

**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.

XOLAIR® (omalizumab) for injection, for subcutaneous use  
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. (5.1)

**RECENT MAJOR CHANGES**

Indications and Usage (1.2, 1.3) 3/2014  
Dosage and Administration (2.3) 3/2014

**INDICATIONS AND USAGE**

Xolair is an anti-IgE antibody 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 (1.1)
- Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment (1.2)

Important Limitations of use:

- Not indicated for other allergic conditions or other forms of urticaria. (1.1, 1.2, 1.3)
- Not indicated for acute bronchospasm or status asthmaticus. (1.1, 1.3, 5.3)
- Not indicated for pediatric patients less than 12 years of age. (1.1, 1.2, 1.3, 8.4)

**DOSAGE AND ADMINISTRATION**

For subcutaneous (SC) administration only. (2.1, 2.3)

Divide doses of more than 150 mg among more than one injection site to limit injections to not more than 150 mg per site. (2.4)

- Allergic Asthma: Xolair 150 to 375 mg SC every 2 or 4 weeks.  
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)

- Chronic Idiopathic Urticaria: Xolair 150 or 300 mg SC every 4 weeks.  
Dosing in CIU is not dependent on serum IgE level or body weight. (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 Reduction—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**

- Allergic Asthma: The most common adverse reactions (≥1% more frequent in Xolair-treated patients) in clinical studies were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. (6.1)
- Chronic Idiopathic Urticaria: The most common adverse events (≥2% Xolair-treated patients and more frequent than in placebo) included the following: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough. (6.2)

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

**DRUG INTERACTIONS**

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2014

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1 **FULL PRESCRIBING INFORMATION**  
2

**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)*].**

3  
4 **1 INDICATIONS AND USAGE**  
5

6 **1.1 Allergic Asthma**

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

10  
11 Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.  
12

13 **1.2 Chronic Idiopathic Urticaria (CIU)**

14 Xolair is indicated for the treatment of adults and adolescents (12 years of age and above)  
15 with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine  
16 treatment.  
17

18 **1.3 Important Limitations of Use:**

- 19
  - Xolair is not indicated for treatment of other allergic conditions or other forms of  
20 urticaria.
  - Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus.  
21
  - Xolair is not indicated for use in pediatric patients less than 12 years of age.  
22  
23

24 **2 DOSAGE AND ADMINISTRATION**  
25

26 **2.1 Dose for Allergic Asthma**

27 Administer Xolair 150 to 375 mg by subcutaneous (SC) injection every 2 or 4 weeks.  
28 Determine doses (mg) and dosing frequency by serum total IgE level (IU/mL), measured  
29 before the start of treatment, and body weight (kg). *See the dose determination charts below*  
30 *(Table 1 and Table 2) for appropriate dose assignment.*  
31

32 Periodically reassess the need for continued therapy based upon the patient's disease severity  
33 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  
 for Allergic Asthma

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	<b>SEE TABLE 2</b>
> 200–300	300			
> 300–400				
> 400–500				
> 500–600				

34

**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  
 for Allergic Asthma

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

35

**2.2 Dosing Adjustments for Allergic Asthma**

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

36

37

38

39

40

41

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.

42

43

- Interruptions lasting less than one year: Dose based on serum IgE levels obtained at the initial dose determination.

- 44       • Interruptions lasting one year or more: Re-test total serum IgE levels for dose  
45       determination.  
46

### 47       **2.3 Dose for Chronic Idiopathic Urticaria**

48       Administer Xolair 150 or 300 mg by subcutaneous injection every 4 weeks.

49  
50       Dosing of Xolair in CIU patients is not dependent on serum IgE (free or total) level or body  
51       weight.

52  
53       The appropriate duration of therapy for CIU has not been evaluated. Periodically reassess  
54       the need for continued therapy.  
55

### 56       **2.4 Preparation and Administration**

57       Prepare Xolair for subcutaneous injection using Sterile Water for Injection (SWFI), USP,  
58       ONLY. Each vial of Xolair is for single use only and contains no preservatives.  
59

#### 60       *Reconstitution*

61       The lyophilized product takes 15–20 minutes to dissolve. The fully reconstituted product  
62       will appear clear or slightly opalescent and it is acceptable if there are a few small bubbles  
63       or foam around the edge of the vial. The reconstituted product is somewhat viscous; in  
64       order to obtain the full 1.2 mL dose, ALL OF THE PRODUCT MUST BE WITHDRAWN  
65       from the vial before expelling any air or excess solution from the syringe.  
66

67       Use the solution within 8 hours following reconstitution when stored in the vial at 2–8°C  
68       (36–46°F), or within 4 hours of reconstitution when stored at room temperature.

69       Reconstituted Xolair vials should be protected from sunlight.  
70

#### 71       *Preparation*

72       **STEP 1:** Draw 1.4 mL of SWFI, USP into a 3 mL syringe equipped with a 1 inch,  
73       18-gauge needle.

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

76       **STEP 3:** Keeping the vial upright, gently swirl the upright vial for approximately  
77       1 minute to evenly wet the powder. Do not shake.

78       **STEP 4:** After completing STEP 3, gently swirl the vial for 5-10 seconds approximately  
79       every 5 minutes in order to dissolve any remaining solids. There should be no  
80       visible gel like particles in the solution. Do not use if foreign particles are  
81       present.  
82

83       Note: If it takes longer than 20 minutes to dissolve completely, repeat STEP 4  
84       until there are no visible gel-like particles in the solution. Do not use if the  
85       contents of the vial do not dissolve completely by 40 minutes.  
86

- 87 **STEP 5:** Invert the vial for 15 seconds in order to allow the solution to drain toward the  
88 stopper. Using a new 3 mL syringe equipped with a 1-inch, 18-gauge needle,  
89 insert the needle into the inverted vial. Position the needle tip at the very bottom  
90 of the solution in the vial stopper when drawing the solution into the syringe.  
91 Before removing the needle from the vial, pull the plunger all the way back to  
92 the end of the syringe barrel in order to remove all of the solution from the  
93 inverted vial.
- 94 **STEP 6:** Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.
- 95 **STEP 7:** Expel air, large bubbles, and any excess solution in order to obtain the required  
96 1.2 mL dose. A thin layer of small bubbles may remain at the top of the solution  
97 in the syringe.  
98

