Kansas City
An Independent Licensee of the Blue Cross and Blue Shield Association

Xolair® (omalizumab injection for subcutaneous [SC] use)

Policy Number: 5.02.503  Last Review: 07/2021
Origination: 8/2003  Next Review: 07/2022

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Xolair (omalizumab) when it is determined to be medically necessary because the following criteria have been met.

When Policy Topic is covered
Food and Drug Administration (FDA)-Approved Indications:

1. Asthma in Patients with Moderate to Severe Persistent Disease.¹
   A) Initial Therapy. Approve for up to 4 months if the patient meets the following criteria (i, ii, iii, iv, v and vi):
      i. Patient is ≥ 6 years of age¹,²²-²⁴; AND
      ii. Xolair is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND
      iii. Baseline IgE level is ≥ 30 IU/mL¹⁻⁹,¹¹,²²-²⁴; AND
      iv. The patient has a baseline positive skin test or in vitro testing (i.e., a blood test for allergen-specific IgE antibodies such as an enzyme-linked immunoabsorbant assay [e.g., ImmunoCAP™, ELISA] or the radioallergosorbent test [RAST]) for one or more perennial aeroallergens (e.g., house dust mite [Dermatophagoides farinae, D. pteronyssinus], animal dander [dog, cat], cockroach, feathers, mold spores), AND/OR for one or more seasonal aeroallergens (grass, pollen, weeds); AND
      v. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
         a) An inhaled corticosteroid (ICS) [e.g., Flovent® HFA {fluticasone inhalation aerosol}, Flovent® Diskus® {fluticasone inhalation powder}, Arnuity™ Ellipta® {fluticasone furoate inhalation powder}, Asmanex® Twinthaler® {mometasone inhalation powder}, Asmanex® HFA {mometasone inhalation aerosol}, Aerospan™ {flunisolide HFA inhalation aerosol}, Alvesco® {ciclesonide inhalation aerosol}, Pulmicort Flexhaler® {budesonide inhalation powder}, QVAR® {beclomethasone HFA inhalation aerosol}]; AND
         b) At least ONE of the following (1, 2, 3 or 4):
            1. Inhaled long-acting beta-agonist (LABA) [e.g., Serevent® Diskus® {salmeterol xinafoate inhalation powder}]; OR
            2. Inhaled long-acting muscarinic antagonist (LAMA) [e.g., Spiriva® Respimat® {tiotropium bromide inhalation spray}]; OR

NOTE: Use of a combination inhaler containing both an ICS and a LABA would fulfill the requirement for both criteria a and b (e.g., Advair® Diskus/HFA [fluticasone propionate and salmeterol inhalation powder/aerosol], Symbicort® [budesonide and formoterol fumarate inhalation aerosol], Breo® Ellipta® [fluticasone furoate and vilanterol inhalation powder], and Dulera® [mometasone furoate and formoterol fumarate inhalation aerosol]); OR
3. Leukotriene receptor antagonist (LTRA) [e.g. montelukast tablets/granules {Singulair®, generics}, Accolate® {zafirlukast tablets}]; OR
4. Theophylline (Theo-24, Uniphyl, TheoChron ER, generics); AND
   vi. Patient’s asthma continues to be uncontrolled as defined by ONE of the following (a, b, c, d, or e)
   a) The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
   b) The patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) visit in the previous year; OR
   c) Patient has a forced expiratory volume in 1 second (FEV₁) < 80% predicted; OR
   d) Patient has an FEV₁/forced vital capacity (FVC) < 0.80; OR
   e) The patient’s asthma worsens upon tapering of oral corticosteroid therapy.

B) Patients Continuing Xolair Therapy. Approve for 1 year if the patient meets the following criteria (i and ii):
   i. Xolair is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND
   ii. The patient has responded to therapy (e.g., decreased asthma symptoms or exacerbations; decreased hospitalizations, emergency room, urgent care, or physician visits due to asthma; decreased reliever/rescue medication use; increased lung function parameters [forced expiratory volume in 1 second {FEV₁}, peak expiratory flow{PEF}]), as determined by the prescribing physician.¹⁰,⁴⁸

2. Chronic Idiopathic Urticaria (Chronic Spontaneous Urticaria).¹
   A) Initial Therapy. Approve for up to 4 months if the patient meets the following criteria (i, ii, iii, and iv):
   i. Patient is ≥ 12 years of age; AND
   ii. Xolair is prescribed by, or in consultation with, an allergist, immunologist, or dermatologist; AND
   iii. Patient has urticaria for > 6 weeks, with symptoms present > 3 days per week despite daily non-sedating H₁ antihistamine therapy (e.g., cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine) with doses that have been titrated up to a maximum of four times the standard FDA-approved dose; AND
   iv. Patient has tried therapy with a leukotriene modifier (e.g., montelukast) with a daily non-sedating H₁ antihistamine; AND
   B) Patients Continuing Xolair Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
   i. Patient is ≥ 12 years of age; AND
   ii. Xolair is prescribed by, or in consultation with, an allergist, immunologist, or dermatologist; AND
   iii. The patient has responded to therapy (e.g., decreased severity of itching, decreased number and/or size of hives) as determined by the prescribing physician.

