of IgE levels during Omlyclo 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 Omlyclo has been interrupted for one year or more.

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

Special populations
Elderly (65 years of age and older)
There are limited data available on the use of omalizumab in patients older than 65 years but there is no evidence that elderly patients require a different dose from younger adult patients.

Renal or hepatic impairment
There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of omalizumab. Because omalizumab clearance at clinical doses is dominated by the reticular endothelial system (RES) it is unlikely to be altered by renal or hepatic impairment. While no particular dose adjustment is recommended for these patients, omalizumab should be administered with caution (see section 4.4).

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

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

Method of administration

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

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

Patients with no known history of anaphylaxis may self-inject Omlyclo 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 Omlyclo according to the instructions provided in the package leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

General

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

Omalizumab has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Omalizumab is not indicated for the treatment of these conditions.

Omalizumab therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). Caution should be exercised when administering omalizumab in these patient populations.

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

Immune system disorders

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

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

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

Churg-Strauss syndrome and hypereosinophilic syndrome
Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids.

In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy.

In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

Discontinuation of omalizumab should be considered in all severe cases with the above mentioned immune system disorders.

Parasitic (helminth) infections

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Allergic asthma

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

Chronic rhinosinusitis with nasal polyps (CRSwNP)

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300 – 1,000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foeto/neonatal toxicity. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to omalizumab showed the prevalence of major congenital anomalies was similar

(8.1 % vs. 8.9 %) between EXPECT and disease-matched (moderate and severe asthma) patients. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

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

Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3).

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

Breast-feeding

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

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

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

Summary of the safety profile
During allergic asthma clinical trials in adult and adolescent patients 12 years of age and older, the most commonly reported adverse reactions were headaches and injection site reactions, including injection site pain, swelling, erythema and pruritus. In clinical trials in children 6 to < 12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity. In clinical trials in patients ≥ 18 years of age in CRSwNP, the most commonly reported adverse reactions were headache, dizziness, arthralgia, abdominal pain upper and injection site reactions.

Tabulated list of adverse reactions
Table 4 lists the adverse reactions recorded in clinical studies in the total allergic asthma and CRSwNP safety population treated with omalizumab by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000). Reactions reported in

the post-marketing setting are listed with frequency not known (cannot be estimated from the available data).

Table 4 Adverse reactions in allergic asthma and CRSwNP

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

*: Very common in children 6 to < 12 years of age
**: In children 6 to < 12 years of age
[#]: Common in nasal polyp trials
†: Unknown in allergic asthma trials

Description of selected adverse reactions

Immune system disorders
For further information, see section 4.4.

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

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

Platelets
In clinical trials few patients had platelet counts below the lower limit of the normal laboratory range. Isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

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

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

Reporting of suspected adverse reactions

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

4.9 Overdose

Maximum tolerated dose of Omlyclo has not been determined. Single intravenous doses up to 4,000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period and this dose did not result in any untoward acute effects.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mechanism of action

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and prevents binding of IgE to FcεRI (high-affinity IgE receptor) on basophils and mast cells, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

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

Pharmacodynamic effects

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

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

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

Clinical efficacy and safety

Allergic asthma
Adults and adolescents ≥ 12 years of age
The efficacy and safety of omalizumab were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12 – 79 years, who had reduced lung function (FEV_1 40 – 80 % predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and a long-acting beta2-agonist. Subcutaneous omalizumab or placebo were administered as add-on therapy to > 1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22 %, 27 %, and 35 % of patients, respectively).

The rate of asthma exacerbations requiring treatment with bursts of systemic corticosteroids was the primary endpoint. Omalizumab reduced the rate of asthma exacerbations by 19 % ($p = 0.153$). Further evaluations which did show statistical significance ($p < 0.05$) in favour of omalizumab included reductions in severe exacerbations (where patient's lung function was reduced to below 60 % of personal best and requiring systemic corticosteroids) and asthma-related emergency visits (comprised of hospitalisations, emergency room, and unscheduled doctor visits), and improvements in Physician's overall assessment of treatment effectiveness, Asthma-related Quality of Life (AQL), asthma symptoms and lung function.

In a subgroup analysis, patients with pre-treatment total IgE ≥ 76 IU/ml were more likely to experience clinically meaningful benefit to omalizumab. In these patients in study 1 omalizumab

reduced the rate of asthma exacerbations by 40 % (p = 0.002). In addition more patients had clinically meaningful responses in the total IgE ≥ 76 IU/ml population across the omalizumab severe asthma programme. Table 5 includes results in the study 1 population.

Table 5 Results of study 1

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

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

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

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

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

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

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

Physician's overall assessment of treatment effectiveness:
Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), day and night time symptoms, rescue medication use, spirometry and exacerbations. In all five studies a significantly greater proportion of omalizumab-treated patients were

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

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

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

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

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

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

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

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

Table 6 Demographics and baseline characteristics of nasal polyp studies

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
Bilateral endoscopic nasal polyp score (NPS): mean (SD), range 0–8	6.2 (1.0)	6.3 (0.9)
Nasal congestion score (NCS): mean (SD), range 0–3	2.4 (0.6)	2.3 (0.7)
Sense of smell score: mean (SD), range 0–3	2.7 (0.7)	2.7 (0.7)
SNOT-22 total score: mean (SD) range 0–110	60.1 (17.7)	59.5 (19.3)
Blood eosinophils (cells/µl): mean (SD)	346.1 (284.1)	334.6 (187.6)
Total IgE IU/ml: mean (SD)	160.9 (139.6)	190.2 (200.5)
Asthma (%)	53.6	60.6
Mild (%)	37.8	32.5
Moderate (%)	58.1	58.4
Severe (%)	4.1	9.1
Aspirin exacerbated respiratory disease (%)	19.6	35.4
Allergic rhinitis	43.5	42.5

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

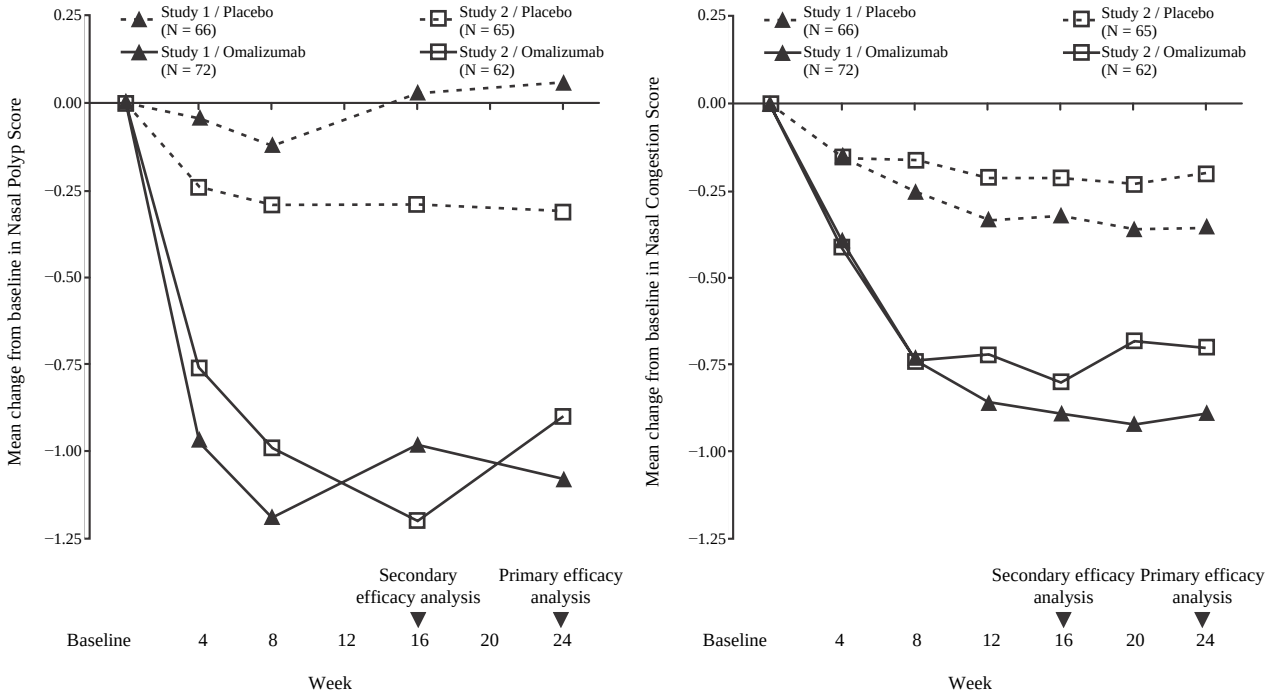
The co-primary endpoints were bilateral nasal polyps score (NPS) and average daily nasal congestion score (NCS) at Week 24. In both nasal polyp studies 1 and 2, patients who received omalizumab had statistically significant greater improvements from baseline at Week 24 in NPS and weekly average NCS than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

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

	Nasal polyp study 1		Nasal polyp study 2		Nasal polyp pooled results	
	Placebo	**Omalizumab**	**Placebo**	**Omalizumab**	**Placebo**	**Omalizumab**
N	66	72	65	62	131	134
Nasal polyp score						
Baseline mean	6.32	6.19	6.09	6.44	6.21	6.31
LS mean change at	0.06	−1.08	−0.31	−0.90	−0.13	−0.99
Week 24						
Difference (95 % CI)	−1.14 (−1.59, −069)		−0.59 (−1.05, −012)		−0.86 (−1.18, −0.54)	
p-value	< 0.0001		0.0140		< 0.0001	
7-day average of daily nasal congestion score						
Baseline mean	2.46	2.40	2.29	2.26	2.38	2.34
LS mean change at	−0.35	−0.89	−0.20	−0.70	−0.28	−0.80
Week 24						
Difference (95 % CI)	−0.55 (−0.84, −0.25)		−0.50 (−0.80, −0.19)		−0.52 (−0.73, −0.31)	
p-value	0.0004		0.0017		< 0.0001	
TNSS						
Baseline mean	9.33	8.56	8.73	8.37	9.03	8.47
LS mean change at	−1.06	−2.97	−0.44	−2.53	−0.77	−2.75
Week 24						
Difference (95 % CI)	−1.91 (−2.85, −0.96)		−2.09 (−3.00, −1.18)		−1.98 (−2.63, −1.33)	
p-value	0.0001		< 0.0001		< 0.0001	
SNOT-22						
Baseline mean	60.26	59.82	59.80	59.21	60.03	59.54
LS mean change at	−8.58	−24.70	−6.55	−21.59	−7.73	−23.10
Week 24						
Difference (95 % CI)	−16.12 (−21.86, −10.38)		−15.04 (−21.26, −8.82)		−15.36 (−19.57, −11.16)	
p-value	< 0.0001		< 0.0001		< 0.0001	
(MID = 8.9)						
UPSIT						
Baseline mean	13.56	12.78	13.27	12.87	13.41	12.82
LS mean change at	0.63	4.44	0.44	4.31	0.54	4.38
Week 24						
Difference (95 % CI)	3.81 (1.38, 6.24)		3.86 (1.57, 6.15)		3.84 (2.17, 5.51)	
p-value	0.0024		0.0011		< 0.0001	

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

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



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

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

5.2 Pharmacokinetic properties

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

Absorption

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

Administration of omalizumab manufactured as a lyophilised or liquid formulation resulted in similar serum concentration-time profiles of omalizumab.