#### 99 Administration

100 Administer Xolair by subcutaneous injection. The injection may take 5-10 seconds to  
101 administer because the solution is slightly viscous. Each vial delivers 1.2 mL (150 mg) of  
102 Xolair. Do not administer more than 150 mg per injection site. Divide doses of more than  
103 150 mg among two or more injection sites (Table 3).  
104

**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

105 \*All doses in the table are approved for use in allergic asthma  
106 patients. The 150 mg and 300 mg Xolair doses are intended for use  
107 in CIU patients.  
108

### 109 3 DOSAGE FORMS AND STRENGTHS

110 150 mg of omalizumab as lyophilized, sterile powder in a single-use 5 mL vial.  
111

### 112 4 CONTRAINDICATIONS

113 The use of Xolair is contraindicated in the following:

114 Severe hypersensitivity reaction to Xolair or any ingredient of Xolair [*see Warnings and*  
115 *Precautions (5.1)*].  
116

### 117 5 WARNINGS AND PRECAUTIONS

118

119 **5.1 Anaphylaxis**

120 Anaphylaxis has been reported to occur after administration of Xolair in premarketing  
121 clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these  
122 reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or  
123 angioedema of the throat or tongue. Some of these events have been life-threatening. In  
124 premarketing clinical trials in allergic asthma, anaphylaxis was reported in 3 of 3507  
125 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two  
126 patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90  
127 minutes after administration in two patients and 2 hours after administration in one patient.  
128 In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use  
129 was estimated to be at least 0.2% of patients based on an estimated exposure of about  
130 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as  
131 early as after the first dose of Xolair, but also has occurred beyond one year after beginning  
132 regularly scheduled treatment.

133

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

140

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

143

144 **5.2 Malignancy**

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

153

154 **5.3 Acute Asthma Symptoms**

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

157

158 **5.4 Corticosteroid Reduction**

159 Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of Xolair  
160 therapy for allergic asthma. Decrease corticosteroids gradually under the direct supervision  
161 of a physician. In CIU patients, the use of Xolair in combination with corticosteroids has  
162 not been evaluated.

163

164 **5.5 Eosinophilic Conditions**

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

173  
174 **5.6 Fever, Arthralgia, and Rash**

175 In post-approval use, some patients have experienced a constellation of signs and symptoms  
176 including arthritis/arthralgia, rash, fever and lymphadenopathy with an onset 1 to 5 days  
177 after the first or subsequent injections of Xolair. These signs and symptoms have recurred  
178 after additional doses in some patients. Although circulating immune complexes or a skin  
179 biopsy consistent with a Type III reaction were not seen with these cases, these signs and  
180 symptoms are similar to those seen in patients with serum sickness. Physicians should stop  
181 Xolair if a patient develops this constellation of signs and symptoms [*see Adverse*  
182 *Reactions (6.4)*].

183  
184 **5.7 Parasitic (Helminth) Infection**

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

188  
189 In a one-year clinical trial conducted in Brazil in patients at high risk for geohelminthic  
190 infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of Xolair-  
191 treated patients experienced an infection, as diagnosed by standard stool examination,  
192 compared to 42% (29/69) of placebo controls. The point estimate of the odds ratio for  
193 infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study  
194 a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have  
195 received Xolair than a patient who did not have an infection. Response to appropriate anti-  
196 geohelminth treatment of infection as measured by stool egg counts was not different  
197 between treatment groups.

198  
199 **5.8 Laboratory Tests**

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

206  
207 **6 ADVERSE REACTIONS**

208 Use of Xolair has been associated with:

- 209
  - Anaphylaxis [*see Boxed Warning and Warnings and Precautions (5.1)*]

- 210 • Malignancies [*see Warnings and Precautions (5.2)*]  
211

212 Because clinical trials are conducted under widely varying conditions, adverse reaction  
213 rates observed in the clinical trials of a drug cannot be directly compared to rates in the  
214 clinical trials of another drug and may not reflect the rates observed in clinical practice.  
215

## 216 **6.1 Clinical Trials Experience in Allergic Asthma**

217

### 218 *Adult and Adolescent Patients 12 years of Age and Older*

219 The data described below reflect Xolair exposure for 2076 adult and adolescent patients  
220 ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one  
221 year or more, in either placebo-controlled or other controlled asthma studies. The mean age  
222 of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60%  
223 were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or  
224 4 weeks or, for patients assigned to control groups, standard therapy with or without a  
225 placebo.  
226

227 The adverse events most frequently resulting in clinical intervention (e.g., discontinuation  
228 of Xolair, or the need for concomitant medication to treat an adverse event) were injection  
229 site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis  
230 (16%), headache (15%), and pharyngitis (11%). These events were observed at similar  
231 rates in Xolair-treated patients and control patients.  
232

233 Table 4 shows adverse reactions from four placebo-controlled asthma studies that  
234 occurred  $\geq 1\%$  and more frequently in patients receiving Xolair than in those receiving  
235 placebo. Adverse events were classified using preferred terms from the International  
236 Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately  
237 from the reporting of other adverse events and are described following Table 4.  
238

**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

239

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

242

243 **Injection Site Reactions**

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

248

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

251

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

254

255 **6.2 Clinical Trials Experience in Chronic Idiopathic Urticaria**

256

257 *Adult and Adolescent Patients 12 years of Age and Older*

258 The safety of Xolair for the treatment of CIU was assessed in three placebo-controlled,  
259 multiple-dose clinical studies of 12 weeks' (CIU Study 2) and 24 weeks' duration (CIU  
260 Studies 1 and 3). In CIU Studies 1 and 2, patients received Xolair 75, 150, or 300 mg or  
261 placebo every 4 weeks in addition to their baseline level of H1 antihistamine therapy  
262 throughout the treatment period. In CIU Study 3 patients were randomized to Xolair 300  
263 mg or placebo every 4 weeks in addition to their baseline level of H1 antihistamine therapy.  
264 The data described below reflect Xolair exposure for 733 patients enrolled and receiving at  
265 least one dose of Xolair in the three clinical trials, including 684 patients exposed for 12  
266 weeks and 427 exposed for 24 weeks. The mean age of patients receiving Xolair 300 mg  
267 was 43 years, 75% were women, and 89% were white. The demographic profiles for  
268 patients receiving Xolair 150 mg and 75 mg were similar.