3. Nasal polyps as add-on maintenance treatment in adults with inadequate response to nasal corticosteroids.

Other Uses with Supportive Evidence

4. Allergic Rhinitis, Seasonal or Perennial.
   A) Initial Therapy. Approve for up to 4 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
   i. Patient is ≥ 6 years of age; AND
ii. Xolair is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND

iii. Baseline IgE level of ≥ 30 IU/mL; AND

iv. Patient has seasonal or perennial allergic rhinitis as demonstrated by baseline positive skin testing (e.g., grass, tree, or weed pollen, mold spores, house dust mite, animal dander, cockroach) AND/OR baseline positive in vitro testing (i.e., a blood test for allergen-specific IgE antibodies) for one or more relevant allergens (e.g., grass, tree, or weed pollen, mold spores, house dust mite, animal dander, cockroach); AND

v. Patient has tried therapy with at least one drug from TWO of the following groups of drugs at the same time (a, b, c, or d):
   a) Oral second-generation/less-sedating antihistamines (e.g., cetirizine, desloratadine, fexofenadine, levocetirizine, or loratadine) [Rx or OTC]; OR
   b) Intranasal antihistamines (e.g., azelastine nasal spray [Astelin®, generics], Astepro® [azelastine nasal spray, generics] or Patanase® [olopatadine nasal spray]); OR
   c) Intranasal corticosteroids (e.g., fluticasone); OR
   d) Montelukast; AND

vi. Patient meets one of the following (a, b, or c):
   a) Patient has had immunotherapy, is receiving immunotherapy, or will be receiving immunotherapy; OR
   b) There is no immunotherapy available for the allergen identified as causing clinically significant allergy; OR
   c) The patient has contraindications to immunotherapy (e.g., patients receiving beta blockers or patients with medical conditions that reduce their ability to survive a systemic allergic reaction [e.g., markedly compromised lung function, poorly controlled asthma, unstable angina, recent myocardial infarction or significant dysrhythmia, uncontrolled hypertension, failure of a major organ system such as renal failure]).

B) Patients Continuing Xolair Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
   i. Patient is ≥ 6 years of age; AND
   ii. Xolair is prescribed by, or in consultation with, an allergist, immunologist, or pulmonologist; AND
   iii. The patient has responded to therapy (e.g., decreased symptoms of sneezing; itchy nose; watery, red, or itchy eyes; itchy throat; nasal congestion) as determined by the prescribing physician.

Several controlled clinical studies have been performed assessing the efficacy of Xolair in treating patients with seasonal or perennial allergic rhinitis. Adequate controlled clinical studies have included patients ≥ 12 years of age. Dosing and frequency are determined by serum total IgE level (which is measured before the start of therapy) and the patient’s body weight. Based on the prescribing information for Xolair, an IgE level of ≥ 30 IU/mL is required to calculate a dose. In addition, most of the clinical studies used a baseline IgE level of ≥ 30 IU/mL for inclusion. The 2015 American Academy of Otolaryngology (AAO) Clinical Practice Guidelines on Allergic Rhinitis recommends intranasal steroids as an initial choice for the treatment of allergic rhinitis due to their proven efficacy, superiority over other therapies and good safety record. Oral second-generation antihistamines may also be an appropriate first-line therapy, especially if the patient has primary complaints of sneezing and itching. Other therapeutic options include intranasal antihistamines and oral LTRAs; however, the guidelines do not recommend LTRAs as primary therapy. It is noted that combination pharmacologic therapy may be necessary in patients who have an inadequate response to monotherapy. The AAO guidelines state that clinicians should offer immunotherapy for patients who do not have an acceptable response to other pharmacologic therapy options, but do not mention the use of Xolair in this setting. A 2008 practice parameter for management of rhinitis notes that determination of specific IgE by skin testing or in vitro testing is indicated to provide evidence of an allergic basis for the patient’s symptoms, confirm suspected causes of the patient’s symptoms, or assess the sensitivity to a specific allergen for avoidance measures and/or allergen immunotherapy. In one double-blind,
placebo-controlled study involving 159 patients, the use of Xolair for 9 weeks prior to rush
immunotherapy (RIT) resulted in a lower rate of any systemic or other adverse reaction on the day of
RIT, including a statistically significant reduction in the incidence of anaphylaxis (5.6% for Xolair plus
RIT vs. 25.6% for placebo plus RIT; P = 0.026). Well-controlled clinical studies have demonstrated
that allergen immunotherapy is beneficial in allergic rhinitis caused by: pollens, dust mites, animal
allergens, fungi, and cockroaches. Immunotherapy usually is given for at least 3 to 5 years and
longer in some patients. The major risk in patients with allergic rhinitis receiving immunotherapy is
anaphylaxis. A recent meta-analysis reported that in nine studies including patients with allergic
rhinitis, Xolair significantly reduced daily nasal symptom scores; rescue medication use was also
decreased (in studies that evaluated medication use as an endpoint). In the professional opinion of
specialist physicians reviewing the data, we have adopted this criterion.

When Policy Topic is not covered
Xolair has not been shown to be effective, or there are limited or preliminary data or potential safety
concerns that are not supportive of general approval for the following conditions. Rationale for non-
coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of
Conditions Not Recommended for Approval.)

Xolair for all other conditions would be considered investigational.

