

XOLAIR- omalizumab injection, solution
Genentech, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Xolair safely and effectively. See full prescribing information for Xolair.

Initial U.S. Approval: 2003

WARNING: ANAPHYLAXIS

See full prescribing information for complete boxed warning

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred after the first dose of Xolair but also has occurred beyond 1 year after beginning treatment. Closely observe patients for an appropriate period of time after Xolair administration and be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur.

RECENT MAJOR CHANGES

Indications and Usage, Pediatric Patients (Age 0 to <12) (1)	01/2010
Use in Specific Populations, Pediatric Use (Age 0 to <12) (8.4)	01/2010
Warnings and Precautions, Fever, Arthralgia, and Rash (5.6)	07/10
Adverse Reactions, Postmarketing Experience (6.2)	0710

INDICATIONS AND USAGE

Xolair is indicated for:

- Moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.

Important Limitations of use:

- Not indicated for other allergic conditions. (1)
- Not indicated for acute bronchospasm or status asthmaticus (1, 5.3)
- Not indicated for pediatric patients less than 12 years of age (1, 8.4)

DOSAGE AND ADMINISTRATION

For subcutaneous (SC) administration only.

Administer Xolair 150 to 375 mg SC every 2 or 4 weeks. (2.1)

- Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts (2.1)
- Divide doses of more than 150 mg among more than one injection site to limit injections to not more than 150 mg per site. (2.3)

DOSAGE FORMS AND STRENGTHS

- Lyophilized, sterile powder in a single-use 5mL vial, 150 mg (3)

CONTRAINDICATIONS

- Severe hypersensitivity reaction to Xolair or any ingredient of Xolair. (4, 5.1)

WARNINGS AND PRECAUTIONS

- Anaphylaxis—Administer only in a healthcare setting prepared to manage anaphylaxis that can be life-threatening and observe patients for an appropriate period of time after administration. (5.1)
- Malignancy—Malignancies have been observed in clinical studies. (5.2)
- Acute Asthma Symptoms—Do not use for the treatment of acute bronchospasm or status asthmaticus. (5.3)
- Corticosteroid Reductions—Do not abruptly discontinue corticosteroids upon initiation of Xolair therapy. (5.4)
- Fever, Arthralgia, and Rash—Stop Xolair if patients develop signs and symptoms similar to serum sickness (5.6)
- Eosinophilic Conditions—Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac

complications, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.5)

----- **ADVERSE REACTIONS** -----

In the adult and adolescent patients (≥ 12 years of age), the most commonly observed adverse reactions in clinical studies ($\geq 1\%$ more frequent in Xolair-treated patients) were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----- **DRUG INTERACTIONS** -----

- No formal drug interaction studies have been performed. (7)

----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: No adequate data in humans. Xolair Pregnancy Exposure Registry available (1-866-496-5247) (8.1)

See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**.

Revised: 1/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: Anaphylaxis

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

2.2 Dosing Adjustments

2.3 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

5.2 Malignancy

5.3 Acute Asthma Symptoms

5.4 Corticosteroid Reduction

5.5 Eosinophilic Conditions

5.6 Fever, Arthralgia, and Rash

5.7 Parasitic (Helminth) Infection

5.8 Laboratory Tests

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: Anaphylaxis

Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

Xolair (omalizumab) is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.

Important Limitations of Use

- Xolair is not indicated for treatment of other allergic conditions.
- Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus.
- Xolair is not indicated for use in pediatric patients less than 12 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

Administer Xolair (omalizumab) 150 to 375 mg by subcutaneous (SC) injection every 2 or 4 weeks. Determine doses (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). *See the dose determination charts below (Table 1 and Table 2) for appropriate dose assignment.*

Periodically reassess the need for continued therapy based upon the patient's disease severity and level of asthma control.