269 Table 5 shows adverse events that occurred in  $\geq 2\%$  of patients receiving Xolair (150 or  
270 300 mg) and more frequently than those receiving placebo. Adverse events are pooled  
271 from Study 2 and the first 12 weeks of Studies 1 and 3.

272

**Table 5**

Adverse Events Occurring in  $\geq 2\%$  in Xolair-Treated Patients and More Frequently than in  
Patients Treated with Placebo (Day 1 to Week 12)

Adverse Events (by MedDRA Preferred Term)	CIU Studies 1, 2 and 3 Pooled		
	150mg (n=175)	300mg (n=412)	Placebo (n=242)
<u>Gastrointestinal disorders*</u>			
Nausea	2 (1.1%)	11 (2.7%)	6 (2.5%)
<u>Infections and infestations*</u>			
Nasopharyngitis	16 (9.1%)	27 (6.6%)	17 (7.0%)
Sinusitis	2 (1.1%)	20 (4.9%)	5 (2.1%)
Upper respiratory tract infection	2 (1.1%)	14 (3.4%)	5 (2.1%)
Viral upper respiratory tract infection	4 (2.3%)	2 (0.5%)	(0.0%)
<u>Musculoskeletal and connective tissue disorders*</u>			
Arthralgia	5 (2.9%)	12 (2.9%)	1 (0.4%)
<u>Nervous system disorders*</u>			
Headache	21 (12.0%)	25 (6.1%)	7 (2.9%)
<u>Respiratory, thoracic, and mediastinal disorders*</u>			
Cough	2 (1.1%)	9 (2.2%)	3 (1.2%)

\* MedDRA (15.1) System Organ Class

273

274 Additional events reported during the 24 week treatment period in Studies 1 and 3 [ $\geq 2\%$  of  
275 patients receiving Xolair (150 or 300 mg) and more frequently than those receiving  
276 placebo] included: toothache, fungal infection, urinary tract infection, myalgia, pain in

277 extremity, musculoskeletal pain, peripheral edema, pyrexia, migraine, sinus headache,  
278 anxiety, oropharyngeal pain, asthma, urticaria, and alopecia.

279

### 280 **Injection Site Reactions**

281 Injection site reactions of any severity occurred during the studies in more Xolair-treated  
282 patients [11 patients (2.7%) at 300 mg, 1 patient (0.6%) at 150 mg] compared with 2  
283 placebo-treated patients (0.8%). The types of injection site reactions included: swelling,  
284 erythema, pain, bruising, itching, bleeding and urticaria. None of the events resulted in  
285 study discontinuation or treatment interruption.

286

### 287 **6.3 Immunogenicity**

288 Antibodies to Xolair were detected in approximately 1/1723 (< 0.1%) of patients treated  
289 with Xolair in the clinical studies for approval of asthma. There were no detectable  
290 antibodies in the patients treated in the phase 3 CIU clinical trials, but due to levels of  
291 Xolair at the time of anti-therapeutic antibody sampling and missing samples for some  
292 patients, antibodies to Xolair could only have been determined in 88% of the 733 patients  
293 treated in these clinical studies. The data reflect the percentage of patients whose test  
294 results were considered positive for antibodies to Xolair in ELISA assays and are highly  
295 dependent on the sensitivity and specificity of the assays. Additionally, the observed  
296 incidence of antibody positivity in the assay may be influenced by several factors including  
297 sample handling, timing of sample collection, concomitant medications, and underlying  
298 disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence  
299 of antibodies to other products may be misleading.

300

### 301 **6.4 Postmarketing Experience**

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

306

307 Anaphylaxis: Based on spontaneous reports and an estimated exposure of about  
308 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis  
309 attributed to Xolair use was estimated to be at least 0.2% of patients. Diagnostic criteria of  
310 anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise,  
311 and/or reduced blood pressure with or without associated symptoms, and a temporal  
312 relationship to Xolair administration with no other identifiable cause. Signs and symptoms  
313 in these reported cases included bronchospasm, hypotension, syncope, urticaria,  
314 angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous  
315 angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or  
316 syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in  
317 hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24%  
318 of the cases.

319

320 Of the reported cases of anaphylaxis attributed to Xolair, 39% occurred with the first dose,  
321 19% occurred with the second dose, 10% occurred with the third dose, and the rest after  
322 subsequent doses. One case occurred after 39 doses (after 19 months of continuous

323 therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). The  
324 time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30  
325 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90  
326 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6  
327 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and  
328 greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were  
329 unknown.

330

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

335

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

338

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

343

344 Hematologic: Severe thrombocytopenia has been reported.

345

346 Skin: Hair loss has been reported.

347

## 348 **7 DRUG INTERACTIONS**

349 No formal drug interaction studies have been performed with Xolair.

350

351 In patients with allergic asthma the concomitant use of Xolair and allergen immunotherapy  
352 has not been evaluated.

353

354 In patients with CIU the use of Xolair in combination with immunosuppressive therapies  
355 has not been studied.

356

## 357 **8 USE IN SPECIFIC POPULATIONS**

358

### 359 **8.1 Pregnancy**

360

361 *Pregnancy Category B*

362

363 *Pregnancy Exposure Registry*

364 There is a pregnancy exposure registry that monitors pregnancy outcomes in women  
365 exposed to Xolair during pregnancy. Encourage patients to call 1-866-4XOLAIR (1-866-  
366 496-5247) or visit [www.xolairpregnancyregistry.com](http://www.xolairpregnancyregistry.com) for information about the pregnancy  
367 exposure registry and the enrollment procedure.