1. Atopic Dermatitis (AD). Several case series have reported inconsistent results with the use of
Xolair in adult and pediatric patients with AD. Three of these case series directly assessed the
use of Xolair for treating AD, while a fourth study was using Xolair for managing persistent asthma
in patients with concomitant AD. A fifth case series report assessed the use of Xolair for treating
AD in patients with persistent asthma. One small study (n = 10) was conducted in patients with
AD and a history of allergic asthma with elevated IgE levels. In total, seven patients had ≥ 25%
reduction in objective AD scores; three patients had no clinically relevant reduction. Another small
study (n = 9) was conducted in patients with severe AD refractory to at least two systemic
agents. Of the nine patients, three patients also had asthma; all patients had elevated IgE
levels. In total, two patients experienced good control of AD, while four patients achieved only a
slight improvement in the AD lesions. Another small study (n = 8) evaluated Xolair in patients 4 to
22 years of age with severe refractory AD. Significant reductions in the serum level of cytokines
implicated in the pathogenesis of AD were observed in patients receiving Xolair. Improvements in
clinical outcomes (as measured by Scoring Atopic Dermatitis [SCORAD]) were observed with
Xolair therapy; however, these were not significantly different from the improvements observed
with placebo. An open-label pilot study (n = 10) evaluated Xolair in adult patients with severe AD
and elevated IgE levels whose AD was refractory to two or more conventional systemic treatment
options. All patients underwent immunoglobulin apheresis (immunoadsorption) to reduce IgE
levels as much as possible and then began Xolair 450 mg SC administered every 2 weeks for 24
weeks. IgE levels fell during immunoadsorption and continued to decrease with Xolair therapy.
Throughout the study, clinical improvements (measured by SCORAD as well as a subjective
visual analog scale) were observed. However, the small study size, open-label design, and
additional therapy received (immunoadsorption) make the efficacy of Xolair in this study difficult to
interpret. Additional well-controlled clinical trials are needed to determine if Xolair has a role in the
treatment of AD.

2. Eosinophilic Gastroenteritis (EG), Eosinophilic Esophagitis (EE), or Eosinophilic Colitis.
There are limited and conflicting data on the use of Xolair for the treatment of eosinophilic
gastrointestinal conditions. In a case series evaluating patients with eosinophil-associated
gastrointestinal disorders, Xolair was effective in decreasing absolute eosinophil count, allergen
skin test wheal and erythema responses, and symptom scores. Subsequently, a small (n = 15),
open-label, single-arm, unblinded study (published) evaluated Xolair for the treatment of patients
12 to 75 years of age with EE. Following 12 weeks of Xolair therapy (dose calculated in mg/kg
per IU IgE units/mL), tissue IgE levels were significantly reduced in 13 of the 15 patients, with full
remission (defined as histologic and clinical improvement) present in 33% of patients. Conversely,
a prospective, randomized, double-blind, placebo-controlled trial (n = 30) also examined the effects of Xolair in patients 12 to 60 years of age with EE who were either refractory to or relapsed after a trial of topical corticosteroids.38-39 Patients received either Xolair or placebo every 2 to 4 weeks for 16 weeks (dose of Xolair based on weight and serum IgE level). Xolair therapy was not found to improve the symptoms of EE (dysphagia scores) or eosinophil counts in biopsy samples when compared with placebo. An additional case series including two patients with multiple food allergies and EE reported an improvement in patient symptoms with Xolair therapy, but did not find an improvement in esophageal endoscopy and histology in short-term follow-up.40 The 2013 American College of Gastroenterology guidelines for the diagnosis and management of esophageal eosinophilia and EE do not recommend Xolair therapy for these conditions; the guidelines note that Xolair was ineffective in a case series involving two patients (referenced above). It is recognized that corticosteroids (systemic or topical administered by swallowing a formulation for inhalation) are the standard treatment for management of both EG and EE.40-42 Adequate controlled clinical studies have not been conducted in patients less than 12 years of age with EG, EE, or eosinophilic colitis.40 A 2014 updated food allergy practice parameter from the AAAAI, ACAAI, and JCAAI Joint Task Force also addresses EE and EG, but does not address Xolair as a treatment for these conditions.43

3. Latex Allergy in Health Care Workers with Occupational Latex Allergy. A small (European) study assessed the effects of Xolair treatment in health care workers (n = 18) with occupational latex allergy.54 Xolair use in these patients resulted in a reduction in mean conjunctival challenge test scores as compared with placebo-treated patients after 16-weeks of therapy. Also, three patients who did not respond to Xolair treatment during the double-blind phase responded during the 16-week open-label phase. Thus the overall ocular response rate for all patients in the open-label phase was 93.8% (n = 15/16). Also 11 of 15 patients in the open-label phase had a negative response to a latex glove challenge test (4 patients had a mild response). Well-controlled trials are needed.