Table 1: Administration Every 4 Weeks: Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 4 Weeks for Adults and Adolescents 12 Years of Age and Older

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg)			
	30-60	> 60-70	> 70-90	> 90-150
≥ 30-100	150	150	150	300
> 100-200	300	300	300	
> 200-300	300			
> 300-400	SEE TABLE 2			
> 400-500				
> 500-600				
> 600-700				

Table 2: Administration Every 2 Weeks: Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 2 Weeks for Adults and Adolescents 12 Years of Age and Older

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg)			
	30-60	> 60-70	> 70-90	> 90-150
≥ 30-100	SEE TABLE 1			
> 100-200				
> 200-300		225	225	300
> 300-400	225	225	300	
> 400-500	300	300	375	
> 500-600	300	375	DO NOT DOSE	
> 600-700	375			

2.2 Dosing Adjustments

Adjust doses for significant changes in body weight (see Table 1 and Table 2).

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.

- Interruptions lasting less than one year: Dose based on serum IgE levels obtained at the initial dose determination.
- Interruptions lasting one year or more: Re-test total serum IgE levels for dose determination.

2.3 Preparation and Administration

Prepare Xolair for subcutaneous injection using Sterile Water for Injection (SWFI), USP, ONLY. Each vial of Xolair is for single use only and contains no preservatives.

Reconstitution

The lyophilized product takes 15-20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent and it is acceptable if there are a few small bubbles or foam around the edge of the vial. The reconstituted product is somewhat viscous; in order to obtain the full 1.2 mL dose, ALL OF THE PRODUCT MUST BE WITHDRAWN from the vial before expelling any air or excess solution from the syringe.

Use the solution within 8 hours following reconstitution when stored in the vial at 2-8°C (36-46°F), or

within 4 hours of reconstitution when stored at room temperature. Reconstituted Xolair vials should be protected from sunlight.

Preparation

STEP 1: Draw 1.4 mL of SWFI, USP into a 3 mL syringe equipped with a 1 inch, 18-gauge needle.

STEP 2: Place the vial upright on a flat surface and using standard aseptic technique, insert the needle and inject the SWFI, USP directly onto the product.

STEP 3: Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.

STEP 4: After completing STEP 3, gently swirl the vial for 5-10 seconds approximately every 5 minutes in order to dissolve any remaining solids. There should be no visible gel like particles in the solution. Do not use if foreign particles are present.

Note: If it takes longer than 20 minutes to dissolve completely, repeat STEP 4 until there are no visible gel-like particles in the solution. Do not use if the contents of the vial do not dissolve completely by 40 minutes.

STEP 5: Invert the vial for 15 seconds in order to allow the solution to drain toward the stopper. Using a new 3 mL syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper 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.

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

STEP 7: Expel air, large bubbles, and any excess solution in order to obtain the required 1.2 mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe.

Administration

Administer Xolair by subcutaneous injection. The injection may take 5-10 seconds to administer because the solution is slightly viscous. Each vial delivers 1.2 mL (150 mg) of Xolair. Do not administer more than 150 mg per injection site. Divide doses of more than 150 mg among two or more injection sites. (Table 3).

Table 3: Number of Injections and Total Injection Volumes

Xolair Dose (mg)	Number of Injections	Total Volume Injected (mL)
150	1	1.2
225	2	1.8
300	2	2.4
375	3	3.0

3 DOSAGE FORMS AND STRENGTHS

150 mg of omalizumab as lyophilized, sterile powder in a single-use 5 mL vial.

4 CONTRAINDICATIONS

The use of Xolair is contraindicated in the following:

Severe hypersensitivity reaction to Xolair or any ingredient of Xolair [see Warnings and

Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials the frequency of anaphylaxis attributed to Xolair use was estimated to be 0.1%. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment.

Administer Xolair only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Observe patients closely for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports [*see Adverse Reactions (6)*]. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.

Discontinue Xolair in patients who experience a severe hypersensitivity reaction [*see Contraindications (4)*].

5.2 Malignancy

Malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of adults and adolescents (≥ 12 years of age) with asthma and other allergic disorders. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known [*see Adverse Reactions (6)*].