Distribution

In vitro, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than one million Daltons in molecular weight are not observed *in vitro* or *in vivo*. The apparent volume of distribution in patients following subcutaneous administration was 78 ± 32 ml/kg.

Elimination

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

Characteristics in patient populations

Age, Race/Ethnicity, Gender, Body Mass Index
The population pharmacokinetics of omalizumab were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for age (6 – 76 years for patients with allergic asthma; 18 to 75 years for patients with CRSwNP), race/ethnicity, gender or Body Mass Index (see section 4.2).

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

5.3 Preclinical safety data

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

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

Formal carcinogenicity studies have not been conducted with omalizumab.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

24 months.
The product may be kept for a total of 7 days at 25 °C.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

A pack containing 1 pre-filled syringe.

6.6 Special precautions for disposal and other handling

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

Disposal instructions

Dispose of the used syringe immediately in a sharps container.

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

7. MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1817/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Omlyclo 150 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection)

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergic asthma

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

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

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

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

Chronic rhinosinusitis with nasal polyps (CRSwNP)

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

Chronic spontaneous urticaria (CSU)

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

4.2 Posology and method of administration

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

Posology

Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)
Dosing for allergic asthma and CRSwNP follows the same dosing principles. The appropriate dose and frequency of omalizumab for these conditions is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements, 75 to 600 mg of omalizumab in 1 to 4 injections may be needed for each administration.

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

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts.

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

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

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

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

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

	Body weight (kg)									
Baseline IgE (IU/ml)	≥ 20–25*	> 25–30*	> 30–40	> 40–50	> 50–60	> 60–70	> 70–80	> 80–90	> 90–125	> 125–150
≥ 30–100	75	75	75	150	150	150	150	150	300	300
> 100–200	150	150	150	300	300	300	300	300	450	600
> 200–300	150	150	225	300	300	450	450	450	600	
> 300–400	225	225	300	450	450	450	600	600		
> 400–500	225	300	450	450	600	600				
> 500–600	300	300	450	600	600					
> 600–700	300		450	600						
> 700–800	ADMINISTRATION EVERY 2 WEEKS SEE TABLE 3									
> 800–900										
> 900–1,000										
> 1,000–1,100										

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

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

	Body weight (kg)									
Baseline IgE (IU/ml)	≥ 20–25*	> 25–30*	> 30–40	> 40–50	> 50–60	> 60–70	> 70–80	> 80–90	> 90–125	> 125–150
≥ 30–100	ADMINISTRATION EVERY 4 WEEKS SEE TABLE 2									
> 100–200										
> 200–300										375
> 300–400									450	525
> 400–500							375	375	525	600
> 500–600						375	450	450	600	
> 600–700		225			375	450	450	525		
> 700–800	225	225	300	375	450	450	525	600		
> 800–900	225	225	300	375	450	525	600			
> 900–1,000	225	300	375	450	525	600				
> 1,000–1,100	225	300	375	450	600					
> 1,100–1,200	300	300	450	525	600	Insufficient data to recommend a dose				
> 1,200–1,300	300	375	450	525						
> 1,300–1,500	300	375	525	600						

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

Treatment duration, monitoring and dose adjustments

Allergic asthma

Omlyclo is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12 – 16 weeks for omalizumab treatment to show effectiveness. At 16 weeks after commencing Omlyclo therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue treatment following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician's overall assessment of treatment effectiveness).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

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

Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

Discontinuation of treatment generally results in a return to elevated free IgE levels and associated symptoms. Total IgE levels are elevated during treatment and remain elevated for up to one year after

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

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

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

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

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

Special populations
Elderly (65 years of age and older)
There are limited data available on the use of omalizumab in patients older than 65 years but there is no evidence that elderly patients require a different dose from younger adult patients.

Renal or hepatic impairment
There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of omalizumab. Because omalizumab clearance at clinical doses is dominated by the reticular endothelial system (RES) it is unlikely to be altered by renal or hepatic impairment. While no particular dose adjustment is recommended for these patients, omalizumab should be administered with caution (see section 4.4).

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

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

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

Method of administration

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

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

Patients with no known history of anaphylaxis may self-inject Omlyclo 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 Omlyclo according to the instructions provided in the package leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

General

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

Omalizumab has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Omalizumab is not indicated for the treatment of these conditions.

Omalizumab therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). Caution should be exercised when administering omalizumab in these patient populations.

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

Immune system disorders

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

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

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

Churg-Strauss syndrome and hypereosinophilic syndrome
Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids.

In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy.

In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

Discontinuation of omalizumab should be considered in all severe cases with the above mentioned immune system disorders.

Parasitic (helminth) infections

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Allergic asthma

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

Chronic rhinosinusitis with nasal polyps (CRSwNP)

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

Chronic spontaneous urticaria (CSU)

In clinical studies in CSU, omalizumab was used in conjunction with antihistamines (anti-H1, anti-H2) and leukotriene receptor antagonists (LTRAs). There was no evidence that the safety of omalizumab was altered when used with these medicinal products relative to its known safety profile in allergic asthma. In addition, a population pharmacokinetic analysis showed no relevant effect of H2 antihistamines and LTRAs on omalizumab pharmacokinetics (see section 5.2).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3).

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

Breast-feeding

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

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

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

Summary of the safety profile
During allergic asthma clinical trials in adult and adolescent patients 12 years of age and older, the most commonly reported adverse reactions were headaches and injection site reactions, including injection site pain, swelling, erythema and pruritus. In clinical trials in children 6 to < 12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity. In clinical trials in patients ≥ 18 years of age in CRSwNP, the most commonly reported adverse reactions were headache, dizziness, arthralgia, abdominal pain upper and injection site reactions.

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

Table 4 Adverse reactions in allergic asthma and CRSwNP

Infections and infestations	
Uncommon	Pharyngitis
Rare	Parasitic infection
Blood and lymphatic system disorders	
Not known	Idiopathic thrombocytopenia, including severe cases
Immune system disorders	
Rare	Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development
Not known	Serum sickness, may include fever and lymphadenopathy
Nervous system disorders	
Common	Headache*
Uncommon	Syncope, paraesthesia, somnolence, dizziness[#]
Vascular disorders	
Uncommon	Postural hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	Allergic bronchospasm, coughing
Rare	Laryngoedema
Not known	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
Gastrointestinal disorders	
Common	Abdominal pain upper**[,#]
Uncommon	Dyspeptic signs and symptoms, diarrhoea, nausea
Skin and subcutaneous tissue disorders	
Uncommon	Photosensitivity, urticaria, rash, pruritus

Rare	Angioedema
Not known	Alopecia
Musculoskeletal and connective tissue disorders	
Common	Arthralgia†
Rare	Systemic lupus erythematosus (SLE)
Not known	Myalgia, joint swelling
General disorders and administration site conditions	
Very common	Pyrexia**
Common	Injection site reactions such as swelling, erythema, pain, pruritus
Uncommon	Influenza-like illness, swelling arms, weight increase, fatigue

*: Very common in children 6 to < 12 years of age
**: In children 6 to < 12 years of age
#: Common in nasal polyp trials
†: Unknown in allergic asthma trials

Chronic spontaneous urticaria (CSU)

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

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

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

The adverse reactions are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions listed first. The corresponding frequency category for each adverse reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

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

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

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

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

Description of selected adverse reactions

Immune system disorders
For further information, see section 4.4.

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

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

Platelets
In clinical trials few patients had platelet counts below the lower limit of the normal laboratory range. Isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

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

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

Reporting of suspected adverse reactions

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

4.9 Overdose

Maximum tolerated dose of Omlyclo has not been determined. Single intravenous doses up to 4,000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period and this dose did not result in any untoward acute effects.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)

Mechanism of action
Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and prevents binding of IgE to FcεRI (high-affinity IgE receptor) on basophils and mast cells, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

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

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

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

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

Chronic spontaneous urticaria (CSU)

Mechanism of action
Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and lowers free IgE levels. The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE. Subsequently, IgE receptors (FcεRI) on cells down-regulate. It is not entirely understood how this results in an improvement of CSU symptoms.

Pharmacodynamic effects
In clinical studies in CSU patients, maximum suppression of free IgE was observed 3 days after the first subcutaneous dose. After repeated dosing once every 4 weeks, pre-dose serum free IgE levels remained stable between 12 and 24 weeks of treatment. After discontinuation of omalizumab, free IgE levels increased towards pre-treatment levels over a 16-week treatment-free follow-up period.

Clinical efficacy and safety

Allergic asthma
Adults and adolescents ≥ 12 years of age
The efficacy and safety of omalizumab were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12 – 79 years, who had reduced lung function (FEV_1 40 – 80 % predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and a long-acting beta2-agonist. Subcutaneous omalizumab or placebo were administered as add-on therapy to > 1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22 %, 27 %, and 35 % of patients, respectively).