4. Peanut and Other Food Allergies. Limited data are available regarding the use of Xolair to facilitate desensitization to food allergens. A Phase II multicenter clinical trial was initiated using Xolair in patients with peanut allergy; however, it was discontinued prematurely due to concerns regarding the safety of the oral peanut challenges in some patients.55 Insufficient data were obtained to reach any conclusions about the efficacy of Xolair. Another pilot study also used Xolair to facilitate rapid oral desensitization in high-risk peanut-allergic patients (8 to 16 years of age).56 In total, 13 patients were pretreated with Xolair for 12 weeks prior to rush oral desensitization, followed by an escalation phase where patients were administered increasing amounts of peanut flour daily. At 20 weeks following the rush desensitization, Xolair was discontinued, but the peanut flour dosing continued. For the primary outcome, all 13 patients reached the maximum rush desensitization dose on Day 1; 12 of the 13 patients (92%) reached the 4,000 mg maintenance dose (secondary outcome). At Week 32, 11 patients tolerated a double-blind, placebo-controlled food challenge. There are also minimal data on the use of Xolair in patients with severe cow’s milk allergy.57-58,63-64 In one Phase I study (n = 11) patients were given Xolair for 9 weeks prior to rapid desensitization treatment.57 In total, 9 of the 11 patients were able to tolerate desensitization to a daily maintenance dose of 2,000 mg of milk within a 7 to 11 week period. Another case-series describes five pediatric patients treated with Xolair for 4 months until they had a negative basophil allergen threshold sensitivity test (CD-sens).58 Once the CD-sense test was negative, the patients were administered a milk challenge. Following Xolair therapy, all five patients ultimately had a negative milk challenge. Another Phase I study also evaluated the safety and tolerability of Xolair in patients with multiple food allergies undergoing a rush immunotherapy protocol to multiple foods.59 In this study (n = 25), Xolair was administered for 8 weeks prior to and 8 weeks following the initiation of rush oral immunotherapy using up to five different food allergens. The goal maintenance dose was 4,000 mg protein per allergen. All patients were able to reach the goal dose by 9 months, with the median time to reach the maintenance dose of 18 weeks. One randomized, double-blind, placebo-controlled study evaluated Xolair combined with oral immunotherapy for the treatment of cow’s milk allergy in
pediatric and adult patients. Following 4 months of therapy with either Xolair or placebo, open-label milk oral immunotherapy was initiated and escalated to maintenance from Week 22 to Week 40, followed by daily oral immunotherapy through Month 28. At Month 28, Xolair therapy was discontinued and patients passing an oral food challenge continued oral immunotherapy for an additional 8 weeks. A rechallenge was initiated at Month 21 to assess sustained unresponsiveness. Small, non-significant improvements in the proportion of patients passing the oral food challenge (at Month 28) and the sustained unresponsiveness challenge at Month 32 were observed with Xolair vs. placebo. Guidelines for the diagnosis and management of food allergy in the US (published in 2010) indicate there are currently no medications recommended to prevent IgE-mediated or non-IgE-mediated food-induced allergic reactions from occurring in an individual with existing food allergies. Allergen avoidance and use of antihistamines are recommended for treatment of food-induced allergic reactions. The 2014 updated food allergy practice parameter from the AAAAI, ACAAI, and JCAAI Joint Task Force also states that immunotherapies (such as the oral immunotherapy desensitization described above) show promise for the treatment of food allergy; however, there is currently inadequate evidence that the therapeutic benefit outweighs the risk. Trials of these have been uncontrolled, small studies, which are subject to selection bias and uncertain safety profiles. However, treatment with anti-IgE monoclonal antibodies might increase the threshold for doses needed to stimulate an allergic reaction and potentially may enhance the safety profile for patients. Additional well-controlled trials are needed.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

**Considerations**

**Dosing Adjustments**

Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than 1 year should be based on serum IgE levels obtained at the initial dose determination. Total serum IgE levels may be re-tested for dose determination if treatment with Xolair has been interrupted for one year or more. Doses should be adjusted for significant changes in body weight.

This Blue Cross and Blue Shield of Kansas City policy was developed using available resources such as, but not limited to: Food and Drug Administrative (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

**Description of Procedure or Service**

Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody which selectively binds to human immunoglobulin E (IgE), thus inhibiting IgE from binding to the surface of mast cells and basophils (at the high-affinity IgE receptor [FcεRI]), and resulting in a decrease of mediators released in the allergic response. Xolair treatment also reduces the number of FcεRI receptors on basophils in atopic patients. Xolair is indicated for use in adults and adolescents (aged ≥ 12 years) with moderate to severe persistent asthma and who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair decreases the incidence of asthma exacerbations in these patients. Doses and dosing frequency in asthma are determined by serum total IgE level (which is measured before the start of therapy) and the patient’s body weight. Xolair is also indicated for the treatment of adults and adolescents (aged ≥ 12 years) with chronic idiopathic urticaria (CIU) who remain symptomatic despite H1 antihistamine treatment. Dosing in patients with CIU does not depend on serum IgE (free or total) or on body weight. In CIU, Xolair binds to IgE and lowers free IgE levels; subsequently, FcεRI on cells down-regulate. How these effects of Xolair result in an improvement in CIU symptoms is not known. Limitations of use. Xolair is not indicated for the following conditions: treatment of other allergic conditions or other forms of urticaria; for relief of acute bronchospasm or status asthmaticus; or for use in pediatric patients < 12 years of age.
Xolair (Omalizumab) is administered subcutaneously every 2 or 4 weeks. Doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). Dosages will be approved per the following schedule:

### 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*) with Asthma

<table>
<thead>
<tr>
<th>Pre-treatment Serum IgE (IU/mL)</th>
<th>Body Weight (kg)</th>
<th>30-60</th>
<th>&gt; 60-70</th>
<th>&gt; 70-90</th>
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<tr>
<td>&gt;30-100</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>300</td>
<td></td>
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<tr>
<td>&gt; 100-200</td>
<td>300</td>
<td>300</td>
<td>300</td>
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<td>&gt; 200-300</td>
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<td>&gt; 300-400</td>
<td>See Table 2</td>
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<td>&gt; 400-500</td>
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<td>&gt; 500-600</td>
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</tbody>
</table>

**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*) with Asthma

<table>
<thead>
<tr>
<th>Pre-treatment Serum IgE (IU/mL)</th>
<th>Body Weight (kg)</th>
<th>30-60</th>
<th>&gt; 60-70</th>
<th>&gt; 70-90</th>
<th>&gt; 90-150</th>
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<tr>
<td>&gt;30-100</td>
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<tr>
<td>&gt; 100-200</td>
<td>225</td>
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<tr>
<td>&gt; 200-300</td>
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<td>300</td>
<td>375</td>
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<td>375</td>
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<tr>
<td>&gt; 500-600</td>
<td>375</td>
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</tbody>
</table>

**Usual dosing for children 6 to under 12 years** is 75mg to 375mg subcutaneously every 2 or 4 weeks. Doses and dosing frequency are determined by serum total IgE level, measured before the start of treatment, and body weight. Please reference FDA labeling for a dosing chart.

