NOVARTIS

1. NAME OF THE MEDICINAL PRODUCT

XOLAIR® 75 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (reconstituted) contains 75 mg of omalizumab whereas one vial (before reconstitution) contains 129.6 mg of omalizumab. Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line. After reconstitution the vial contains 125 mg/ml of omalizumab (75 mg in 0.6 ml).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

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

Solvent: clear and colorless solution in a glass ampoule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_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. Xolair treatment should only be considered for patients with convincing IgE mediated asthma (see section 4.2).

4.2 Posology and method of administration

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

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

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

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that patients with IgE below 76 IU/ml have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting therapy.

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

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

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

Method of administration

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

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

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

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

Full instructions for use are provided in section 6.6.

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

Dose (mg)	Number of vials		Number of injections	Total injection volume (ml)
	75 mg[a]	150 mg[b]		
75	1[c]	0	1	0.6
150	0	1	1	1.2
225	1[c]	1	2	1.8
300	0	2	2	2.4
375	1[c]	2	3	3
450	0	3	3	3.6
525	1[c]	3	4	4.2
600	0	4	4	4.8

[A]0.6 ml = maximum delivered volume per vial (Xolair 75 mg).
[B]1.2 ml = maximum delivered volume per vial (Xolair 150 mg).
[C]or use 0.6 ml from a 150 mg vial.

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

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

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

	Body weight (kg)									
Baseline IgE (IU/mL)	≥20- 25	>25- 30	>30- 40	>40- 50	>50- 60	>60- 70	>70- 80	>80- 90	>90-125	>125-150
≥ 30- 100	ADMINISTRATION EVERY 4 WEEKS									
> 100- 200	SEE ABOVE									
> 200- 300										375
> 300-400									450	525
> 400-500							375	375	525	600
> 500-600						375	450	450	600	
> 600-700		225			375	450	450	525		
> 700-800	225	225	300	375	450	450	525	600		
> 800-900	225	225	300	375	450	525	600			
> 900-1000	225	300	375	450	525	600				
> 1000-1100	225	300	375	450	600	Insufficient Data to Recommend a Dose				
> 1100-1200	300	300	450	525	600					
> 1200-1300	300	375	450	525						
> 1300-1500	300	375	525	600						

Treatment duration, monitoring and dose adjustments

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

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

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

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

Special populations

Renal or hepatic impairment

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

Geriatric patients (65 years or above)

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

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

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

General

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

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

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

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

Immune system disorders

- Allergic reactions

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

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

- Serum sickness

Serum sickness and serum-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanized-monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against omalizumab. The onset has typically been 1to5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgias, rash (urticarial or other forms), fever and lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder, and patients should be advised to report any suspected symptoms.

- Churg-Strauss syndrome and hypereosinophilic syndrome

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

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

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

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

Malignancies
For further information please see section 4.8.

Arterial Thromboembolic Events (ATE)
For further information please see section 4.8.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

4.6 Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk summary

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

Clinical considerations

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

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

Data

Human data

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

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

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

Animal data

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

Lactation

Risk summary

While omalizumab presence in human milk after administration of Xolair has not been studied, IgGs are present in human milk and therefore it is expected that omalizumab will be present in human milk. The frequency of infant infections identified in EXPECT was evaluated as an indirect measure of immune system development after exposure during pregnancy or through breast-feeding. The majority of infants in the primary analytic population (77.5%, 186/240) were breastfed. Serious adverse events (SAEs) categorized as “infections and infestations” were observed in 11.4% (5/44) of infants who were not breastfed, 10.4% (16/154) of infants who were exposed to Xolair through breast-feeding, and 12.5% (4/32) of infants who were breast-fed without exposure to Xolair through breast-feeding. The study has methodological limitations, including a nonrandomized study design.

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

Females and males of reproductive potential

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

Infertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Adverse Drug Reactions

Summary of the safety profile

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

Tabulated summary of adverse drug reactions from the clinical studies

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

Table 4: Adverse drug reactions from the clinical studies

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

Adverse drug reactions from spontaneous reports (frequency not known)

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

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

Skin and subcutaneous tissue disorders: Alopecia.

Blood and lymphatic system disorders: Idiopathic severe thrombocytopenia.

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

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

Anaphylaxis

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

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

Thrombocytopenia

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

Parasitic infections

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

Malignancies

During initial clinical trials in adults and adolescents 12 years of age and older, there was a numerical imbalance in cancers arising in the active treatment group, compared with the control group. The number of observed cases was uncommon (<1/100) in both the active and the control group. In a subsequent observational study comparing 5,007 Xolair-treated and 2,829 non-Xolair-treated patients followed for up to 5 years, the incidence rates of primary malignancies per 1,000 patient years were 16.01 (295/18,426 patient years) and 19.07 (190/9,963 patients years), respectively, which does not indicate an increased malignancy risk (rate ratio 0.84, 95% confidence interval, 0.62to 1.13). In a further analysis of randomized, double-blind, placebo-controlled clinical trials including 4,254 patients on Xolair and 3,178 patients on placebo, Xolair treatment was not associated with an increased malignancy risk based on incidence rates per 1,000 patient years of 4.14 (14/3,382 patient years) for Xolair treated patients and 4.45 (11/2,474 patient years) for placebo patients (rate ratio 0.93, 95% confidence interval 0.39to 2.27). The overall observed incidence rate of malignancy in the Xolair clinical trial program was comparable to that reported in the general population.