5.3 Acute Asthma Symptoms

Xolair has not been shown to alleviate asthma exacerbations acutely. Do not use Xolair to treat acute bronchospasm or status asthmaticus.

5.4 Corticosteroid Reduction

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of Xolair therapy. Decrease corticosteroids gradually under the direct supervision of a physician.

5.5 Eosinophilic Conditions

In rare cases, patients with asthma on therapy with Xolair may present with serious systemic eosinophilia sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Xolair and these underlying conditions has not been established.

5.6 Fever, Arthralgia, and Rash

In post-approval use, some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash (urticaria or other forms), fever and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of Xolair. These signs and symptoms have recurred after additional doses in some patients. Although circulating immune complexes or a skin biopsy consistent with a Type III reaction were not seen with these cases, these signs and symptoms are similar to those seen in patients with serum sickness. Physicians should stop Xolair if a patient develops this constellation of signs and symptoms. [see *Adverse Reactions, Postmarketing Experience (6.2)*]

5.7 Parasitic (Helminth) Infection

Monitor patients at high risk of geohelminth infection while on Xolair therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping Xolair treatment.

In a one-year clinical trial conducted in Brazil in patients at high risk for geohelminthic infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of Xolair-treated patients experienced an infection, as diagnosed by standard stool examination, compared to 42% (29/69) of placebo controls. The point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received Xolair than a patient who did not have an infection. Response to appropriate anti-geohelminth treatment of infection as measured by stool egg counts was not different between treatment groups.

5.8 Laboratory Tests

Serum total IgE levels increase following administration of Xolair due to formation of Xolair:IgE complexes [see *Clinical Pharmacology (12.2)*]. Elevated serum total IgE levels may persist for up to 1 year following discontinuation of Xolair. Do not use serum total IgE levels obtained less than 1 year following discontinuation to reassess the dosing regimen because these levels may not reflect steady state free IgE levels.

6 ADVERSE REACTIONS

Use of Xolair has been associated with:

- Anaphylaxis [see *Boxed Warning and Warning and Precautions (5.1)*]
- Malignancies [see *Warnings and Precautions (5.2)*]

Anaphylaxis was reported in 3 of 3507 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient. In clinical trials the observed incidence of malignancy among Xolair-treated patients (0.5%) was numerically higher than among patients in control groups (0.2%).

6.1 Clinical Trials Experience

Adult and Adolescent Patients 12 years of Age and Older

The data described below reflect Xolair exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo. Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of one drug cannot be directly compared with rates in the clinical studies of another drug and may not reflect the rates observed in medical practice.

The adverse events most frequently resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse event) were injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in Xolair-treated patients and control patients.

Table 4 shows adverse reactions from four placebo-controlled asthma studies that occurred $\geq 1\%$ and more frequently in patients receiving Xolair than in those receiving placebo. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events and are described following Table 4 .

Table 4: Adverse Reactions $\geq 1\%$ More Frequent in Xolair-Treated Adult or Adolescent Patients 12 years of age and older: Four placebo-controlled asthma studies

Adverse reaction	Xolair n = 738 (%)	Placebo n = 717 (%)
<u>Body as a whole</u>		
Pain	7	5
Fatigue	3	2
<u>Musculoskeletal system</u>		
Arthralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
<u>Nervous system</u>		
Dizziness	3	2
<u>Skin and appendages</u>		
Pruritus	2	1
Dermatitis	2	1
<u>Special senses</u>		
Earache	2	1

There were no differences in the incidence of adverse reactions based on age (among patients under 65), gender or race.

Injection Site Reactions

Injection site reactions of any severity occurred at a rate of 45% in Xolair-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group (12% versus 9%).

The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

Immunogenicity

Antibodies to Xolair were detected in approximately 1/1723 ($< 0.1\%$) of patients treated with Xolair. The data reflect the percentage of patients whose test results were considered positive for antibodies to Xolair in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay.

Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence of antibodies to other products may be misleading.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xolair in adult and adolescent patients 12 years of age and older. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylaxis: Based on spontaneous reports and an estimated exposure of about 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to Xolair administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases.