**The usual dosage for chronic spontaneous urticaria is 150 to 300mg every 4 weeks and is not dependent on serum IgE (free or total) level or body weight.**

The usual dosage for nasal polyps is 75 to 600 mg subcutaneously every 2 or 4 weeks. Doses and dosing frequency are determined by serum total IgE level, measured before the start of treatment, and body weight. **(Ref)**
## Omalizumab Doses Administered Subcutaneously Every 4 Weeks (Ref)

<table>
<thead>
<tr>
<th>Pretreatment serum IgE</th>
<th>Body weight</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>30 to 40 kg</td>
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<tr>
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## Omalizumab Doses Administered Subcutaneously Every 2 Weeks (Ref)

<table>
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<th>Pretreatment serum IgE</th>
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</thead>
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<tr>
<td></td>
<td>30 to 40 kg</td>
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<tr>
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<td>See table</td>
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<tr>
<td>Pretreatment serum IgE</td>
<td>Body weight</td>
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<td>------------------------</td>
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<tr>
<td>&gt;500 to 600 units/mL</td>
<td>See previous table.</td>
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<tr>
<td>&gt;600 to 700 units/mL</td>
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<tr>
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<tr>
<td>&gt;800 to 900 units/mL</td>
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<tr>
<td>&gt;900 to 1,000 units/mL</td>
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<td>450 mg</td>
</tr>
<tr>
<td>&gt;1,300 to 1,500 units/mL</td>
<td>525 mg</td>
</tr>
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</table>

Dosage adjustment
Dosing should be adjusted during therapy for significant changes in body weight. Dosing should not be adjusted based on total IgE levels taken during treatment or <1 year following interruption of therapy. If therapy has been interrupted for ≥1-year, total IgE levels may be reevaluated for dosage determination. (Ref)

Rationale
Adult/Adolescent Allergic Asthma
The first two pivotal studies (similar design and fully published) involved 1,071 adult/adolescent patients (n = 525 in Study 1\(^{1,3}\) and n = 546 in Study 2\(^{1,5-6}\)) with moderate to severe allergic asthma. After a 4- to
A 6-week run-in period, patients entered a 16-week stable-steroid phase (SSP), where the inhaled beclomethasone dipropionate (BDP) dose remained the same while patients were randomized to placebo or Xolair SC. After the SSP, patients continued on their randomized treatment for 12 weeks in the steroid-reduction phase (SRP), in which the inhaled BDP dose was decreased until discontinuation, asthma worsening, or a drop in forced expiratory volume in 1 second (FEV₁) of ≥ 20%.

In Study 1, Xolair use resulted in a 48% reduction in the mean number of asthma exacerbations vs. placebo in the SSP (0.28 vs. 0.54 mean exacerbations per person, respectively; P = 0.006) and a 41% reduction in the SRP (0.39 vs. 0.66 mean exacerbations per person, respectively; P = 0.003). In Study 2, Xolair use resulted in a 58% reduction in the mean number of asthma exacerbations vs. placebo in the SSP (0.28 vs. 0.66, respectively; P < 0.001) and a 52% reduction in the SRP (0.36 vs. 0.75, respectively; P < 0.001). Also, in both pivotal studies, Xolair resulted in a higher percentage of patients able to discontinue inhaled BDP (Study 1: 39.6% vs. 19.1%, respectively [P < 0.001]; Study 2: 43% vs. 19%, respectively [P-value not noted]). The following statistically significant changes were noted: more patients able to reduce their inhaled BDP dose, lower symptom scores, less use of rescue medication, and better improvements in mean FEV₁. A 24-week extension phase for Studies 1 and 2 maintained similar results, including lower concomitant use of other asthma medications. During the 24-week, double-blind extension phase of Study 1, Xolair-treated patients maintained significantly lower inhaled corticosteroid doses (mean BDP equivalent dose was 227 mcg/day) vs. placebo-treated patients (mean BDP equivalent dose was 335 mcg/day).

One published analysis was performed using pooled data (n = 1,070) from Studies 1 and 2 to determine baseline patient characteristics which were predictive of the best response to Xolair use in patients with allergic asthma. From these pooled data it was noted that by Week 16, the incidence of experiencing an exacerbation episode was 16% with Xolair vs. 30% with placebo, which correlated with statistically significantly longer times to first asthma exacerbation with Xolair use as compared with placebo use (P < 0.001). Three factors were identified which were predictive of a greater probability of response with Xolair use: high BDP use (≥ 800 mcg/day), history of emergency asthma treatment in the past year (defined as overnight hospital admission or treatment in an intensive care unit [ICU] for asthma or one emergency department or doctor’s office visit for urgent asthma treatment), or low FEV₁ (≤ 65% of predicted). The percentage of patients who had at least one of these three predictive factors was 76% (n = 742/979). Of the Xolair-treated patients who responded at Week 16, 61% of patients had responded at Week 4 and 87% of patients had responded at Week 12.

Table 1. Odds Ratios for Response with Xolair Use Relative to Placebo for Predictive Factors.