Arterial Thromboembolic Events (ATE)

In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATEs was observed. ATE included stroke, transient ischemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patients years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% confidence interval 0.91to 1.91). In a separate analysis of pooled clinical trials including all randomized double-blind, placebo-controlled clinical trials of 8 or more weeks duration, the rate of ATE per 1000 patient years was 2.69 (5/1,856 patients years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24 to 5.71).

4.9 Overdose

No case of overdose has been reported. A maximum tolerated dose of Xolair has not been determined. Single intravenous doses up to 4,000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20- week period and this dose did not result in any untoward acute effects.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

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

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

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

Clinical studies

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

In identical 16-week studies 1 and 2 the safety and efficacy of omalizumab as add-on therapy were demonstrated in 1,071 allergic asthmatics, who were symptomatic despite treatment with inhaled corticosteroids (beclomethasone dipropionate 500 to 1,200 micrograms/day).

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

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

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

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

In study 4 the safety and efficacy of omalizumab were demonstrated in 405 patients with co-morbid

allergic asthma and perennial allergic rhinitis. Eligible patients had both symptomatic allergic asthma and perennial allergic rhinitis. Patients were treated with omalizumab or placebo for 28 weeks as add- on therapy to ≥400 micrograms of Budesonide Turbohaler. Inhaled long-acting beta2 agonists (39%) and nasal corticosteroids (17%) were allowed.

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

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

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

In study 5 the efficacy and safety of Xolair were demonstrated in a 28-week study involving 419 severe allergic asthmatics, ages 12to 79 years, who had reduced lung function (FEV1 40to 80% predicted) and poor asthma symptom control despite receiving >1,000 micrograms of beclomethasone dipropionate (or equivalent) plus long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone dipropionate (or equivalent) plus long-acting beta2- agonist. Oral corticosteroid (22%), theophylline (27%) and anti-leukotriene (35%) maintenance therapies were allowed. In the treatment phase concomitant asthma therapy was not changed.

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

5.2 Pharmacokinetic properties

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 7to 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.

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 of omalizumab 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.

Characteristics in patient populations

Age, Race/Ethnicity, Gender, Body Mass Index

The population pharmacokinetics of omalizumab were analyzed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary in asthma patients for age (12to 76 years), race, ethnicity or gender or body mass index.

Patients with renal or hepatic impairment

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

5.3 Non-clinical safety data

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

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

Formal carcinogenicity studies have not been conducted with omalizumab.

In reproduction studies in cynomolgus monkeys subcutaneous doses up to 75 mg/kg (about 12-fold exposure ratio based on 28-day AUC values at 75 mg/kg versus the clinical maximum dose) did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on foetal or neonatal growth when administered throughout late gestation, delivery and nursing.

Omalizumb is excreted in milk in cynomolgus monkeys. Milk levels of omalizumab were 1.5% of the maternal blood concentration.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sucrose
Histidine
Histidine hydrochloride monohydrate
Polysorbate 20

Solvent:
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

4 years

After reconstitution: The chemical and physical stability of the reconstituted product have been demonstrated for 8 hours at 2°C to 8°C and for 4 hours at 30°C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 8 hours at 2°C to 8°C or 2 hours at 25°C.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Xolair 75mg:
Powder vial: Clear, colourless type I glass vial with a butyl rubber stopper and grey flip-off seal.
Solvent ampoule: Clear, colourless type I glass ampoule containing 2 ml water for injection.
Package of one vial of powder for solution for injection and one ampoule of water for injection.

6.6 Instructions for use, handling and disposal

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

Xolair 75 mg powder for solution for injection are supplied in a single-use vial and contain no antibacterial preservatives. Chemical and physical stability of the reconstituted product has been demonstrated for 8 hours at 2°C to 8°C and for 4 hours at 30°C. From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 8 hours at 2°C to 8°C or 2 hours at 25°C., unless reconstitution has taken place in controlled and validated aseptic conditions.

The lyophilised product takes 15 to 20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted product will appear clear to slightly opalescent, colorless to pale brownish-yellow and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted product care must be taken to WITHDRAW ALL OF THE PRODUCT from the vial before expelling any air or excess solution from the syringe in order to obtain the 0.6ml (75mg).

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

1. Draw 0.9 ml of water for injections from the ampoule into a syringe equipped with a large-bore 18-gauge needle.

2. With the vial placed upright on a flat surface, insert the needle and transfer the water for injections into the vial containing the lyophilised powder using standard aseptic techniques,

directing the water for injections directly onto the powder.

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

4. To aid in dissolution after completing step 3, gently swirl the vial for 5to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

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

When the product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted product will appear clear or slightly opaque. Do not use if solid particles are present.

5. Invert the vial for at least 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-ml syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Keeping the vial inverted position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.

6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

7. Expel air, large bubbles, and any excess solution in order to obtain the required 0.6 ml dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, it may take take 5to 10 seconds to administer the solution by subcutaneous injection.

The vial delivers 0.6 ml (75 mg) of Xolair.

8. The injections are administered subcutaneously in the arm, thigh, or lower abdomen (but not the area of 5 centimeters around the navel). Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. If you need to give more than one injection for the full dose, choose a different injection site each time you inject.

Xolair 75 mg powder for solution for injection is supplied in a single-use vial and contains no antibacterial preservatives.

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

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

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

7. PRODUCT OWNER

Novartis Pharma AG
CH 4056, Basel
Switzerland

8. DATE OF REVISION OF THE TEXT

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