Of the reported cases of anaphylaxis attributed to Xolair, 39% occurred with the first dose, 19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). The time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were unknown.

Twenty-three patients who experienced anaphylaxis were rechallenged with Xolair and 18 patients had a recurrence of similar symptoms of anaphylaxis. In addition, anaphylaxis occurred upon rechallenge with Xolair in 4 patients who previously experienced urticaria only.

Eosinophilic Conditions: Eosinophilic conditions have been reported [*see Warnings and Precautions (5.5)*].

Fever, Arthralgia, and Rash: A constellation of signs and symptoms including arthritis/arthralgia, rash (urticaria or other forms), fever and lymphadenopathy similar to serum sickness have been reported in postapproval use of Xolair [*see Warnings and Precautions (5.6)*]

Hematologic: Severe thrombocytopenia has been reported.

Skin: Hair loss has been reported.

7 DRUG INTERACTIONS

No formal drug interaction studies have been performed with Xolair. The concomitant use of Xolair and allergen immunotherapy has not been evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies of Xolair in pregnant women. Reproduction studies have been performed in *Cynomolgus* monkeys at subcutaneous doses up to 10 times the maximum recommended human dose on a mg/kg basis and have revealed no evidence of impaired fertility or harm to the fetus due to Xolair. Because animal reproduction studies are not always predictive of human response, administer Xolair during pregnancy only if clearly needed [see *Nonclinical Toxicology (13.2)*].

Pregnancy Exposure Registry

To monitor outcomes of pregnant women exposed to Xolair, including women who are exposed to at least one dose of Xolair within 8 weeks prior to conception or any time during pregnancy, a pregnancy exposure registry has been established. Encourage patients to call 1-866-4XOLAIR (1-866-496-5247) to enroll in the Xolair Pregnancy Exposure Registry. Call this number to obtain further information about this registry.

8.3 Nursing Mothers

There are no data from controlled clinical trials on the use of Xolair by nursing mothers. It is not known whether Xolair is excreted in human breast milk. However, IgG is excreted in human breast milk and therefore it is expected that Xolair will be excreted in human breast milk. The potential for Xolair absorption or harm to the infant is unknown; therefore caution should be exercised when Xolair is administered to a nursing woman.

The excretion of omalizumab in milk was evaluated in female *Cynomolgus* monkeys at a subcutaneous dose approximately 10 times the maximum recommended human dose on a mg/kg basis. Neonatal plasma levels of omalizumab after in utero exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of omalizumab were 1.5% of maternal blood concentration [see *Nonclinical Toxicology (13.2)*].

8.4 Pediatric Use

Safety and effectiveness of Xolair were evaluated in 2 studies in 926 (Xolair 624; placebo 302) asthma patients 6 to <12 years of age. One study was a pivotal study of similar design and conduct to that of adult and adolescent studies 1 and 2 [see *Clinical Trials (14)*]. The other study was primarily a safety study and included evaluation of efficacy as a secondary outcome. In the pivotal study, Xolair-treated patients had a statistically significant reduction in the rate of exacerbations (exacerbation was defined as worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose), but other efficacy variables such as nocturnal symptom scores, beta-agonist use, and measures of airflow (FEV₁) were not significantly different in Xolair-treated patients compared to placebo. Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥12 years old and the modest efficacy of Xolair in the pivotal pediatric study, the risk-benefit assessment does not support the use of Xolair in patients 6 to <12 years of age. Although patients treated with Xolair in these two studies did not develop anaphylaxis or malignancy, the studies are not adequate to address these concerns because patients with a history of anaphylaxis or malignancy were excluded, and the duration of exposure and sample size were not large enough to exclude these risks in patients 6 to <12 years of age. Furthermore, there is no reason to expect that younger pediatric patients would not be at risk of anaphylaxis and malignancy seen in adult and adolescent patients with Xolair. [see *Warnings and Precautions (5.1) (5.2)*; and *Adverse Reactions (6)*].