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<th>95% CI</th>
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<td>0.88, 3.99</td>
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<td>1.15</td>
<td>0.54, 2.44</td>
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<td>History of emergency asthma treatment in past year only</td>
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<td>1.60</td>
<td>0.75, 3.42</td>
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<td>BDP dose ≥ 800 mcg/day AND History of emergency asthma treatment in past year</td>
<td>124</td>
<td>3.54</td>
<td>1.69, 7.43</td>
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<tr>
<td>FEV₁ ≤ 65% predicted AND History of emergency asthma treatment in past year</td>
<td>77</td>
<td>3.38</td>
<td>1.32, 8.66</td>
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<tr>
<td>All three predictive factors present (BDP dose ≥ 800 mcg/day, FEV₁ ≤ 65% predicted, AND History of emergency asthma treatment in past year)</td>
<td>85</td>
<td>4.20</td>
<td>1.69, 10.45</td>
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OR – Odds ratio; CI – Confidence interval; BDP – Beclomethasone dipropionate; FEV₁ – Forced expiratory volume in one second.

A third pivotal study (Study 3) involved 341 patients with moderate to severe allergic asthma, but had a slightly different study design than Studies 1 and 2 (no restriction on baseline FEV₁, higher baseline inhaled corticosteroid doses, oral corticosteroid use as maintenance was allowed, long-acting beta-
agonists [LABAs] were allowed, a 16-week SRP [rather than 12-week SRP in Studies 1 and 2], and all patients were switched to inhaled fluticasone propionate). In this study, asthma exacerbation rates were not different between Xolair and placebo (in the SSP, rates for patients receiving inhaled corticosteroids only were 15.9% for Xolair vs. 15% for placebo, and for patients receiving both inhaled and oral corticosteroids rates were 32% for Xolair vs. 22.2% for placebo; in the SRP, rates for patients only using inhaled corticosteroids were 22.2% for Xolair vs. 26.7% for placebo, and for patients using both inhaled and oral corticosteroids rates were 42% for Xolair vs. 42.2% for placebo). The lack of a treatment difference may be due to differences in patient population (vs. Studies 1 and 2), study sample size, or other factors.1 In the three pivotal studies, there was no observed reduction in asthma exacerbations in Xolair-treated patients who had a FEV\textsubscript{1} > 80% at the time of randomization.

The previously discussed pivotal studies involved patients with moderate to severe persistent allergic asthma who were primarily being treated with inhaled corticosteroids.\textsuperscript{1-8} Aside from the third pivotal study, other commonly recommended therapies were not allowed, such as use of LABAs or oral corticosteroids.

**Asthma Guidelines**

The 2016 updated Global Initiative for Asthma (GINA) guidelines for asthma management and prevention note that use of anti-IgE therapy (Xolair) may be beneficial in patients with elevated serum levels of IgE and severe allergic asthma.\textsuperscript{10} The guidelines recommend a stepwise approach to asthma treatment. Xolair therapy may be considered in patients with moderate to severe allergic asthma that is uncontrolled by inhaled corticosteroid (ICS) and LABA therapy with or without an additional controller medication (in addition to an as needed reliever medication). Appropriate candidates for Xolair therapy should have elevated IgE levels; however, the guidelines note that the required IgE level varies between countries and defer to the 2014 European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines for the definition, evaluation, and treatment of severe asthma, which define appropriate IgE levels for consideration of Xolair therapy. The ERS/ATS guidelines suggest a trial of Xolair in both adults and children with severe allergic asthma (levels of evidence: low [adults] and very low [children]), provided the patients meet certain qualifications.\textsuperscript{11} If a trial of Xolair is considered, patients (adults and children ≥ 6 years of age) should have confirmed IgE-dependent allergic asthma that is uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance and their total serum IgE level should be ≥ 30 IU/mL and < 700 IU/mL (although it is noted that in three studies this range was wider from 30 IU/mL to 1,300 IU/mL). The prescribing physician should assess the patient’s response to therapy taking into consideration asthma control, exacerbation reduction, unscheduled healthcare utilization, and quality of life. It is also noted that further administration of Xolair is unlikely to be beneficial if a patient does not respond to therapy within the first 4 months of treatment.

The 2007 updated National Asthma Education and Prevention Program (NAEPP) guidelines for the diagnosis and management of asthma note that anti-IgE (Xolair) is approved for patients 12 years and older with severe persistent asthma who have proven sensitivity to aeroallergens (e.g., dust mite, cockroach, cat, or dog).\textsuperscript{12} The recommended daily controller medications (per the NAEPP guidelines) for asthma patients (youths ≥ 12 years of age and adults) prior to use of Xolair are high-dose inhaled corticosteroids plus a LABA with or without oral corticosteroids. It also notes that Xolair is the only adjunctive therapy to demonstrate added efficacy to the previously mentioned recommended controllers in patients who have severe persistent allergic asthma.

**Adult/Adolescent Chronic Idiopathic Urticaria (CIU)**

Efficacy and safety of Xolair in the treatment of CIU was assessed in two multicenter, placebo-controlled, Phase III, pivotal studies in adults and adolescent patients 12 to 75 years of age.\textsuperscript{1} Disease severity was measured by a weekly urticaria activity score over 7 days (UAS\textsubscript{7}) [scale 0 to 42 with higher score indicating greater activity]. UAS\textsubscript{7} is a composite of the weekly itch severity score (ISS) [range 0 to 21] and the weekly hive count score (range 0 to 21). Patients had a UAS\textsubscript{7} of ≥ 16, and a
weekly itch severity score of ≥ 8 for the 6 days before randomization, despite having used an H₁
antihistamine for at least 2 weeks. In both of the studies, patients who received Xolair 150 mg or 300
mg had greater decreases from baseline in weekly ISS and weekly hive count scores than placebo at
week 12. Note that the 95% Confidence interval (CI) in Study 1 and Study 2 is the least squares mean
difference for treatment vs. placebo.