368

369 *Risk Summary*

370 Adequate and well-controlled studies with Xolair have not been conducted in pregnant  
371 women. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4%  
372 for major malformations, and 15 to 20% for pregnancy loss. In animal reproduction  
373 studies, no evidence of fetal harm was observed in Cynomolgus monkeys with  
374 subcutaneous doses of omalizumab up to 10 times the maximum recommended human dose  
375 (MRHD). Because animal reproduction studies are not always predictive of human  
376 response, Xolair should be used during pregnancy only if clearly needed.

377

#### 378 *Clinical Considerations*

379 In general, monoclonal antibodies are transported across the placenta in a linear fashion as  
380 pregnancy progresses, with the largest amount transferred during the third trimester.

381

#### 382 *Data*

##### 383 *Animal Data*

384 Reproductive studies have been performed in Cynomolgus monkeys at subcutaneous doses  
385 of omalizumab up to 75 mg/kg (approximately 10 times the MRHD on a mg/kg basis). No  
386 evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when  
387 omalizumab was administered throughout organogenesis. Omalizumab did not elicit  
388 adverse effects on fetal or neonatal growth when administered throughout late gestation,  
389 delivery and nursing. Neonatal serum levels of omalizumab after in utero exposure and 28  
390 days of nursing were between 11% and 94% of the maternal serum level. Levels of  
391 omalizumab in milk were 0.15% of maternal serum concentration.

392

### 393 **8.3 Nursing Mothers**

394 It is not known whether Xolair is present in human breast milk; however, IgG is present in  
395 human milk in small amounts. In Cynomolgus monkeys, milk levels of omalizumab were  
396 measured at 0.15% of the maternal serum concentration [see *Use in Specific Populations*  
397 (8.1)]. The developmental and health benefits of breastfeeding should be considered along  
398 with the mother's clinical need for Xolair and any potential adverse effects on the breastfed  
399 child from Xolair or from the underlying maternal condition. Exercise caution when  
400 administering Xolair to a nursing woman.

401

### 402 **8.4 Pediatric Use**

#### 403 *Allergic Asthma*

404 Safety and effectiveness of Xolair for allergic asthma were evaluated in 2 studies in 926  
405 (Xolair 624; placebo 302) asthma patients 6 to <12 years of age. One study was a pivotal  
406 study of similar design and conduct to that of adult and adolescent Asthma Studies 1 and 2  
407 [see *Clinical Trials (14.1)*]. The other study was primarily a safety study and included  
408 evaluation of efficacy as a secondary outcome. In the pivotal study, Xolair-treated patients  
409 had a statistically significant reduction in the rate of exacerbations (exacerbation was  
410 defined as worsening of asthma that required treatment with systemic corticosteroids or a  
411 doubling of the baseline ICS dose), but other efficacy variables such as nocturnal symptom  
412 scores, beta-agonist use, and measures of airflow (FEV<sub>1</sub>) were not significantly different in  
413 Xolair-treated patients compared to placebo. Considering the risk of anaphylaxis and  
414 malignancy seen in Xolair-treated patients ≥ 12 years old and the modest efficacy of Xolair  
415 in the pivotal pediatric study, the risk-benefit assessment does not support the use of Xolair  
416 in patients 6 to <12 years of age. Although patients treated with Xolair in these two studies

417 did not develop anaphylaxis or malignancy, the studies are not adequate to address these  
418 concerns because patients with a history of anaphylaxis or malignancy were excluded, and  
419 the duration of exposure and sample size were not large enough to exclude these risks in  
420 patients 6 to <12 years of age. Furthermore, there is no reason to expect that younger  
421 pediatric patients would not be at risk of anaphylaxis and malignancy seen in adult and  
422 adolescent patients with Xolair [see *Warnings and Precautions (5.1) (5.2); and Adverse*  
423 *Reactions (6)*].

424

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

427

#### 428 *Chronic Idiopathic Urticaria*

429 The safety and effectiveness of Xolair for adolescent patients with CIU were evaluated in  
430 39 patients 12 to 17 years of age (Xolair 29, placebo 10) included in three randomized,  
431 placebo-controlled CIU studies. A numerical decrease in weekly itch score was observed,  
432 and adverse reactions were similar to those reported in patients 18 years and older.

433

434 Clinical studies with Xolair have not been conducted in CIU patients below the age of 12  
435 years. Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients  $\geq$   
436 12 years old, the risk-benefit assessment does not support the use of Xolair in patients <12  
437 years of age. Therefore, the use of Xolair in this patient population is not recommended.

438

### 439 **8.5 Geriatric Use**

440 In clinical studies 134 allergic asthma patients and 37 CIU phase 3 study patients 65 years  
441 of age or older were treated with Xolair. Although there were no apparent age-related  
442 differences observed in these studies, the number of patients aged 65 and over is not  
443 sufficient to determine whether they respond differently from younger patients.

444

## 445 **10 OVERDOSAGE**

446 The maximum tolerated dose of Xolair has not been determined. Single intravenous doses  
447 of up to 4,000 mg have been administered to patients without evidence of dose limiting  
448 toxicities. The highest cumulative dose administered to patients was 44,000 mg over a  
449 20 week period, which was not associated with toxicities.

450

## 451 **11 DESCRIPTION**

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

457

458 Xolair is a sterile, white, preservative free, lyophilized powder contained in a single use vial  
459 that is reconstituted with Sterile Water for Injection (SWFI), USP, and administered as a  
460 subcutaneous (SC) injection. Each 202.5 mg vial of omalizumab also contains L-histidine  
461 (1.8 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 20 (0.5 mg) and  
462 sucrose (145.5 mg) and is designed to deliver 150 mg of omalizumab in 1.2 mL after  
463 reconstitution with 1.4 mL SWFI, USP.