Studies in patients 0-5 years of age were not required because of the safety concerns of anaphylaxis and malignancy associated with the use of Xolair in adults and adolescents.

8.5 Geriatric Use

In clinical trials 134 patients 65 years of age or older were treated with Xolair. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

10 OVERDOSAGE

The maximum tolerated dose of Xolair has not been determined. Single intravenous doses of up to 4000 mg have been administered to patients without evidence of dose limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20 week period, which was not associated with toxicities.

11 DESCRIPTION

Xolair (omalizumab) is a recombinant DNA-derived humanized IgG1 κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149 kiloDaltons. Xolair is produced by a Chinese hamster ovary cell suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Xolair is a sterile, white, preservative free, lyophilized powder contained in a single use vial that is reconstituted with Sterile Water for Injection (SWFI), USP, and administered as a subcutaneous (SC) injection. Each 202.5 mg vial of omalizumab also contains L-histidine (1.8 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 20 (0.5 mg) and sucrose (145.5 mg) and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (Fc ϵ RI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on Fc ϵ RI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with Xolair also reduces the number of Fc ϵ RI receptors on basophils in atopic patients.

12.2 Pharmacodynamics

In clinical studies, serum free IgE levels were reduced in a dose dependent manner within 1 hour following the first dose and maintained between doses. Mean serum free IgE decrease was greater than 96% using recommended doses. Serum total IgE levels (i.e., bound and unbound) increased after the first dose due to the formation of omalizumab:IgE complexes, which have a slower elimination rate compared with free IgE. At 16 weeks after the first dose, average serum total IgE levels were five-fold higher compared with pre-treatment when using standard assays. After discontinuation of Xolair dosing, the Xolair-induced increase in total IgE and decrease in free IgE were reversible, with no observed rebound in IgE levels after drug washout. Total IgE levels did not return to pre-treatment levels for up to one year after discontinuation of Xolair.

12.3 Pharmacokinetics

After SC administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single SC 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 Xolair, 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.

In vitro, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than 1 million daltons in molecular weight are not observed in vitro or in vivo. Tissue distribution studies in Cynomolgus monkeys showed no specific uptake of ¹²⁵I-omalizumab by any organ or tissue. The apparent volume of distribution in patients following SC administration was 78 \pm 32 mL/kg.

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the liver reticuloendothelial system (RES) and endothelial cells. Intact IgG is also excreted in bile. In studies with mice and monkeys, omalizumab:IgE complexes were eliminated by interactions with Fcγ receptors within the RES at rates that were generally faster than IgG clearance. In asthma patients omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4 ± 1.1 mL/kg/day. In addition, doubling body weight approximately doubled apparent clearance.

Special Populations

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed in animals to evaluate the carcinogenic potential of Xolair.

No evidence of mutagenic activity was observed in Ames tests using six different strains of bacteria with and without metabolic activation at omalizumab concentrations up to 5000 μg/mL.

There were no effects on fertility and reproductive performance in male and female Cynomolgus monkeys that received Xolair at subcutaneous doses up to 75 mg/kg/week (approximately 5 times the maximum recommended human dose on an AUC basis).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies:

Reproductive studies have been performed in Cynomolgus monkeys at subcutaneous doses up to 75 mg/kg (approximately 10 times the maximum recommended human dose on a mg/kg basis) and have revealed no evidence of maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing. IgG molecules are known to cross the placental barrier [see *Use in Specific Populations (8.1)*].

Lactation Studies:

The excretion of omalizumab in milk was evaluated in female Cynomolgus monkeys receiving a subcutaneous dose of 75 mg/kg/week (approximately 10 times the maximum recommended human dose on a mg/kg basis). Neonatal plasma levels of omalizumab after in utero exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of Xolair were 1.5% of maternal blood concentration. [see *Use in Specific Population (8.3)*].