The rate of asthma exacerbations requiring treatment with bursts of systemic corticosteroids was the primary endpoint. Omalizumab reduced the rate of asthma exacerbations by 19 % ($p = 0.153$). Further evaluations which did show statistical significance ($p < 0.05$) in favour of omalizumab included reductions in severe exacerbations (where patient's lung function was reduced to below 60 % of personal best and requiring systemic corticosteroids) and asthma-related emergency visits (comprised of hospitalisations, emergency room, and unscheduled doctor visits), and improvements in Physician's overall assessment of treatment effectiveness, Asthma-related Quality of Life (AQL), asthma symptoms and lung function.

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

Table 6 Results of study 1

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

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

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

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

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

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

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

Physician's overall assessment of treatment effectiveness:
Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), day and night time symptoms, rescue medication use, spirometry and exacerbations. In all five studies a significantly greater proportion of omalizumab-treated patients were judged to have achieved either a marked improvement or complete control of their asthma compared to placebo patients.

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

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

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

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

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

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

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

Table 7 Demographics and baseline characteristics of nasal polyp studies

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
Bilateral endoscopic nasal polyp score (NPS): mean (SD), range 0–8	6.2 (1.0)	6.3 (0.9)
Nasal congestion score (NCS): mean (SD), range 0–3	2.4 (0.6)	2.3 (0.7)
Sense of smell score: mean (SD), range 0–3	2.7 (0.7)	2.7 (0.7)
SNOT-22 total score: mean (SD) range 0–110	60.1 (17.7)	59.5 (19.3)
Blood eosinophils (cells/µl): mean (SD)	346.1 (284.1)	334.6 (187.6)
Total IgE IU/ml: mean (SD)	160.9 (139.6)	190.2 (200.5)
Asthma (%)	53.6	60.6
Mild (%)	37.8	32.5
Moderate (%)	58.1	58.4
Severe (%)	4.1	9.1
Aspirin exacerbated respiratory disease (%)	19.6	35.4
Allergic rhinitis	43.5	42.5

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

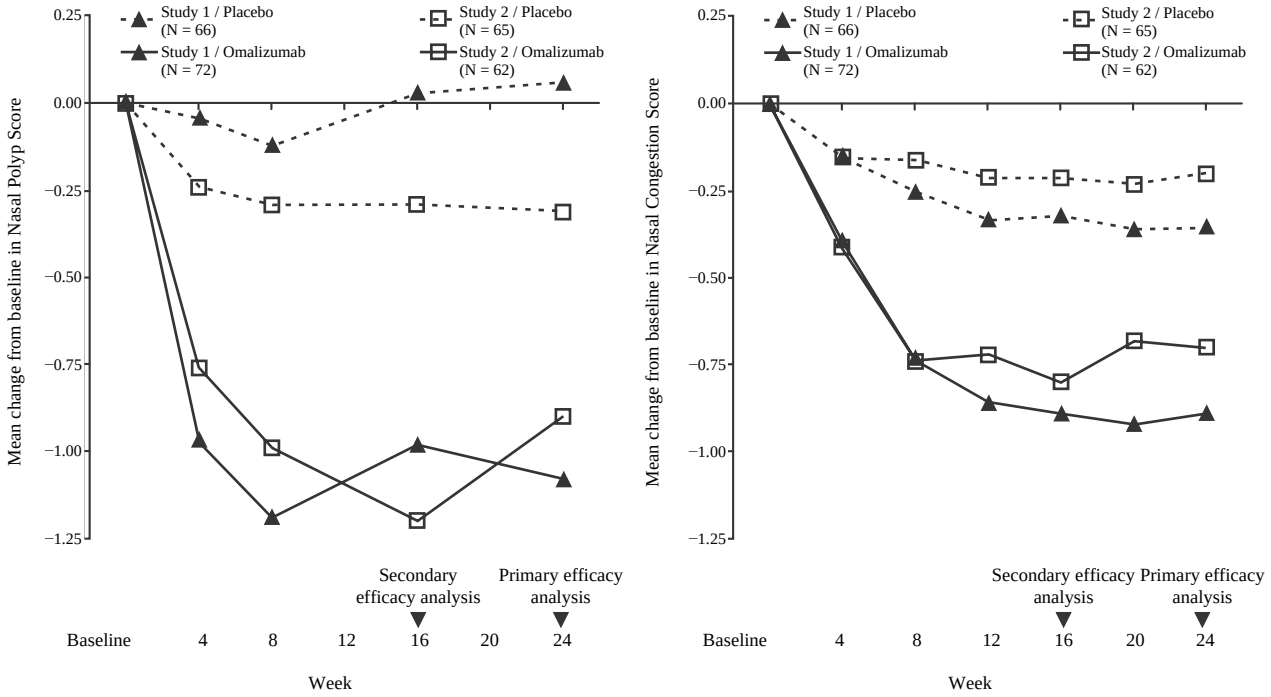
The co-primary endpoints were bilateral nasal polyps score (NPS) and average daily nasal congestion score (NCS) at Week 24. In both nasal polyp studies 1 and 2, patients who received omalizumab had statistically significant greater improvements from baseline at Week 24 in NPS and weekly average NCS than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

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

	Nasal polyp study 1		Nasal polyp study 2		Nasal polyp pooled results	
	Placebo	**Omalizumab**	**Placebo**	**Omalizumab**	**Placebo**	**Omalizumab**
N	66	72	65	62	131	134
Nasal polyp score						
Baseline mean	6.32	6.19	6.09	6.44	6.21	6.31
LS mean change at	0.06	−1.08	−0.31	−0.90	−0.13	−0.99
Week 24						
Difference (95 % CI)	−1.14 (−1.59, −069)		−0.59 (−1.05, −012)		−0.86 (−1.18, −0.54)	
p-value	< 0.0001		0.0140		< 0.0001	
7-day average of daily nasal congestion score						
Baseline mean	2.46	2.40	2.29	2.26	2.38	2.34
LS mean change at	−0.35	−0.89	−0.20	−0.70	−0.28	−0.80
Week 24						
Difference (95 % CI)	−0.55 (−0.84, −0.25)		−0.50 (−0.80, −0.19)		−0.52 (−0.73, −0.31)	
p-value	0.0004		0.0017		< 0.0001	
TNSS						
Baseline mean	9.33	8.56	8.73	8.37	9.03	8.47
LS mean change at	−1.06	−2.97	−0.44	−2.53	−0.77	−2.75
Week 24						
Difference (95 % CI)	−1.91 (−2.85, −0.96)		−2.09 (−3.00, −1.18)		−1.98 (−2.63, −1.33)	
p-value	0.0001		< 0.0001		< 0.0001	
SNOT-22						
Baseline mean	60.26	59.82	59.80	59.21	60.03	59.54
LS mean change at	−8.58	−24.70	−6.55	−21.59	−7.73	−23.10
Week 24						
Difference (95 % CI)	−16.12 (−21.86, −10.38)		−15.04 (−21.26, −8.82)		−15.36 (−19.57, −11.16)	
p-value	< 0.0001		< 0.0001		< 0.0001	
(MID = 8.9)						
UPSIT						
Baseline mean	13.56	12.78	13.27	12.87	13.41	12.82
LS mean change at	0.63	4.44	0.44	4.31	0.54	4.38
Week 24						
Difference (95 % CI)	3.81 (1.38, 6.24)		3.86 (1.57, 6.15)		3.84 (2.17, 5.51)	
p-value	0.0024		0.0011		< 0.0001	

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

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



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

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

Chronic spontaneous urticaria (CSU)

The efficacy and safety of omalizumab were demonstrated in two randomised, placebo-controlled phase III studies (study 1 and 2) in patients with CSU who remained symptomatic despite H1 antihistamine therapy at the approved dose. A third study (study 3) primarily evaluated the safety of omalizumab in patients with CSU who remained symptomatic despite treatment with H1 antihistamines at up to four times the approved dose and H2 antihistamine and/or LTRA treatment. The three studies enrolled 975 patients aged between 12 and 75 years (mean age 42.3 years; 39 patients 12 – 17 years, 54 patients ≥ 65 years; 259 males and 716 females). All patients were required to have inadequate symptom control, as assessed by a weekly urticaria activity score (UAS7, range 0–42) of ≥ 16, and a weekly itch severity score (which is a component of the UAS7; range 0–21) of ≥ 8 for the 7 days prior to randomisation, despite having used an antihistamine for at least 2 weeks beforehand.

In studies 1 and 2, patients had a mean weekly itch severity score of between 13.7 and 14.5 at baseline and a mean UAS7 score of 29.5 and 31.7 respectively. Patients in safety study 3 had a mean weekly itch severity score of 13.8 and a mean UAS7 score of 31.2 at baseline. Across all three studies, patients reported receiving on average 4 to 6 medications (including H1 antihistamines) for CSU symptoms prior to study enrollment. Patients received omalizumab at 75 mg, 150 mg or 300 mg or placebo by subcutaneous injection every 4 weeks for 24 and 12 weeks in studies 1 and 2, respectively, and 300 mg or placebo by subcutaneous injection every 4 weeks for 24 weeks in study 3. All studies had a 16-week treatment-free follow-up period.