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## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

#### *Allergic Asthma*

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

#### *Chronic Idiopathic Urticaria*

Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate. The mechanism by which these effects of omalizumab result in an improvement of CIU symptoms is unknown.

### **12.2 Pharmacodynamics**

#### *Allergic Asthma*

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.

#### *Chronic Idiopathic Urticaria*

In clinical studies in CIU patients, Xolair treatment led to a dose-dependent reduction of serum free IgE and an increase of serum total IgE levels, similar to the observations in allergic asthma patients. Maximum suppression of free IgE was observed 3 days following the first subcutaneous dose. After repeat dosing once every 4 weeks, predose serum free IgE levels remained stable between 12 and 24 weeks of treatment. Total IgE levels in serum increased after the first dose due to the formation of omalizumab-IgE complexes which have a slower elimination rate compared with free IgE. After repeat dosing once every 4 weeks at 75 mg up to 300 mg, average predose serum total IgE levels at Week 12 were two-to three-fold higher compared with pre-treatment levels, and remained stable between 12 and 24 weeks of treatment. After discontinuation of Xolair dosing, free IgE levels increased and total IgE levels decreased towards pre-treatment levels over a 16-week follow-up period.

### **12.3 Pharmacokinetics**

After SC administration, omalizumab was absorbed with an average absolute bioavailability of 62%. Following a single SC dose in adult and adolescent patients with

511 asthma, omalizumab was absorbed slowly, reaching peak serum concentrations after an  
512 average of 7-8 days. In patients with CIU, the peak serum concentration was reached at a  
513 similar time after a single SC dose. The pharmacokinetics of omalizumab was linear at  
514 doses greater than 0.5 mg/kg. In patients with asthma, following multiple doses of Xolair,  
515 areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were  
516 up to 6-fold of those after the first dose. In patients with CIU, omalizumab exhibited linear  
517 pharmacokinetics across the dose range of 75 mg to 600 mg given as single subcutaneous  
518 dose. Following repeat dosing from 75 to 300 mg every 4 weeks, trough serum  
519 concentrations of omalizumab increased proportionally with the dose levels.

520  
521 In vitro, omalizumab formed complexes of limited size with IgE. Precipitating complexes  
522 and complexes larger than 1 million daltons in molecular weight were not observed in vitro  
523 or in vivo. Tissue distribution studies in Cynomolgus monkeys showed no specific uptake  
524 of <sup>125</sup>I-omalizumab by any organ or tissue. The apparent volume of distribution of  
525 omalizumab in patients with asthma following SC administration was 78 ± 32 mL/kg. In  
526 patients with CIU, based on population pharmacokinetics, distribution of omalizumab was  
527 similar to that in patients with asthma.

528  
529 Clearance of omalizumab involved IgG clearance processes as well as clearance via  
530 specific binding and complex formation with its target ligand, IgE. Liver elimination of  
531 IgG included degradation in the liver reticuloendothelial system (RES) and endothelial  
532 cells. Intact IgG was also excreted in bile. In studies with mice and monkeys,  
533 omalizumab:IgE complexes were eliminated by interactions with Fcγ receptors within the  
534 RES at rates that were generally faster than IgG clearance. In asthma patients omalizumab  
535 serum elimination half-life averaged 26 days, with apparent clearance averaging  
536 2.4 ± 1.1 mL/kg/day. Doubling body weight approximately doubled apparent clearance. In  
537 CIU patients, at steady state, based on population pharmacokinetics, omalizumab serum  
538 elimination half-life averaged 24 days and apparent clearance averaged 240 mL/day  
539 (corresponding to 3.0 mL/kg/day for an 80 kg patient).

540  
541 *Special Populations*

542  
543 *Allergic Asthma*

544 The population pharmacokinetics of omalizumab was analyzed to evaluate the effects of  
545 demographic characteristics in patients with allergic asthma. Analyses of these data  
546 suggested that no dose adjustments are necessary for age (12-76 years), race, ethnicity, or  
547 gender.

548  
549 *Chronic Idiopathic Urticaria*

550 The population pharmacokinetics of omalizumab was analyzed to evaluate the effects of  
551 demographic characteristics and other factors on omalizumab exposure in patients with  
552 CIU. Covariate effects were evaluated by analyzing the relationship between omalizumab  
553 concentrations and clinical responses. These analyses demonstrate that no dose adjustments  
554 are necessary for age (12 to 75 years), race/ethnicity, gender, body weight, body mass index  
555 or baseline IgE level.

556

557 **13 NONCLINICAL TOXICOLOGY**

558

559 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

562

563 There were no effects on fertility and reproductive performance in male and female  
564 Cynomolgus monkeys that received Xolair at subcutaneous doses up to 75 mg/kg/week  
565 (approximately 10 times the maximum recommended human dose on a mg/kg basis).  
566

567 **14 CLINICAL STUDIES**

568

569 **14.1 Allergic Asthma**

570

571 *Adult and Adolescent Patients 12 Years of Age and Older*

572 The safety and efficacy of Xolair were evaluated in three randomized, double-blind,  
573 placebo-controlled, multicenter trials.  
574

575 The trials enrolled patients 12 to 76 years old, with moderate to severe persistent (NHLBI  
576 criteria) asthma for at least one year, and a positive skin test reaction to a perennial  
577 aeroallergen. In all trials, Xolair dosing was based on body weight and baseline serum total  
578 IgE concentration. All patients were required to have a baseline IgE between 30 and  
579 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a  
580 dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of Xolair or a matching  
581 volume of placebo over each 4-week period. The maximum Xolair dose per 4 weeks was  
582 750 mg.  
583

584 In all three trials an exacerbation was defined as a worsening of asthma that required  
585 treatment with systemic corticosteroids or a doubling of the baseline ICS dose. Most  
586 exacerbations were managed in the out-patient setting and the majority were treated with  
587 systemic steroids. Hospitalization rates were not significantly different between Xolair and  
588 placebo-treated patients; however, the overall hospitalization rate was small. Among those  
589 patients who experienced an exacerbation, the distribution of exacerbation severity was  
590 similar between treatment groups.  
591