14 CLINICAL STUDIES

Adult and Adolescent Patients 12 Years of Age and Older

The safety and efficacy of Xolair were evaluated in three randomized, double-blind, placebo-controlled, multicenter trials.

The trials enrolled patients 12 to 76 years old, with moderate to severe persistent (NHLBI criteria) asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. In all trials, Xolair dosing was based on body weight and baseline serum total IgE concentration. All patients were required to have a baseline IgE between 30 and 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of Xolair or a matching volume of placebo over each 4-week period. The maximum Xolair dose per

4 weeks was 750 mg.

In all three studies an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose. Most exacerbations were managed in the out-patient setting and the majority were treated with systemic steroids. Hospitalization rates were not significantly different between Xolair and placebo-treated patients; however, the overall hospitalization rate was small. Among those patients who experienced an exacerbation, the distribution of exacerbation severity was similar between treatment groups.

Studies 1 and 2

At screening, patients in Studies 1 and 2 had a forced expiratory volume in one second (FEV₁) between 40% and 80% predicted. All patients had a FEV₁ improvement of at least 12% following beta₂-agonist administration. All patients were symptomatic and were being treated with inhaled corticosteroids (ICS) and short acting beta₂-agonists. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

Each study was comprised of a run-in period to achieve a stable conversion to a common ICS (beclomethasone dipropionate), followed by randomization to Xolair or placebo. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 weeks during which ICS dose reduction was attempted in a step-wise manner.

The distribution of the number of asthma exacerbations per patient in each group during a study was analyzed separately for the stable steroid and steroid-reduction periods.

In both Studies 1 and 2 the number of exacerbations per patient was reduced in patients treated with Xolair compared with placebo (Table 5).

Measures of airflow (FEV₁) and asthma symptoms were also evaluated in these studies. The clinical relevance of the treatment-associated differences is unknown. Results from the stable steroid phase Study 1 are shown in Table 6. Results from the stable steroid phase of Study 2 and the steroid reduction phases of both Studies 1 and 2 were similar to those presented in Table 6.

Table 5: Frequency of Asthma Exacerbations per Patient by Phase in Studies 1 and 2

Exacerbations per patient	Stable Steroid Phase (16 wks)			
	Study 1		Study 2	
	Xolair N = 268 (%)	Placebo N = 257 (%)	Xolair N = 274 (%)	Placebo N = 272 (%)
0	85.8	76.7	87.6	69.9
1	11.9	16.7	11.3	25.0
≥ 2	2.2	6.6	1.1	5.1
p-Value	0.005		< 0.001	
Mean number exacerbations/patient	0.2	0.3	0.1	0.4
Exacerbations per patient	Steroid Reduction Phase (12 wks)			
	Xolair N = 268 (%)	Placebo N = 257 (%)	Xolair N = 274 (%)	Placebo N = 272 (%)
	0	78.7	67.7	83.9
1	19.0	28.4	14.2	26.1
≥ 2	2.2	3.9	1.8	3.7

p-Value	0.004		< 0.001	
Mean number exacerbations/patient	0.2	0.4	0.2	0.3

Table 6: Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Study 1

Endpoint	Xolair N = 268*		Placebo N = 257*	
	Mean Baseline	Median Change (Baseline to Wk 16)	Mean Baseline	Median Change (Baseline to Wk 16)
Total asthma symptom score	4.3	-1.5 [†]	4.2	-1.1 [†]
Nocturnal asthma score	1.2	-0.4 [†]	1.1	-0.2 [†]
Daytime asthma score	2.3	-0.9 [†]	2.3	-0.6 [†]
FEV ₁ % predicted	68	3 [†]	68	0 [†]

Asthma symptom scale: total score from 0 (least) to 9 (most); nocturnal and daytime scores from 0 (least) to 4 (most symptoms).

* Number of patients available for analysis ranges 255-258 in the Xolair group and 238-239 in the placebo group.

[†] Comparison of Xolair versus placebo (p < 0.05).