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

Table 9 Change from baseline to week 12 in weekly itch severity score, studies 1, 2 and 3 (mITT population*)

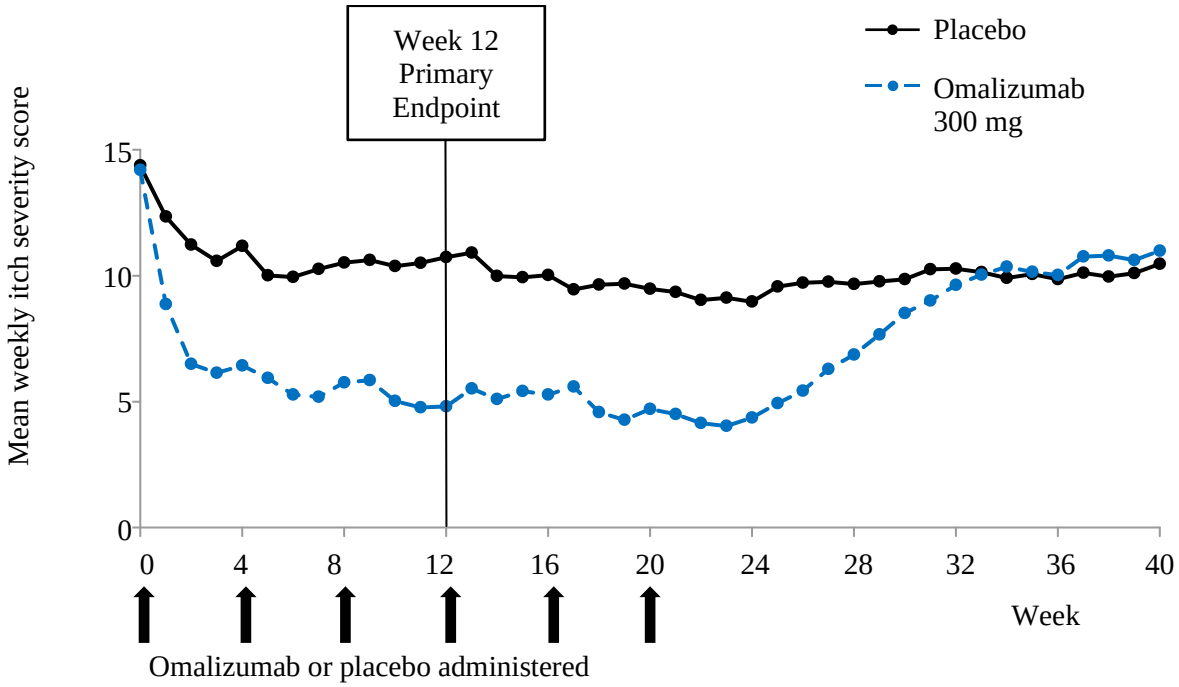
	Placebo	Omalizumab 300 mg
Study 1		
N	80	81
Mean (SD)	−3.63 (5.22)	−9.40 (5.73)
Difference in LS means vs. placebo[1]	–	−5.80
95 % CI for difference	–	−7.49,−4.10
P-value vs. placebo[2]	–	< 0.0001
Study 2		
N	79	79
Mean (SD)	−5.14 (5.58)	−9.77 (5.95)
Difference in LS means vs. placebo[1]	–	−4.81
95 %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

* Modified intent-to-treat (mITT) population: included all patients who were randomised and received at least one dose of study medications.
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 2 shows the mean weekly itch severity score over time in study 1. The mean weekly itch severity scores significantly decreased with a maximum effect around week 12 that was sustained over the 24-week treatment period. The results were similar in study 3.

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

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



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

The magnitude of the efficacy outcomes observed at week 24 of treatment was comparable to that observed at week 12:
For 300 mg, in studies 1 and 3, the mean decrease from baseline in weekly itch severity score was 9.8 and 8.6, the proportion of patients with UAS7≤ 6 was 61.7 % and 55.6 %, and the proportion of patients with complete response (UAS7=0) was 48.1 % and 42.5 %, respectively, (all $p < 0.0001$, when compared to placebo).

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

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

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

5.2 Pharmacokinetic properties

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

Absorption

After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62 %. Following a single subcutaneous dose in adult and adolescent patients with asthma or CSU, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 6 – 8 days. In patients with asthma, following multiple doses of omalizumab, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose.

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

Administration of omalizumab manufactured as a lyophilised or liquid formulation resulted in similar serum concentration-time profiles of omalizumab.

Distribution

In vitro, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than one million Daltons in molecular weight are not observed *in vitro* or *in vivo*. Based on population pharmacokinetics, distribution of omalizumab was similar in patients with allergic asthma and patients with CSU. The apparent volume of distribution in patients with asthma following subcutaneous administration was 78 ± 32 ml/kg.

Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. In asthma patients the omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4 ± 1.1 ml/kg/day. Doubling of body weight approximately doubled apparent clearance. In CSU patients, based on population pharmacokinetic simulations, omalizumab serum elimination half-life at steady state averaged 24 days and apparent clearance at steady state for a patient of 80 kg weight was 3.0 ml/kg/day.

Characteristics in patient populations

Age, Race/ethnicity, Gender, Body Mass Index
Patients with allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)
The population pharmacokinetics of omalizumab were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for age (6 – 76 years for patients with allergic asthma; 18 to 75 for patients with CRSwNP), race/ethnicity, gender or body mass index (see section 4.2).

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

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

5.3 Preclinical safety data

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

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

Formal carcinogenicity studies have not been conducted with omalizumab.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

24 months.

The product may be kept for a total of 7 days at 25 °C.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

A pack containing 1 pre-filled syringe and multipacks containing 6 (6 x 1) or 10 (10 x 1) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Disposal instructions

Dispose of the used syringe immediately in a sharps container.

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

7. MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1817/002
EU/1/24/1817/003
EU/1/24/1817/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer(s) of the biological active substance

CELLTRION INC.
23, Academy-ro,
Yeonsu-gu
Incheon, 22014,
Republic of Korea

Name and address of the manufacturer(s) responsible for batch release
Nuvisan France SARL
2400, Route des Colles,
06410, Biot,
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Omlyclo 75 mg Solution for injection in pre-filled syringe
omalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine hydrochloride monohydrate, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe with needle guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
For single use only.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the syringe in the original package in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1817/001 1 pre-filled syringe with needle guard

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Omlyclo 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

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

Omlyclo 75 mg injection
omalizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine hydrochloride monohydrate, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe with needle guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
For single use only.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the syringe in the original package in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1817/002 1 pre-filled syringe with needle guard

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Omlyclo 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine hydrochloride monohydrate, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

Multipack: 6 (6 × 1) pre-filled syringes with needle guard
Multipack: 10 (10 × 1) pre-filled syringes with needle guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
For single use only.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the syringe in the original package in order to protect from light.

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

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1817/003 6 pre-filled syringes with needle guard (6 x 1)
EU/1/24/1817/004 10 pre-filled syringes with needle guard (10 x 1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Omlyclo 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: L-arginine hydrochloride, L-histidine hydrochloride monohydrate, L-histidine, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
For single use only.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the syringe in the original package in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1817/003 6 pre-filled syringes with needle guard (6 x 1)
EU/1/24/1817/004 10 pre-filled syringes with needle guard (10 x 1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Omlyclo 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

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

Omlyclo 150 mg injection
omalizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Omlyclo 75 mg solution for injection in pre-filled syringe

omalizumab

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side affects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Omlyclo is and what it is used for

Omlyclo contains the active substance omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body. It belongs to a class of medicines called monoclonal antibodies.

Omlyclo is used for the treatment of:
- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps

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

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

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

2. What you need to know before you use Omlyclo

Do not use Omlyclo:
– if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

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

Warnings and precautions
Talk to your doctor before using Omlyclo:
– if you have kidney or liver problems.
– if you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
– if you are travelling to region where infections caused by parasites are common – Omlyclo may weaken your resistance to such infections.
– if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.

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

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

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

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

Children and adolescents
Allergic asthma
Omlyclo is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

Chronic rhinosinusitis with nasal polyps
Omlyclo is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age has not been studied.

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

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

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

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

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

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

3. How to use Omlyclo

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

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

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

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

Training to recognise serious allergic reactions
It is also important that you do not inject Omlyclo yourself until you have been trained by your doctor or nurse on:
– how to recognise the early signs and symptoms of serious allergic reactions.
– what to do if the symptoms occur.
For more information about the early signs and symptoms of serious allergic reactions, see section 4.

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

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

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

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

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

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

Chronic rhinosinusitis with nasal polyps
Omlyclo should not be used in children and adolescents under 18 years of age.

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

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

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

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

4. Possible side effects

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

Serious side effects:

Seek medical attention immediately if you notice any signs of the following side effects:
Rare (may affect up to 1 in 1000 people)
- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Omlyclo you may be more at risk of developing a severe allergic reaction following use of Omlyclo.
- Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, rash, fever, weight loss, and fatigue.

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

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

Common (may affect up to 1 in 10 people)
– reactions at the injection site including pain, swelling, itching and redness
– pain in the upper part of the tummy
– headache (very common in children)
– feeling dizzy
– pain in joints (arthralgia)

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

Rare (may affect up to 1 in 1000 people)
– parasitic infection

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

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

5. How to store Omlyclo

– Keep this medicine out of the sight and reach of children.
– Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month. The carton containing the pre-filled syringe can be stored for a total time of 7 days at room temperature (25 °C) before use.
– Store in the original package in order to protect from light.
– Store in a refrigerator (2 °C – 8 °C). Do not freeze.
– Do not use any pack that is damaged or shows signs of tampering.

6. Contents of the pack and other information

What Omlyclo contains
– The active substance is omalizumab. One syringe of 0.5 ml solution contains 75 mg omalizumab.
– The other ingredients are L-arginine hydrochloride, L-histidine hydrochloride monohydrate, L-histidine, Polysorbate 20 and water for injections.

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

Omlyclo 75 mg solution for injection is available in a pack containing 1 pre-filled syringe

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This leaflet was last revised in

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

INSTRUCTIONS FOR USE OF OMLYCLO PRE-FILLED SYRINGE

Read and follow the Instructions for Use that come with your Omlyclo Pre-filled Syringe before you start using it and each time you get a refill. There may be new information.
This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

Children (6 to less than 12 years of age) should not inject Omlyclo Pre-filled Syringes themselves, however, if deemed appropriate by their healthcare provider, a caregiver may give them their injection after proper training.

Omlyclo Pre-filled Syringes are available in **2 dose strengths** (see *Figure A*). These instructions are to be used for the 75 mg/0.5 mL dose strength. The type of Pre-filled Syringe you receive depends on the dose prescribed by your healthcare provider (see *Figure C: Dosing Chart*). Check the label on the carton and the color of the Plunger rod to make sure that the dose strength is correct.