592 *Asthma Studies 1 and 2*

593 At screening, patients in Asthma Studies 1 and 2 had a forced expiratory volume in one  
594 second (FEV<sub>1</sub>) between 40% and 80% predicted. All patients had a FEV<sub>1</sub> improvement of  
595 at least 12% following beta<sub>2</sub>-agonist administration. All patients were symptomatic and  
596 were being treated with inhaled corticosteroids (ICS) and short acting beta<sub>2</sub>-agonists.  
597 Patients receiving other concomitant controller medications were excluded, and initiation of  
598 additional controller medications while on study was prohibited. Patients currently  
599 smoking were excluded.  
600

601 Each study was comprised of a run-in period to achieve a stable conversion to a common  
602 ICS (beclomethasone dipropionate), followed by randomization to Xolair or placebo.

603 Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an

604 acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase  
605 of 12 weeks during which ICS dose reduction was attempted in a step-wise manner.

606

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

609

610 In both Asthma Studies 1 and 2 the number of exacerbations per patient was reduced in  
611 patients treated with Xolair compared with placebo (Table 6).

612

613 Measures of airflow (FEV<sub>1</sub>) and asthma symptoms were also evaluated in these studies.  
614 The clinical relevance of the treatment-associated differences is unknown. Results from the  
615 stable steroid phase Asthma Study 1 are shown in Table 7. Results from the stable steroid  
616 phase of Asthma Study 2 and the steroid reduction phases of both Asthma Studies 1 and 2  
617 were similar to those presented in Table 7.

**Table 6**

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

Stable Steroid Phase (16 wks)				
Exacerbations per patient	Asthma Study 1		Asthma 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
Steroid Reduction Phase (12 wks)				
Exacerbations per patient	Xolair N=268 (%)	Placebo N=257 (%)	Xolair N=274 (%)	Placebo N=272 (%)
0	78.7	67.7	83.9	70.2
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

618

**Table 7**  
Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Study 1

Endpoint	Xolair N=268 <sup>a</sup>		Placebo N=257 <sup>a</sup>	
	Mean Baseline	Median Change (Baseline to Wk 16)	Mean Baseline	Median Change (Baseline to Wk 16)
Total asthma symptom score	4.3	-1.5 <sup>b</sup>	4.2	-1.1 <sup>b</sup>
Nocturnal asthma score	1.2	-0.4 <sup>b</sup>	1.1	-0.2 <sup>b</sup>
Daytime asthma score	2.3	-0.9 <sup>b</sup>	2.3	-0.6 <sup>b</sup>
FEV <sub>1</sub> % predicted	68	3 <sup>b</sup>	68	0 <sup>b</sup>

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

<sup>a</sup> Number of patients available for analysis ranges 255-258 in the Xolair group and 238-239 in the placebo group.

<sup>b</sup> Comparison of Xolair versus placebo (p<0.05).

619

620 *Asthma Study 3*

621 In Asthma Study 3, there was no restriction on screening FEV<sub>1</sub>, and unlike Asthma Studies  
622 1 and 2, long-acting beta<sub>2</sub>-agonists were allowed. Patients were receiving at least  
623 1000 µg/day fluticasone propionate and a subset was also receiving oral corticosteroids.  
624 Patients receiving other concomitant controller medications were excluded, and initiation of  
625 additional controller medications while on study was prohibited. Patients currently  
626 smoking were excluded.

627

628 The study was comprised of a run-in period to achieve a stable conversion to a common  
629 ICS (fluticasone propionate), followed by randomization to Xolair or placebo. Patients  
630 were stratified by use of ICS-only or ICS with concomitant use of oral steroids. Patients  
631 received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute  
632 exacerbation necessitated an increase. Patients then entered an ICS reduction phase of  
633 16 weeks during which ICS or oral steroid dose reduction was attempted in a step-wise  
634 manner.

635

636 The number of exacerbations in patients treated with Xolair was similar to that in placebo-  
637 treated patients (Table 8). The absence of an observed treatment effect may be related to  
638 differences in the patient population compared with Asthma Studies 1 and 2, study sample  
639 size, or other factors.

**Table 8**  
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
Difference (95% CI)	-4.4 (-17.6, 7.4)		-0.2 (-22.4, 20.1)	

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In all three of the studies, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV<sub>1</sub> > 80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

646

647

648

**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)]

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650

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652

**Pediatric Patients <6 Years of Age**

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

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**14.2 Chronic Idiopathic Urticaria**

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*Adult and Adolescent Patients 12 Years of Age and Older*

The safety and efficacy of Xolair for the treatment of CIU was assessed in two placebo-controlled, multiple-dose clinical studies of 24 weeks' duration (CIU Study 1; n= 319) and 12 weeks' duration (CIU Study 2; n=322). Patients received Xolair 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. A total of 640 patients (165 males, 475 females) were included for the efficacy analyses. Most patients were white (84%) and the median age was 42 years (range 12–72).

664

665

Disease severity was measured by a weekly urticaria activity score (UAS7, range 0–42), which is a composite of the weekly itch severity score (range 0–21) and the weekly hive

666 count score (range 0–21). All patients were required to have a UAS7 of  $\geq 16$ , and a weekly  
667 itch severity score of  $\geq 8$  for the 7 days prior to randomization, despite having used an H1  
668 antihistamine for at least 2 weeks.

669  
670 The mean weekly itch severity scores at baseline were fairly balanced across treatment  
671 groups and ranged between 13.7 and 14.5 despite use of an H1 antihistamine at an approved  
672 dose. The reported median durations of CIU at enrollment across treatment groups were  
673 between 2.5 and 3.9 years (with an overall subject-level range of 0.5 to 66.4 years).