Study 3

In Study 3, there was no restriction on screening FEV₁, and unlike Studies 1 and 2, long-acting beta₂-agonists were allowed. Patients were receiving at least 1000 µg/day fluticasone propionate and a subset was also receiving oral corticosteroids. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

The study was comprised of a run-in period to achieve a stable conversion to a common ICS (fluticasone propionate), followed by randomization to Xolair or placebo. Patients were stratified by use of ICS-only or ICS with concomitant use of oral steroids. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 16 weeks during which ICS or oral steroid dose reduction was attempted in a step-wise manner.

The number of exacerbations in patients treated with Xolair was similar to that in placebo-treated patients (Table 7). The absence of an observed treatment effect may be related to differences in the patient population compared with Studies 1 and 2, study sample size, or other factors.

Table 7: Percentage of Patients with Asthma Exacerbations by Subgroup and Phase in Study 3

	Stable Steroid Phase (16 wks)			
	Inhaled Only		Oral + Inhaled	
	Xolair N = 126	Placebo N = 120	Xolair N = 50	Placebo N = 45
% Patients with ≥ 1 exacerbations	15.9	15.0	32.0	22.2

Difference (95% CI)	0.9 (-9.7, 13.7)	9.8 (-10.5, 31.4)
Steroid Reduction Phase (16 wks)		
	Xolair N = 126	Placebo N = 120
	Xolair N = 50	Placebo N = 45
% Patients with ≥ 1 exacerbations	22.2	26.7
	42.0	42.2
Difference (95% CI)	-4.4 (-17.6, 7.4)	-0.2 (-22.4, 20.1)

In all three of the studies, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV₁ > 80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

Pediatric Patients 6 to < 12 Years of Age

Clinical studies with Xolair in pediatric patients 6 to 11 years of age have been conducted [*see Use in Specific Populations (8.4)*]

Pediatric Patients <6 Years of Age

Clinical studies have with Xolair in pediatric patients less than 6 years of age have not been conducted [*see Use in Specific Populations (8.4)*]

16 HOW SUPPLIED/STORAGE AND HANDLING

Xolair (omalizumab) is supplied as a lyophilized, sterile powder in a single-use, 5 mL vial without preservatives. Each vial delivers 150 mg of Xolair upon reconstitution with 1.4 mL SWFI, USP. Each carton contains one single-use vial of Xolair® (omalizumab) NDC 50242-040-62.

Xolair should be shipped at controlled ambient temperature ($\leq 30^{\circ}\text{C}$ [$\leq 86^{\circ}\text{F}$]). Store Xolair under refrigerated conditions $2\text{-}8^{\circ}\text{C}$ ($36\text{-}46^{\circ}\text{F}$). Do not use beyond the expiration date stamped on carton.

Use the solution for subcutaneous administration within 8 hours following reconstitution when stored in the vial at $2\text{-}8^{\circ}\text{C}$ ($36\text{-}46^{\circ}\text{F}$), or within 4 hours of reconstitution when stored at room temperature.

Reconstituted Xolair vials should be protected from direct sunlight.

17 PATIENT COUNSELING INFORMATION

[*See Medication Guide*]

17.1 Information for Patients

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment. The complete text of the Medication Guide is reprinted at the end of this document.

Inform patients of the risk of life-threatening anaphylaxis with Xolair including the following points [*see Warnings and Precautions (5.1)*]:

- There have been reports of anaphylaxis up to 4 days after administration of Xolair
- Xolair should only be administered in a healthcare setting by healthcare providers.
- Patients should be closely observed following administration
- Patients should be informed of the signs and symptoms of anaphylaxis
- Patients should be instructed to seek immediate medical care should such signs or symptoms occur

Instruct patients receiving Xolair not to decrease the dose of, or stop taking any other asthma medications unless otherwise instructed by their physician. Inform patients that they may not see immediate improvement in their asthma after beginning Xolair therapy.