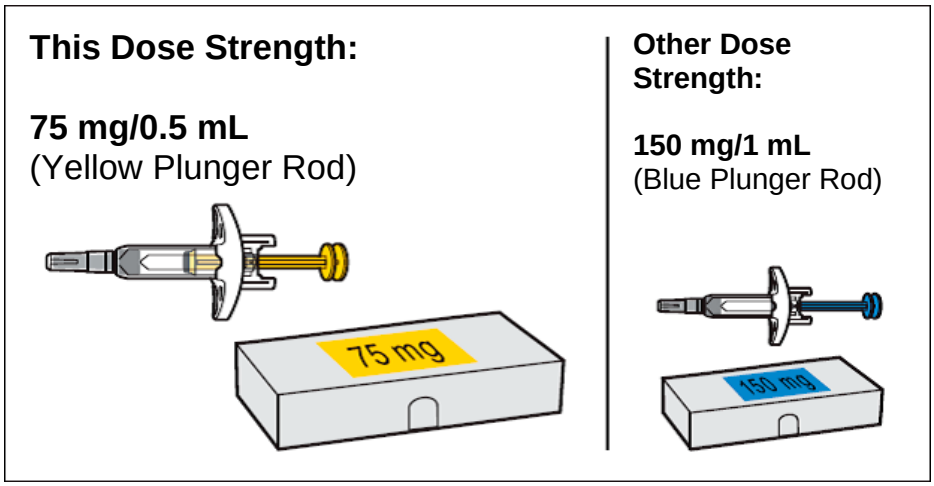

Figure A

Important safety information
- **Keep the Pre-filled Syringe out of the sight and reach of children. Pre-filled Syringe contains small parts.**
- **Do not** open the sealed carton until you are ready to use the Pre-filled Syringe.
- **Do not** use the Pre-filled Syringe if either the seal on the carton or the seal of the plastic tray is broken, as it may not be safe for you to use.
- Never leave the Pre-filled Syringe where others might tamper with it.
- **Do not** shake the Pre-filled Syringe.
- **Do not** remove the Cap until just before you give the injection.
- The Pre-filled Syringe cannot be re-used. Dispose of the used Pre-filled Syringe immediately after use in a sharps disposal container (see step **13. Dispose of the Pre-filled Syringe**).

Storing the Pre-filled Syringe
- Store the Pre-filled Syringe in a refrigerator between 2 °C and 8 °C. Store this medicine sealed inside its carton to protect it from light.
- **Do not** freeze the Pre-filled Syringe.
- Remember to take the Pre-filled Syringe out of the refrigerator and allow it to reach room temperature (25 °C), about 30 minutes, before preparing it for injection. Leave the Pre-filled Syringe in the carton to protect it from light.
- The time that the Pre-filled Syringe is kept at room temperature (25 °C) before use must not exceed 7 days.
- **Do not** use the Pre-filled Syringe after the expiration date which is stated on the carton and the Pre-filled Syringe label. If it has expired, return the entire pack to the pharmacy.
- **Do not** use the Pre-filled Syringe if it has been dropped or is visibly damaged.

Parts of the Pre-filled Syringe (see *Figure B*)

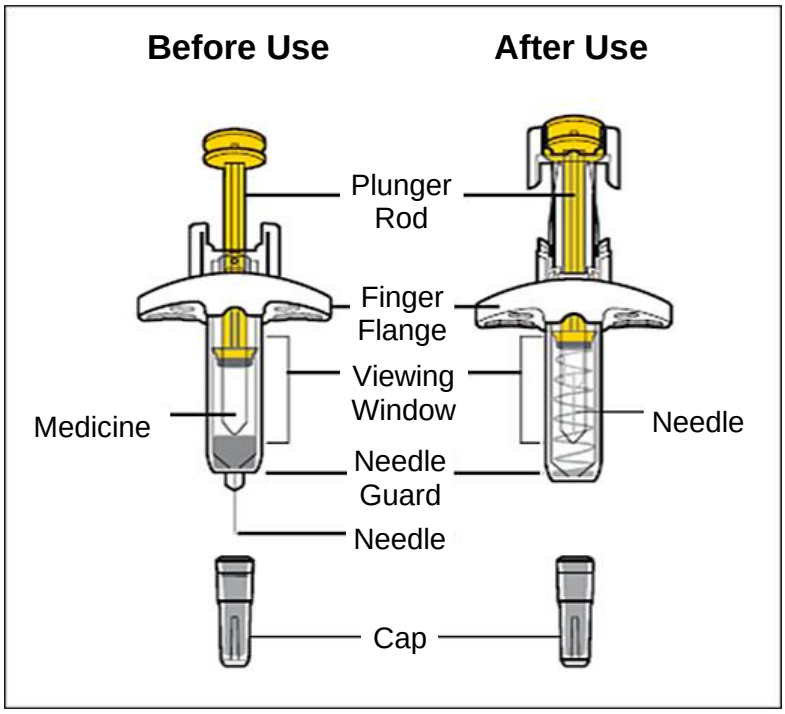

Figure B

Preparing for the Injection

Dose (mg)	Prefilled Syringes Needed	
	Yellow(75 mg/0.5 mL)	Blue (150 mg/1 mL)
75		
150		
225	+	
300		
375	+	
450		
525	+	
600		

Figure A

1. Gather the supplies for the injection

1.a. Prepare a clean, flat surface, such as a table or countertop, in a well-lit area.

1.b. Take the carton(s) containing the Pre-filled Syringe(s) needed to administer your prescribed dose out of the refrigerator.
Note: Depending on the dose prescribed to you by your healthcare provider you may need to prepare one or more Pre-filled Syringes and inject the contents of them all. The following chart shows how many injections of each dose strength are needed for your prescribed dose (see *Figure C: Dosing Chart*).

1.c. Make sure you have the following supplies:
- Carton containing Pre-filled Syringe

Not included in the carton:
- 1 Alcohol swab
- 1 Cotton ball or gauze
- 1 Adhesive bandage
- Sharps disposal container

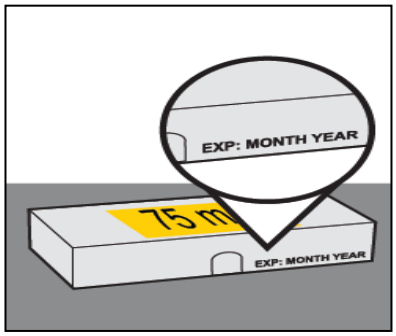

Figure B

2. Check the expiration on the carton (see *Figure D*).

- **Do not** use it if the expiration date has passed. If the expiration date has passed, return the entire pack to the pharmacy.

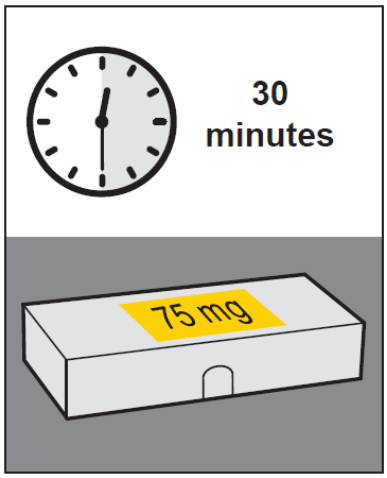

Figure C

3. Wait 30 minutes.

3.a. Leave the **unopened** carton containing the Pre-filled Syringe at room temperature (25°C) for 30 minutes to allow it to warm up (see *Figure E*).

- **Do not** warm the Pre-filled Syringe using heat sources such as hot water or a microwave.
- If the Pre-filled Syringe does not reach room temperature, this could cause the injection to feel uncomfortable and make it hard to push the Plunger rod.

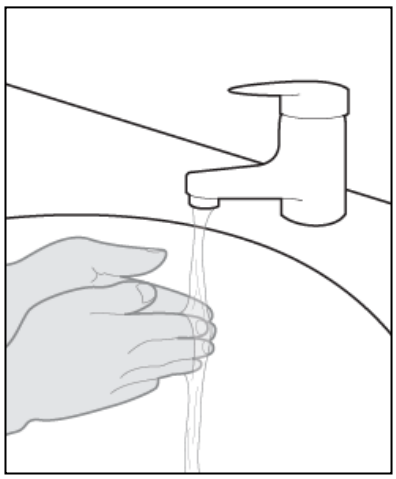

Figure D

4. Wash your hands.

4.a. Wash your hands with soap and water and dry them thoroughly (see *Figure F*).

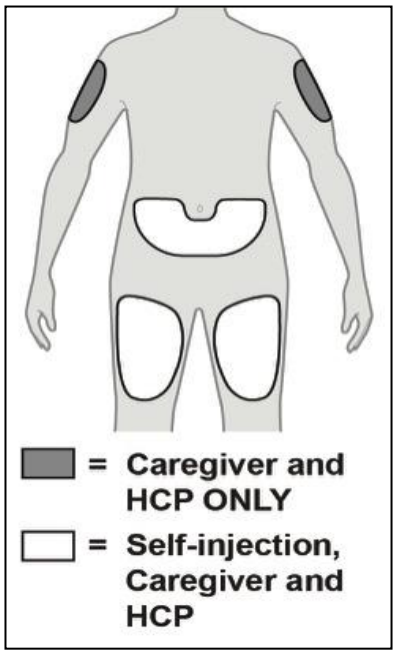

Figure E

5. Choose an injection site (see *Figure G*)

5.a. You may inject into:
- The front of your thighs.
- Your lower abdomen except for the 5 cm around the belly button (navel).
- The outer area of the upper arm if you are a caregiver or healthcare provider (HCP).

- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard, or if there are breaks in the skin.
- **Do not** inject through your clothes.

5.b. Choose a different injection site for each new injection at least 2.5 cm away from the area used for the last injection.