674  
675 In both CIU Studies 1 and 2, patients who received Xolair 150 mg or 300 mg had greater  
676 decreases from baseline in weekly itch severity scores and weekly hive count scores than  
677 placebo at Week 12. Representative results from CIU Study 1 are shown (Table 9); similar  
678 results were observed in CIU Study 2. The 75-mg dose did not demonstrate consistent  
679 evidence of efficacy and is not approved for use.

680

681

682 **Table 9**  
683 Change from Baseline to Week 12 in Weekly Itch Severity Score and  
Weekly Hive Count Score in CIU Study 1<sup>a</sup>

	Xolair 75mg	Xolair 150mg	Xolair 300mg	Placebo
n	77	80	81	80
Weekly Itch Severity Score				
Mean Baseline Score (SD)	14.5 (3.6)	14.1 (3.8)	14.2 (3.3)	14.4 (3.5)
Mean Change Week 12(SD)	-6.46 (6.14)	-6.66 (6.28)	-9.40 (5.73)	-3.63 (5.22)
Difference in LS means vs. placebo	-2.96	-2.95	-5.80	
95% CI for difference	-4.71, -1.21	-4.72, -1.18	-7.49, -4.10	-
Weekly Hive Count Score <sup>b</sup>				
Mean Baseline Score (SD)	17.2 (4.2)	16.2 (4.6)	17.1 (3.8)	16.7 (4.4)
Mean Change Week 12(SD)	-7.36 (7.52)	-7.78 (7.08)	-11.35 (7.25)	-4.37 (6.60)
Difference in LS means vs. placebo	-2.75	-3.44	-6.93	
95% CI for difference	-4.95, -0.54	-5.57, -1.32	-9.10, -4.76	-

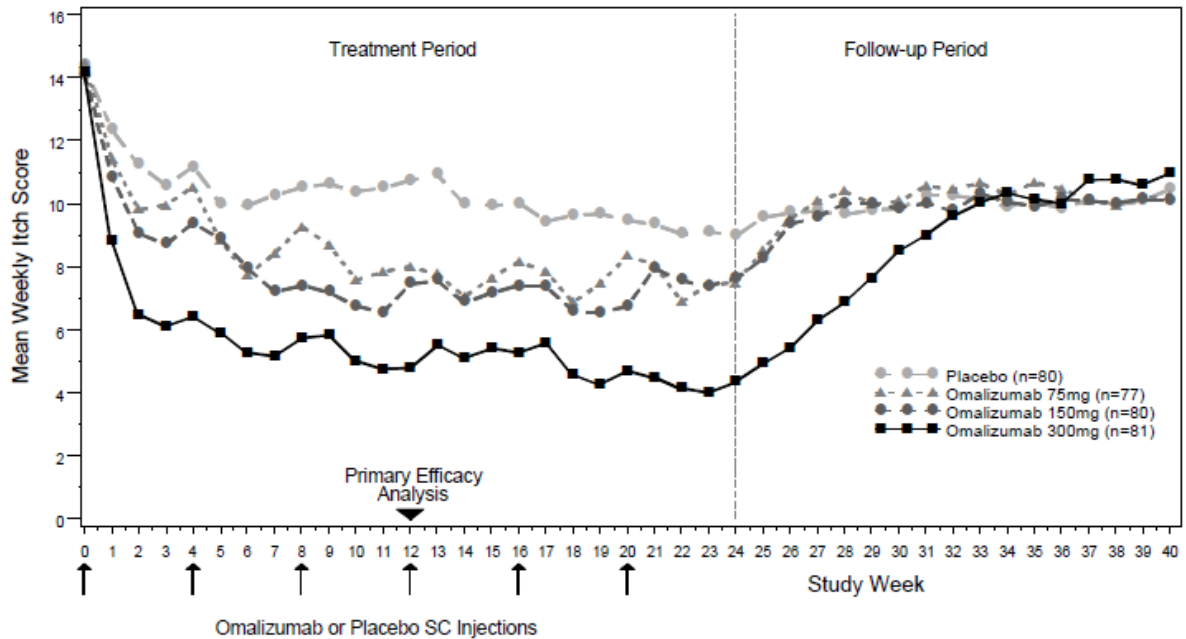
684 <sup>a</sup> Modified intent-to-treat (mITT) population: all patients who were randomized and received at least one  
685 dose of study medication.

686 <sup>b</sup> Score measured on a range of 0–21  
687

688 The mean weekly itch severity score at each study week by treatment groups is shown in  
689 Figure 1. Representative results from CIU Study 1 are shown; similar results were  
690 observed in CIU Study 2. The appropriate duration of therapy for CIU with Xolair has not  
691 been determined.

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693

**Figure 1** Mean Weekly Itch Severity Score by Treatment Group  
Modified Intent to Treat Patients



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In CIU Study 1, a larger proportion of patients treated with Xolair 300 mg (36%) reported no itch and no hives (UAS7=0) at Week 12 compared to patients treated with Xolair 150 mg (15%), Xolair 75 mg (12%), and placebo group (9%). Similar results were observed in CIU Study 2.

702 **16 HOW SUPPLIED/STORAGE AND HANDLING**

703 Xolair is supplied as a lyophilized, sterile powder in a single-use, 5 mL vial without  
704 preservatives. Each vial delivers 150 mg of Xolair upon reconstitution with 1.4 mL SWFI,  
705 USP. Each carton contains one single-use vial of Xolair® (omalizumab) NDC 50242-040-  
706 62.

707

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

711

712 Use the solution for subcutaneous administration within 8 hours following reconstitution  
713 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  
714 at room temperature.

715

716 Reconstituted Xolair vials should be protected from direct sunlight.

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718 **17 PATIENT COUNSELING INFORMATION**

719 See FDA-approved patient labeling (Medication Guide)

720

721 **17.1 Information for Patients**

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

725

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

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

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

740

741 *Pregnancy Exposure Registry*

742 Encourage pregnant women exposed to Xolair to enroll in the Xolair Pregnancy Exposure  
743 Registry [1-866-4XOLAIR (1-866-496-5247)] or visit [www.xolairpregnancyregistry.com](http://www.xolairpregnancyregistry.com)  
744 (8.1).