Pregnancy Exposure Registry

Encourage pregnant women exposed to Xolair to enroll in the Xolair Pregnancy Exposure Registry [1-866-4XOLAIR (1-866-496-5247)] (8.1)

MEDICATION GUIDE

XOLAIR[®]

(omalizumab)

IMPORTANT: XOLAIR SHOULD ALWAYS BE INJECTED IN YOUR DOCTOR'S OFFICE.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT XOLAIR?

A severe allergic reaction called anaphylaxis has happened in some patients after they received Xolair. Anaphylaxis is a life-threatening condition and can lead to death so get emergency medical treatment right away if symptoms occur.

Signs and Symptoms of anaphylaxis include:

- wheezing, shortness of breath, cough, chest tightness, or trouble breathing
- low blood pressure, dizziness, fainting, rapid or weak heartbeat, anxiety, or feeling of “impending doom”
- flushing, itching, hives, or feeling warm
- swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing

Get emergency medical treatment right away if you have signs or symptoms of anaphylaxis after receiving Xolair.

Anaphylaxis from Xolair can happen:

- right after receiving a Xolair injection or hours later
- after any Xolair injection. Anaphylaxis has occurred after the first Xolair injection or after many Xolair injections.

Your healthcare provider should watch you for some time in the office for signs or symptoms of anaphylaxis after injecting Xolair. If you have signs or symptoms of anaphylaxis, tell your healthcare provider right away.

Your healthcare provider should instruct you about getting emergency medical treatment and further medical care if you have signs or symptoms of anaphylaxis after leaving the doctor's office.

WHAT IS XOLAIR?

Xolair is an injectable medicine for patients 12 years of age and older with moderate to severe persistent allergic asthma whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids. A skin or blood test is done to see if you have allergic asthma.

WHAT ELSE SHOULD I KNOW ABOUT XOLAIR?

- You should not receive Xolair if you have ever had an allergic reaction to a Xolair injection.
- Do not change or stop taking any of your other asthma medicines unless your healthcare provider tells you to do so.
- There are other possible side effects with Xolair. Talk to your doctor for more information. You can also go to www.xolair.com or call 1-866-4XOLAIR (1-866-496-5247).
- **You may report side effects to FDA at 1-800-FDA-1088.**

This Medication Guide has been approved by the U.S. Food and Drug Administration.

XOLAIR®

(omalizumab)

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

Jointly marketed by:

Genentech USA, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-499

Novartis Pharmaceuticals Corporation

One Health Plaza

East Hanover, NJ 07936-1080

7390209/XOL-400050

LX1331

4855302

Initial US Approval: June 2003

Revision Date: July 2010

Xolair® is a registered trademark of
Novartis AG Corporation.

©2010 Genentech USA, Inc.

NDC 50242-040-62
LIST NO. 13013

SINGLE-USE VIAL

150 mg

Xolair[®]
Omalizumab
FOR SUBCUTANEOUS USE

KEEP REFRIGERATED. DO NOT FREEZE.

Genentech

 **NOVARTIS**

Xolair 150mg Principal Display Panel

XOLAIR

omalizumab injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:50242-040
Route of Administration	SUBCUTANEOUS	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
OMALIZUMAB (OMALIZUMAB)	OMALIZUMAB	202.5 mg in 1.4 mL

Inactive Ingredients

Ingredient Name	Strength
SUCROSE	145.5 mg in 1.4 mL
HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE	2.8 mg in 1.4 mL
HISTIDINE	1.8 mg in 1.4 mL
POLYSORBATE 20	0.5 mg in 1.4 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50242-040-62	1 in 1 CARTON		
1		1.4 mL in 1 VIAL, SINGLE-USE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103976	06/20/2003	

Labeler - Genentech, Inc. (080129000)**Registrant** - Genentech, Inc. (080129000)**Establishment**

Name	Address	ID/FEI	Business Operations
Genentech, Inc. (SSF)		080129000	ANALYSIS, API MANUFACTURE, MANUFACTURE

Establishment

Name	Address	ID/FEI	Business Operations
Genentech, Inc. (Vacaville)		004074162	API MANUFACTURE

Revised: 7/2010

Genentech, Inc.