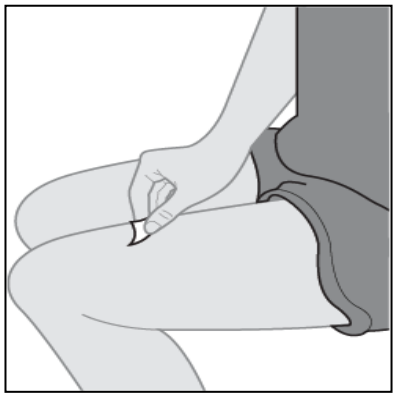

Figure F

6. Clean the injection site.

6.a. Clean the injection site with an alcohol swab using a circular motion (see *Figure H*).
6.b. Let the skin dry before injecting.

- **Do not** blow on or touch the injection site again before giving the injection.

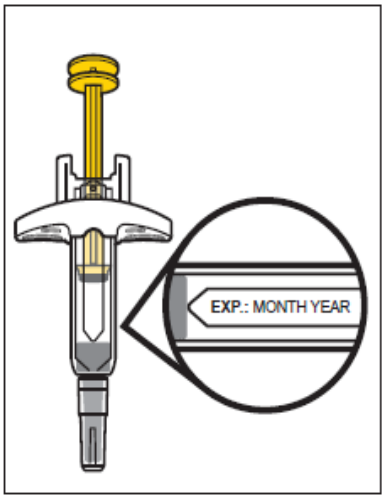

Figure G

7. Inspect the Pre-filled Syringe.

7.a. Open the carton.
Gripping from the syringe body lift the Pre-filled Syringe from the tray.
7.b. Look at the Pre-filled Syringe and make sure you have the correct Medicine (Omlyclo) and dosage.
7.c. Look at the Pre-filled Syringe and make sure it is not cracked or damaged.
7.d. Check the expiration date on the label of the Pre-filled Syringe (see *Figure I*).

- **Do not** use if the expiration date has passed.

Note: If the expiration date is not visible in the viewing window, you may rotate the inner barrel of the Pre-filled Syringe until the expiration date becomes visible.

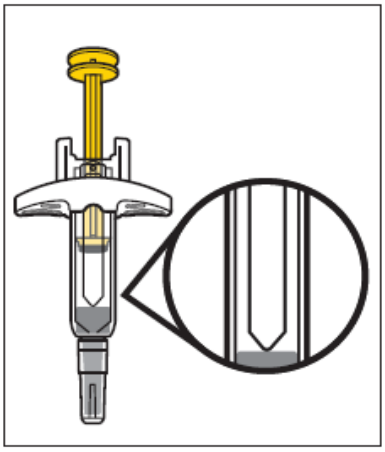

Figure H

8. Inspect the Medicine.

8.a. Look at the Medicine and confirm that the liquid is clear to cloudy, colourless to pale brownish-yellow, and free of particles (see *Figure J*).

- **Do not** use the Pre-filled Syringe if the liquid is discolored, distinctly cloudy, or contains particles in it.
- You may see air bubbles in the liquid. This is normal.

Administering the Injection

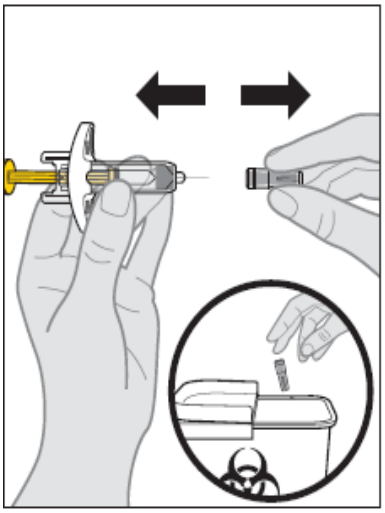

Figure I

9. Remove the Cap.

9.a. Hold the Pre-filled Syringe by the syringe body in one hand. Gently pull the Cap straight off with the other hand.

- **Do not** hold the Plunger rod while removing the Cap.
- You may see a drop of liquid at the tip of the Needle. This is normal.

9.b. Dispose of the Cap right away in a sharps disposal container (see step **13. Dispose of the Pre-filled Syringe** and *Figure K*).

- **Do not** re-cap the Pre-filled Syringe.
- **Do not** remove the Cap until you are ready to inject.
- **Do not** touch the Needle. Doing so may result in a needle stick injury.

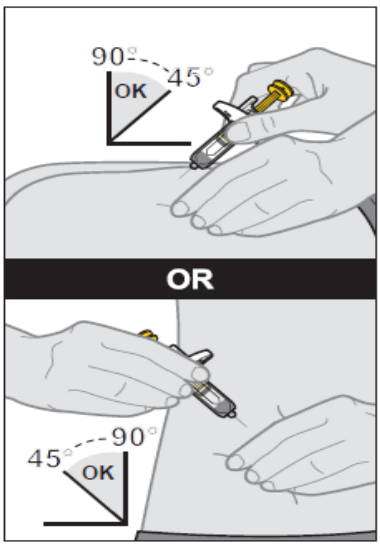

Figure J

10. Insert the Pre-filled Syringe into the injection site.

10.a. Gently pinch a fold of skin at the injection site with one hand.

Note: Pinching the skin is important to make sure that you inject under the skin (into the fatty area) but not any deeper (into muscle).

10.b. With a quick and "dart-like" motion, insert the Needle completely into the fold of skin at a 45 to 90-degree angle (see *Figure L*).

- **Do not** touch the Plunger rod while inserting
the needle into the skin.

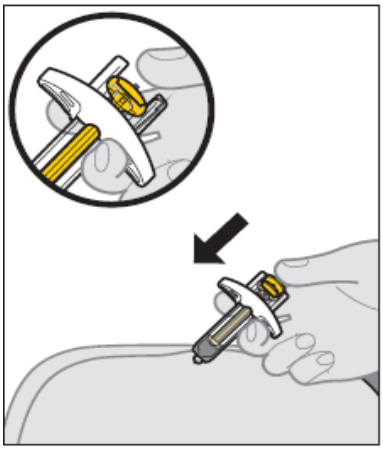

Figure K

11. Give the injection.

11.a. After the Needle is inserted, release the pinch.

11.b. Slowly push the Plunger rod **all the way down** until the full dose of medicine gets injected, and the syringe is empty (see *Figure M*).

- **Do not** change the position of the Pre-filled Syringe after the injection has started.
- If the Plunger rod is not fully pressed, the Needle Guard will not extend to cover the needle when it is removed.

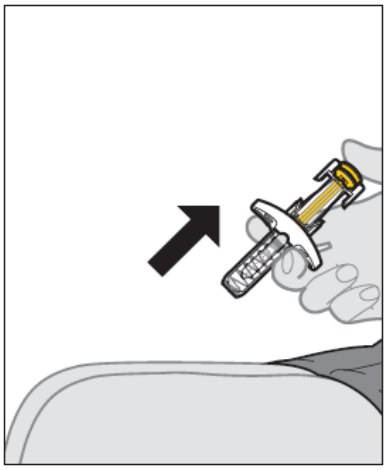

Figure L

12. Remove the Pre-filled Syringe from the injection site.

12.a. After the Pre-filled Syringe is empty, slowly lift your thumb from the Plunger rod until the Needle is completely covered by the Needle Guard (see *Figure N*).

- If the Needle is not covered, proceed carefully to dispose of the syringe (see step **13. Dispose of the Pre-filled Syringe**).
- Some bleeding may occur (see step **14. Care for the injection site.**).
- In case of skin contact with Medicine, wash the area that touched the Medicine with water.
- **Do not** reuse the Pre-filled Syringe.
- **Do not** rub the injection site.

After the injection

Figure M

13. Dispose of the Pre-filled Syringe.

13.a. Put the used Pre-filled Syringe in a sharps disposal container right away after use (see *Figure O*).

- **Do not** throw away (dispose of) the Pre-filled Syringe in your household trash. If you do not have a sharps disposal container, you may use a household container that is closable and puncture resistant. 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.

14. Care for the injection site.

14.a. If some bleeding occurs, treat the injection site by gently pressing, not rubbing, a cotton ball or gauze to the site and apply an adhesive bandage if needed.

Package leaflet: Information for the user

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

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side affects you may get. See the end of section 4 for how to report side effects..

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Omlyclo is and what it is used for

Omlyclo contains the active substance omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body. It belongs to a class of medicines called monoclonal antibodies.

Omlyclo is used for the treatment of:
- allergic asthma
- chronic rhinosinusitis (inflammation of the nose and sinuses) with nasal polyps
- chronic spontaneous urticaria (CSU)

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

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

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

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

2. What you need to know before you use Omlyclo

Do not use Omlyclo:
– if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

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

Warnings and precautions
Talk to your doctor before using Omlyclo:
– if you have kidney or liver problems.
– if you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
– if you are travelling to region where infections caused by parasites are common – Omlyclo may weaken your resistance to such infections.
– if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.

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

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

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

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

Children and adolescents
Allergic asthma
Omlyclo is not recommended for children under 6 years of age. Its use in children under 6 years of age has not been studied.

Chronic rhinosinusitis with nasal polyps
Omlyclo is not recommended for children and adolescents under 18 years of age. Its use in patients under 18 years of age has not been studied.

Chronic spontaneous urticaria (CSU)
Omlyclo is not recommended for children under 12 years of age. Its use in children under 12 years of age has not been studied.

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

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

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

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

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

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

3. How to use Omlyclo

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

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

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

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

Training to recognise serious allergic reactions
It is also important that you do not inject Omlyclo yourself until you have been trained by your doctor or nurse on:
– how to recognise the early signs and symptoms of serious allergic reactions
– what to do if the symptoms occur.
For more information about the early signs and symptoms of serious allergic reactions, see section 4.

How much to use
Allergic asthma and chronic rhinosinusitis with nasal polyps
Your doctor will decide how much Omlyclo you need and how often you will need it. This depends on your body weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in your blood.

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

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

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

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

Keep taking your current medicine for CSU during Omlyclo treatment. Do not stop taking any medicine without talking to your doctor.

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

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

Chronic rhinosinusitis with nasal polyps
Omlyclo should not be used in children and adolescents under 18 years of age.

Chronic spontaneous urticaria (CSU)
Omlyclo can be used in adolescents aged 12 years of age and older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines. The dose for adolescents aged 12 years and above is the same as for adults.