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**MEDICATION GUIDE**  
**XOLAIR®** (ZOHL-air)  
(omalizumab)

**Injection**

Read this Medication Guide before you start receiving and before each dose of Xolair. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is the most important information I should know about Xolair?**

A severe allergic reaction called anaphylaxis can happen when you receive Xolair. The reaction can occur after the first dose, or after many doses. It may also occur right after a Xolair injection or days later. Anaphylaxis is a life-threatening condition and can lead to death. Go to the nearest emergency room right away if you have any of these symptoms of an allergic reaction:

- 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

Your healthcare provider will monitor you closely for symptoms of an allergic reaction while you are receiving Xolair and for a period of time after your injection. Your healthcare provider should talk to you about getting medical treatment if you have symptoms of an allergic reaction after leaving the healthcare provider’s office or treatment center.

**What is Xolair?**

Xolair is an injectable prescription medicine used to treat adults and children 12 years of age and older with:

- moderate to severe persistent allergic asthma who have had a skin or blood test that is positive for allergic asthma and whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids.
- chronic idiopathic urticaria (CIU; chronic hives without a known cause) who continue to have hives that are not controlled by H1 antihistamine treatment.

Xolair is not used to treat other allergic conditions, other forms of urticaria, acute bronchospasm or status asthmaticus.

Xolair is not for use in children less than 12 years of age.

**Do not receive Xolair if you:**

- are allergic to omalizumab or any of the ingredients in Xolair. See the end of this Medication Guide for a complete list of ingredients in Xolair.

**Before receiving Xolair, tell your healthcare provider about all of your medical conditions, including if you:**

- 791 • have any other allergies (such as food allergy or seasonal allergies)
  - 792 • have sudden breathing problems (bronchospasm)
  - 793 • have or have had low white blood cell count (ask your doctor if you are not sure)
  - 794 • have or have had a parasitic infection
  - 795 • have or have had cancer
  - 796 • are pregnant or plan to become pregnant. It is not known if Xolair may harm your
  - 797 unborn baby.
  - 798 • if you become pregnant while taking Xolair, talk to your healthcare provider about
  - 799 registering with the Xolair Pregnancy Registry. You can get more information and
  - 800 register by calling 1-866-4XOLAIR (1-866-496-5247) or visit
  - 801 [www.xolairpregnancyregistry.com](http://www.xolairpregnancyregistry.com). The purpose of this registry is to monitor
  - 802 pregnancy outcomes in women receiving Xolair during pregnancy.
  - 803 • are breastfeeding or plan to breastfeed. It is not known if Xolair passes into your
  - 804 breast milk. Talk with your healthcare provider about the best way to feed your baby
  - 805 while you receive Xolair.
- 806 Tell your healthcare provider about all the medicines you take, including prescription and
- 807 over-the-counter medicines, vitamins, or herbal supplements.
- 808

### **How should I receive Xolair?**

- 810 • Xolair should be given by your healthcare provider, in a healthcare setting.
- 811 • Xolair is given in 1 or more injections under the skin (subcutaneous), 1 time every 2
- 812 or 4 weeks.
- 813 • Your healthcare provider may do certain tests and change your Xolair dose as needed.
- 814 • Do not stop taking any of your other asthma or hive medicine unless your healthcare
- 815 providers tell you to.
- 816 • You may not see improvement in your symptoms right away after Xolair treatment.

### **What are the possible side effects of Xolair?**

#### **Xolair may cause serious side effects, including:**

- 820 • See, “**What is the most important information I should know about Xolair?**”
- 821 • **Cancer.** People who receive treatment with Xolair may have a higher chance for
- 822 getting certain types of cancer.
- 823 • **Fever, muscle aches, and rash.** Some people who take Xolair get these symptoms 1
- 824 to 5 days after receiving a Xolair injection. If you have any of these symptoms, tell
- 825 your healthcare provider.
- 826 • **Parasitic infection.** Some people who are at a high risk for parasite (worm)
- 827 infections, get a parasite infection after receiving Xolair. Your healthcare provider
- 828 can test your stool to check if you have a parasite infection.
- 829 • **High blood levels of a certain antibody (Serum total IgE)**

#### **The most common side effects of Xolair:**

- 832 • In people with allergic asthma: pain especially in your arms and legs, dizziness,
- 833 feeling tired, skin rash, bone fractures, and pain or discomfort of your ears.
- 834 • In people with chronic idiopathic urticaria: nausea, headaches, swelling of the inside
- 835 of your nose, throat or sinuses, cough, joint pain, and upper respiratory tract infection.

836 These are not all the possible side effects of Xolair. Call your doctor for medical advice  
837 about side effects. You may report side effects to FDA at 1-800-FDA-1088.  
838

839 **General information about the safe and effective use of Xolair.**

840 Medicines are sometimes prescribed for purposes other than those listed in a Medication  
841 Guide. You can ask your pharmacist or healthcare provider for information about Xolair  
842 that is written for health professionals. Do not use Xolair for a condition for which it was  
843 not prescribed.

844 For more information, go to [www.xolair.com](http://www.xolair.com) or call 1-866-4XOLAIR (1-866-496-5247).  
845

846 **What are the ingredients in Xolair?**

847 **Active ingredient:** omalizumab

848 **Inactive ingredients:** L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20  
849 and sucrose  
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Manufactured by: <b>Genentech, Inc.</b> A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990	Jointly marketed by: <b>Genentech USA, Inc.</b> A Member of the Roche Group, 1 DNA Way South San Francisco, CA 94080-4990 <b>Novartis Pharmaceuticals Corporation</b> One Health Plaza East Hanover, NJ 07936-1080	<b>Initial US Approval: June 2003</b> <b>Revision Date: [March] 2014</b> Xolair® is a registered trademark of Novartis AG Corporation. <b>©2010 Genentech USA, Inc</b>
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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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