Study 1 (published, pivotal) was a 24-week trial in 319 patients with CIU.¹,¹³ Patients were randomized
to six SC injections of Xolair (75 mg, 150 mg, or 300 mg) given 4 weeks apart or placebo, followed by a
16-week observation period. Patients continued on their stable approved dose of H₁ antihistamine. At
Week 12, the mean change from baseline in the weekly ISS was -6.46 (95% CI: -4.71, -1.21) with
Xolair 75 mg; -6.66 (95% CI: -4.72, -1.18) with Xolair 150 mg; -9.4 (95% CI: -7.49, -4.10) with Xolair
300 mg; and -3.63 with placebo. The difference between Xolair and placebo was significant for all
doses. At Week 12, the mean change from baseline in weekly hive count score was -7.36 (95% CI:  -4.95, -0.54) with Xolair 75 mg; -7.78 (95% CI: -5.57, -1.32) with Xolair 150 mg; -11.35 (95% CI: -9.10,
-4.76) with Xolair 300 mg; and -4.37 with placebo). The appropriate duration of therapy has not been
determined. A greater percentage of patients treated with Xolair 300 mg (36%) reported no itch and no
hives (UAS7 = 0) at Week 12 compared with patients who received Xolair 150 mg (15%), Xolair 75 mg
(12%); and placebo (9%). The mean changes from baseline to Week 24 for weekly ISS, weekly hive
count score, and other secondary endpoints were all of similar magnitude as those observed at Week
12.

Study 2 was a double-blind study (published, pivotal) in patients (n = 323) with moderate to severe CIU
or chronic spontaneous urticaria (CSU) who were symptomatic despite therapy with approved doses of
second generation (non-sedating) H₁ antihistamines.¹⁴ Patients were randomized to three SC
injections of Xolair (75 mg, 150 mg, or 300 mg) given 4 weeks apart or placebo, followed by a 16-week
observation period. Patients continued on their stable dose of H₁ antihistamine during the treatment
period; during the follow-up period patients were allowed to use an approved dose of one additional H₁
antihistamine as well. Rescue medication for symptom relief with 25 mg of diphenhydramine was
allowed. The primary efficacy outcome was the change from baseline in weekly ISS. The baseline
weekly ISS was about 14 in all four groups. At Week 12, the mean change from baseline in the weekly
ISS was -5.9 (95% CI: -2.5, 1.2) with Xolair 75 mg; -8.1 (95% CI: -4.9, -1.2) with Xolair 150 mg (P <
0.01 [compared with placebo]); -9.8 (95% CI: -6.5, 3.1) with Xolair 300 mg (P < 0.001 [compared with
placebo]); and -5.1 with placebo. Most of the secondary outcomes at Week 12 had similar dose-
dependent effects. The percentages of patients with UAS7 ≤ 6 at Week 12 were 19%, 27%, 43%, and
52% for placebo, Xolair 75 mg, Xolair 150 mg, and Xolair 300 mg, respectively.

A third Phase III, double-blind, parallel-group trial was done in patients with CIU/CSU who were 12 to
75 years of age.¹⁵ Patients had a UAS7 of ≥ 16, and a weekly ISS of ≥ 8 for the 7 days before
randomization, despite therapy with H₁ antihistamines (up to four times the approved dose), plus H₂
antihistamines, LTRA, or both. Patients were randomized to either six SC injections of Xolair 300 mg (n
= 252) or placebo (n = 84) every 4 weeks, followed by a 16-week observation period where Xolair was
not given. During the treatment period, patients maintained their stable doses of their pre-
randomization combination with H₁ antihistamine therapy plus H₂ antihistamines, LTRAs, or both.
Rescue medication for symptom relief with diphenhydramine 25 mg was allowed. The primary
objective was to evaluate the overall safety of Xolair compared with placebo. Efficacy (itch severity,
hive, and urticaria activity scores) was evaluated at Weeks 12 and 24. Adverse events overall
incidence, severity, and incidence of serious adverse events were similar between Xolair and placebo.
At Week 12, the mean change from baseline weekly ISS (key efficacy end point) was -8.6 (95% CI:  -9.3,  -7.8) with Xolair vs. -4.0 (95% CI: -5.3, -2.7) with placebo (P < 0.001). Significant improvements in
additional numerous efficacy endpoints were seen at Week 12; these benefits were sustained to Week
24.