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

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

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

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

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

4. Possible side effects

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

Serious side effects:
Seek medical attention immediately if you notice any signs of the following side effects:
Rare (may affect up to 1 in 1000 people)
– Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Omlyclo you may be more at risk of developing a severe allergic reaction following use of Omlyclo.
– Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, rash, fever, weight loss, and fatigue.

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

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

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

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

Rare (may affect up to 1 in 1000 people)
– parasitic infection

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

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

5. How to store Omlyclo

– Keep this medicine out of the sight and reach of children.
– Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month. The carton containing the pre-filled syringe can be stored for a total time of 7 days at room temperature (25 °C) before use.
– Store in the original package in order to protect from light.
– Store in a refrigerator (2 °C – 8 °C). Do not freeze.
– Do not use any pack that is damaged or shows signs of tampering.

6. Contents of the pack and other information What Omlyclo contains

– The active substance is omalizumab. One syringe of 1 ml solution contains 150 mg omalizumab.
– The other ingredients are L-arginine hydrochloride, L-histidine hydrochloride monohydrate, L-histidine, Polysorbate 20 and water for injections.

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

Omlyclo 150 mg solution for injection is available in a pack containing 1 pre-filled syringe and in multipacks containing 6 (6 x 1) or 10 (10 x 1) pre-filled syringes.

Not all pack sizes may be marketed in your country.

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This leaflet was last revised in

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

INSTRUCTIONS FOR USE OF OMLYCLO PRE-FILLED SYRINGE

Read and follow the Instructions for Use that come with your Omlyclo Pre-filled Syringe before you start using it and each time you get a refill. There may be new information.
This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

Children (6 to less than 12 years of age) should not inject Omlyclo Pre-filled Syringes themselves, however, if deemed appropriate by their healthcare provider, a caregiver may give them their injection after proper training.

Omlyclo Pre-filled Syringes are available in **2 dose strengths** (see *Figure A*). These instructions are to be used for the 150 mg/1 mL dose strength. The type of Pre-filled Syringe you receive depends on the dose prescribed by your healthcare provider (see *Figure C: Dosing Chart*). Check the label on the carton and the color of the Plunger rod to make sure that the dose strength is correct.

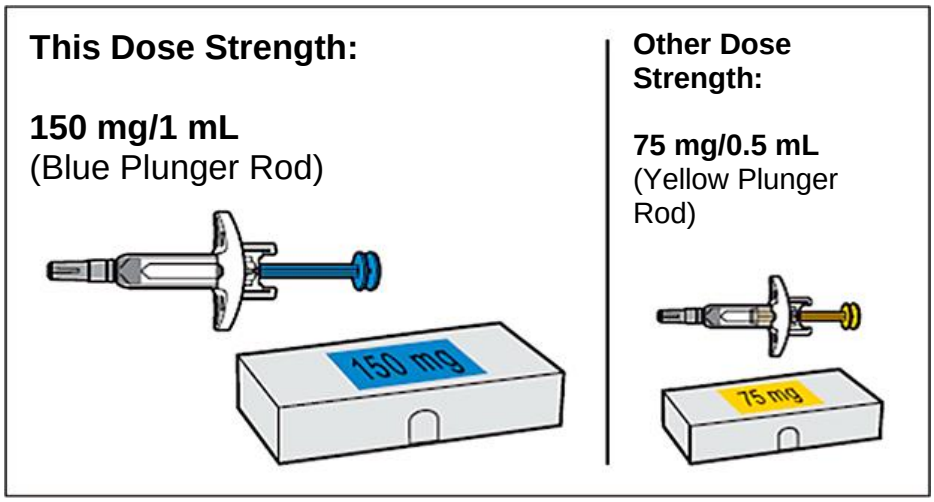

Figure A

Important safety information
- **Keep the Pre-filled Syringe out of the sight and reach of children. Pre-filled Syringe contains small parts.**
- **Do not** open the sealed carton until you are ready to use the Pre-filled Syringe.
- **Do not** use the Pre-filled Syringe if either the seal on the carton or the seal of the plastic tray is broken, as it may not be safe for you to use.
- Never leave the Pre-filled Syringe where others might tamper with it.
- **Do not** shake the Pre-filled Syringe.
- **Do not** remove the Cap until just before you give the injection.
- The Pre-filled Syringe cannot be re-used. Dispose of the used Pre-filled Syringe immediately after use in a sharps disposal container (see step **13. Dispose of the Pre-filled Syringe**).

Storing the Pre-filled Syringe
- Store the Pre-filled Syringe in a refrigerator between 2 °C and 8 °C. Store this medicine sealed inside its carton to protect it from light.
- **Do not** freeze the Pre-filled Syringe.
- Remember to take the Pre-filled Syringe out of the refrigerator and allow it to reach room temperature (25 °C), about 30 minutes, before preparing it for injection. Leave the Pre-filled Syringe in the carton to protect it from light.
- The time that the Pre-filled Syringe is kept at room temperature (25 °C) before use must not exceed 7 days.
- **Do not** use the Pre-filled Syringe after the expiration date which is stated on the carton and the Pre-filled Syringe label. If it has expired, return the entire pack to the pharmacy.
- **Do not** use the Pre-filled Syringe if it has been dropped or is visibly damaged.

Parts of the Pre-filled Syringe (see *Figure B*)

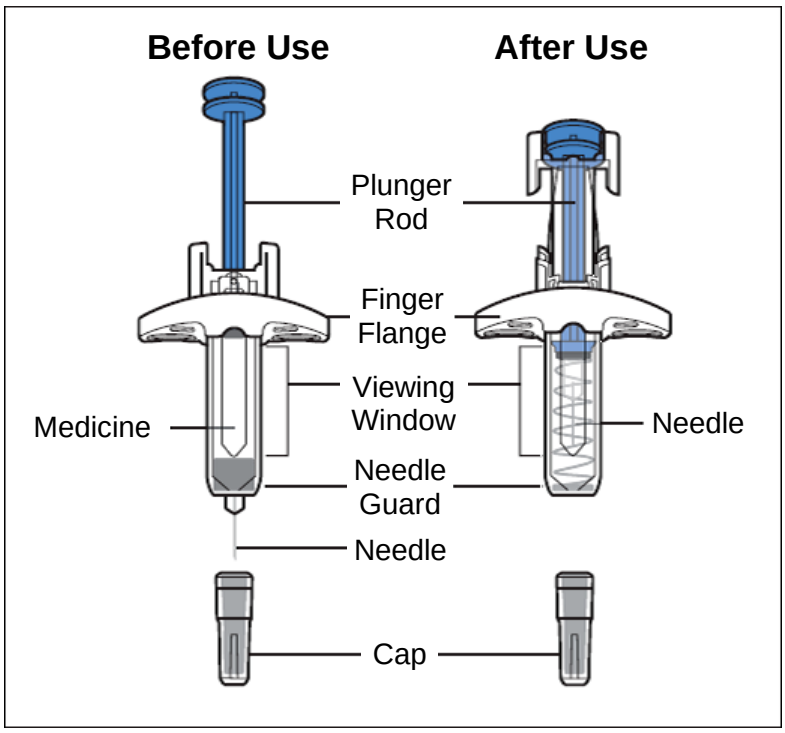

Figure B

Preparing for the Injection

Dose (mg)	Prefilled Syringes Needed	
	Yellow (75 mg/0.5 mL)	Blue (150 mg/1 mL)
75		
150		
225	+	
300		
375	+	
450		
525	+	
600		

Figure C

1. Gather the supplies for the injection

1.a. Prepare a clean, flat surface, such as a table or countertop, in a well-lit area.

1.b. Take the carton(s) containing the Pre-filled Syringe(s) needed to administer your prescribed dose out of the refrigerator.

Note: Depending on the dose prescribed to you by your healthcare provider you may need to prepare one or more Pre-filled Syringes and inject the contents of them all. The following chart shows how many injections of each dose strength are needed for your prescribed dose (see *Figure C: Dosing Chart*).

1.c. Make sure you have the following supplies:

– Carton containing Pre-filled Syringe

Not included in the carton:

– 1 Alcohol swab
– 1 Cotton ball or gauze
– 1 Adhesive bandage
– Sharps disposal container

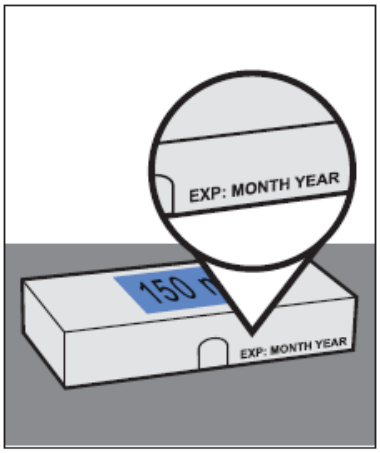

Figure A

2. Check the expiration on the carton (see *Figure D*).

- **Do not** use it if the expiration date has passed. If the expiration date has passed, return the entire pack to the pharmacy.

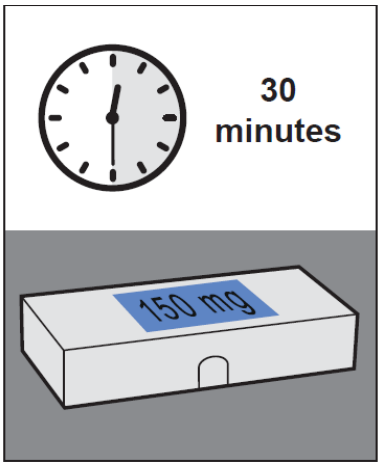

Figure B

3. Wait 30 minutes.

3.a. Leave the **unopened** carton containing the Pre-filled Syringe at room temperature (25°C) for 30 minutes to allow it to warm up (see *Figure E*).

- **Do not** warm the Pre-filled Syringe using heat sources such as hot water or a microwave.
- If the Pre-filled Syringe does not reach room temperature, this could cause the injection to feel uncomfortable and make it hard to push the Plunger rod .

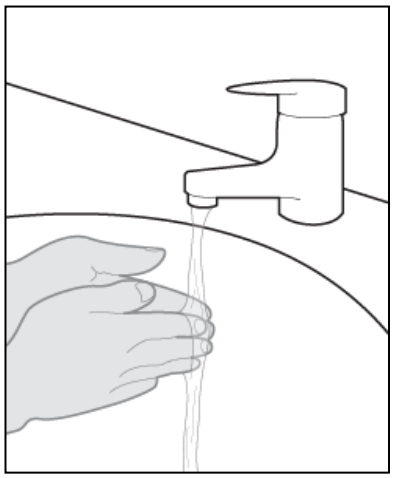

Figure C

4. Wash your hands.

4.a. Wash your hands with soap and water and dry them thoroughly (see *Figure F*).

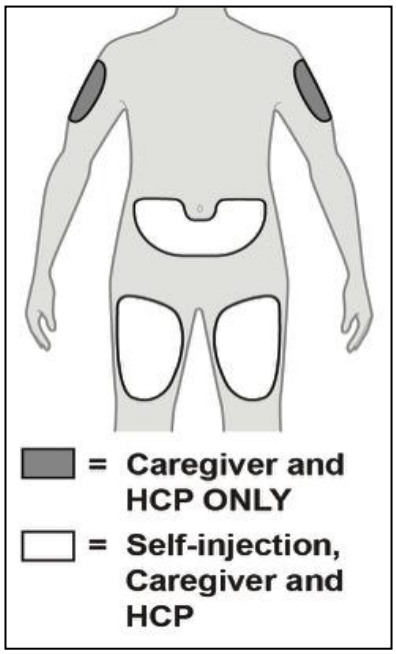

Figure D

5. Choose an injection site (see *Figure G*)

5.a. You may inject into:
- The front of your thighs.
- Your lower abdomen except for the 5 cm around the belly button (navel).
- The outer area of the upper arm if you are a caregiver or healthcare provider (HCP).

- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard, or if there are breaks in the skin.
- **Do not** inject through your clothes.

5.b. Choose a different injection site for each new injection at least 2.5 cm away from the area used for the last injection.

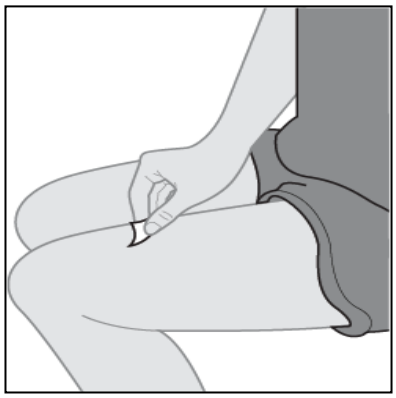

Figure E

6. Clean the injection site.

6.a. Clean the injection site with an alcohol swab using a circular motion (see *Figure H*).

6.b. Let the skin dry before injecting.

- **Do not** blow on or touch the injection site again before giving the injection.

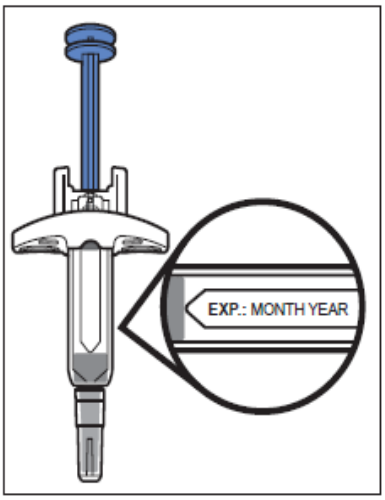

Figure F

7. Inspect the Pre-filled Syringe.

7.a. Open the carton.
Gripping from the syringe body lift the Pre-filled Syringe from the tray.

7.b. Look at the Pre-filled Syringe and make sure you have the correct Medicine (Omlyclo) and dosage.

7.c. Look at the Pre-filled Syringe and make sure it is not cracked or damaged.

7.d. Check the expiration date on the label of the Pre-filled Syringe (see *Figure I*).

- **Do not** use if the expiration date has passed.

Note: If the expiration date is not visible in the viewing window, you may rotate the inner barrel of the Pre-filled Syringe until the expiration date becomes visible.

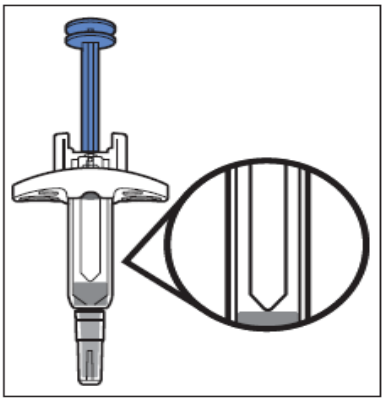

Figure G

8. Inspect the Medicine.

8.a. Look at the Medicine and confirm that the liquid is clear to cloudy, colourless to pale brownish-yellow, and free of particles (see *Figure J*).

- **Do not** use the Pre-filled Syringe if the liquid is discolored, distinctly cloudy, or contains particles in it.
- You may see air bubbles in the liquid. This is normal.

Administering the Injection

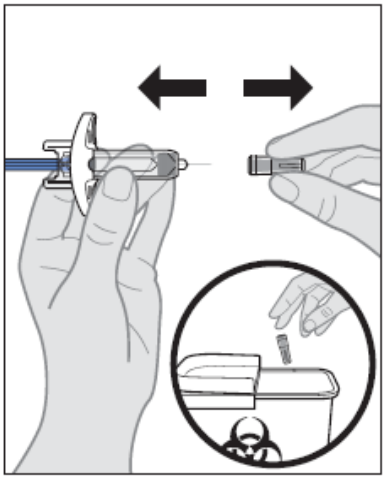

Figure H

9. Remove the Cap.

9.a. Hold the Pre-filled Syringe by the syringe body in one hand. Gently pull the Cap straight off with the other hand.

- **Do not** hold the Plunger rod while removing the Cap.
- You may see a drop of liquid at the tip of the Needle. This is normal.

9.b. Dispose of the Cap right away in a sharps disposal container (see step **13. Dispose of the Pre-filled Syringe** and *Figure K*).

- **Do not** re-cap the Pre-filled Syringe.
- **Do not** remove the Cap until you are ready to inject.
- **Do not** touch the Needle. Doing so may result in a needle stick injury.

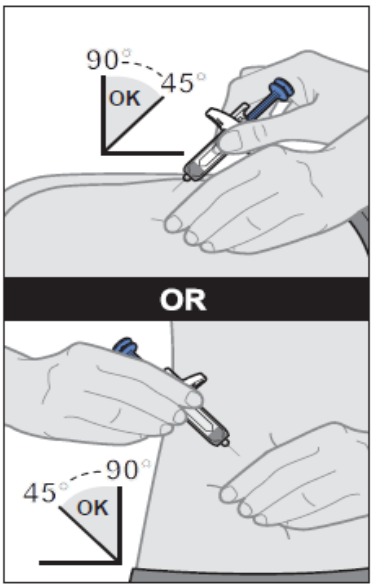

Figure I

10. Insert the Pre-filled Syringe into the injection site.

10.a. Gently pinch a fold of skin at the injection site with one hand.

Note: Pinching the skin is important to make sure that you inject under the skin (into the fatty area) but not any deeper (into muscle).

10.b. With a quick and "dart-like" motion, insert the Needle completely into the fold of skin at a 45 to 90-degree angle (see *Figure L*).

- **Do not** touch the Plunger rod while inserting the needle into the skin.

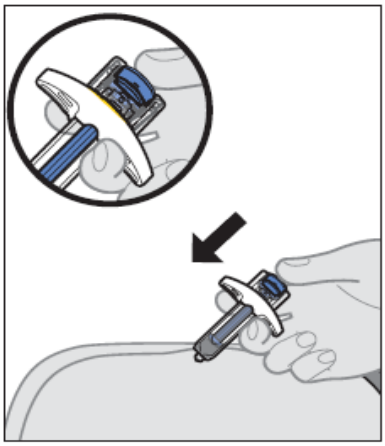

Figure J

11. Give the injection.

11.a. After the Needle is inserted, release the pinch.

11.b. Slowly push the Plunger rod **all the way down** until the full dose of medicine gets injected, and the syringe is empty (see *Figure M*).

- **Do not** change the position of the Pre-filled Syringe after the injection has started.
- If the Plunger rod is not fully pressed, the Needle Guard will not extend to cover the needle when it is removed.

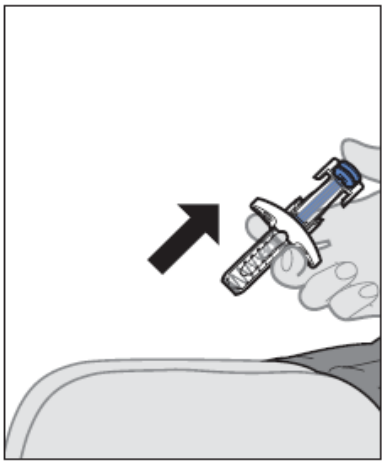

Figure K

12. Remove the Pre-filled Syringe from the injection site.

12.a. After the Pre-filled Syringe is empty, slowly lift your thumb from the Plunger rod until the Needle is completely covered by the Needle Guard (see *Figure N*).

- If the Needle is not covered, proceed carefully to dispose of the syringe (see step **13. Dispose of the Pre-filled Syringe**).
- Some bleeding may occur (see step **14. Care for the injection site.**).
- In case of skin contact with Medicine, wash the area that touched the Medicine with water.
- **Do not** reuse the Pre-filled Syringe.
- **Do not** rub the injection site.

After the injection

Figure L

13. Dispose of the Pre-filled Syringe.

13.a. Put the used Pre-filled Syringe in a sharps disposal container right away after use (see *Figure O*).

- **Do not** throw away (dispose of) the Pre-filled Syringe in your household trash. If you do not have a sharps disposal container, you may use a household container that is closable and puncture resistant. 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.

14. Care for the injection site.

14.a. If some bleeding occurs, treat the injection site by gently pressing, not rubbing, a cotton ball or gauze to the site and apply an adhesive bandage if needed.