Urticaria Guidelines
In 2014, the American Academy of Allergy, Asthma, & Immunology (AAAAI); the American College of
Allergy, Asthma, & Immunology (ACAAI); and the Joint Council of Allergy, Asthma, & Immunology
(JCAAI) published a Joint Task Force Practice Parameter on the diagnosis and management of acute and chronic urticaria.\textsuperscript{19} This parameter recommends a four-step approach to treatment of chronic urticaria. Initially, avoidance of triggers and physical factors is indicated along with a second generation antihistamine (Step 1). Step 2 includes increasing the dose of the antihistamine initiated in Step 1; it is stated that a 2- to 4-fold increase in the FDA-approved dose of the second-generation antihistamine may be effective to achieve symptom control in some patients. Additionally, adding a second non-sedating antihistamine, an H\textsubscript{2} antagonist, an LTRA, or a first generation antihistamine to be taken at bedtime may also be beneficial. If the patient still has poorly controlled symptoms, treatment with hydroxyzine or doxepin may be considered as part of Step 3 therapy. Patients with refractory chronic urticaria (Step 4) may consider other alternative therapies, such as Xolair and cyclosporine. The document notes that Xolair is indicated for the treatment of chronic urticaria only in patients \geq 12 years of age who are unresponsive to H\textsubscript{1} receptor antagonists. Long-term use of corticosteroids for the treatment of chronic urticaria should be avoided due to the risk for AEs and limited efficacy data.

An updated guideline from the 4\textsuperscript{th} International Consensus Meeting on Urticaria (2012) recommends a three-step approach to treatment of chronic urticaria.\textsuperscript{20} Recommended therapy is to start with a standard dose of a non-sedating H\textsubscript{1} antihistamine and if there is an insufficient response after a maximum of 2 weeks, to increase the dose up to four times the standard dosage. In patients who are still refractory to therapy, the third step is to add Xolair, cyclosporine (capsules, oral solution), or montelukast tablets. Short-term corticosteroid therapy for a maximum of 10 days may be used. H\textsubscript{2} antihistamines and dapsone which were included in the previous (2009) guidelines are not included in the updated guidelines.

**Pediatric Allergic Asthma or Chronic Idiopathic Urticaria (Aged \leq 12 Years)**

In a pediatric pivotal study similar to the first two adult/adolescent allergic asthma pivotal studies discussed above, 334 children (aged 6 to 12 years) with moderate to severe allergic asthma controlled with inhaled corticosteroids were randomized to Xolair or placebo.\textsuperscript{22} Xolair was statistically significantly better than placebo for the percentage of patients requiring an urgent, unscheduled physician visit (12.9\% vs. 30.3\% for Xolair and placebo, respectively; P = 0.001), the percentage of patients experiencing a decrease in morning peak expiratory flow (PEF) of \geq 20\% on 2 or 3 successive days (6.7\% vs. 17.4\% for Xolair and placebo, respectively; P = 0.002), awakening on 2 or 3 successive nights that required rescue medication (11.6\% vs. 21.1\% for Xolair and placebo, respectively; P = 0.002), the percentage of patients with exacerbation during SRP requiring doubling of BDP dose or systemic corticosteroids (18.2\% vs. 38.5\% for Xolair and placebo, respectively; P < 0.001), and mean number of exacerbation episodes per patient during SRP requiring doubling of BDP dose or systemic corticosteroids (0.42 vs. 2.72 for Xolair and placebo, respectively; P < 0.001). None of the Xolair-treated patients vs. five placebo-treated patients required hospitalization. After completion of this double-blind study, patients could enter an open-label, 24-week extension phase.\textsuperscript{23} In the extension phase, all children continued to receive inhaled BDP at the lowest acceptable dose for asthma control. Of the children who received Xolair in both phases (total duration of treatment = 1 year), 81.4\% (n = 171) did not require use of any other concomitant asthma medications in the extension phase. Also, the mean BDP dose for these patients who received Xolair for 1 year remained similar from the end of the double-blind phase (72 mcg/day) at Week 28 until the end of the extension phase (77 mcg/day) at Week 52. For patients who no longer required inhaled BDP at the end of the double-blind phase, 90.8\% (n = 98) still required no inhaled BDP at the end of the extension phase. The percentage of Xolair-treated patients who did not experience an asthma exacerbation during Weeks 1 through 16 (double-blind phase) was 84.4\%, during Weeks 16 through 28 (double-blind phase) was 72.4\%, and during Weeks 28 through 52 (extension phase) was 72.4\%. The percentage of Xolair-treated patients who did not experience any asthma exacerbations during the entire 1-year treatment phase was 55\%.

In a second pediatric study, 627 children (aged 6 to < 12 years) with moderate to severe allergic (IgE-mediated) asthma inadequately controlled with at least medium doses of inhaled corticosteroids were randomized to Xolair (n = 421) or placebo (n = 206).\textsuperscript{24} Over a period of 24 weeks (fixed-steroid phase), Xolair-treated patients experienced a 31\% reduction in clinically significant asthma exacerbations vs. placebo (0.45 vs. 0.64 for Xolair and placebo, respectively; P = 0.007). Over a period of 52 weeks,
which included the 24-week fixed-steroid phase and a 28-week adjustable-steroid phase (steroid dosages could be adjusted downwards), Xolair-treated patients experienced a 43% reduction in exacerbations (0.78 vs. 1.36 for Xolair and placebo, respectively; P < 0.001). The mean changes from baseline at 24 weeks in other secondary endpoints (Xolair vs. placebo) were not statistically significant.

A subgroup analysis\(^{25}\) of the second pediatric study\(^{24}\) assessed children with severe asthma inadequately controlled with high-dose inhaled corticosteroids and a LABA, with or without other controller medications. A total of 235 children were included in the efficacy analysis of the subgroup population. Over the 24-week fixed-steroid phase, Xolair reduced the rate of clinically significant asthma exacerbations by 34% vs. placebo (0.42 vs. 0.63 for Xolair and placebo, respectively; P = 0.047). Over 52 weeks, the exacerbation rate was reduced by 50% with Xolair vs. placebo (0.73 vs. 1.44, respectively; P < 0.001).

Based on these two pediatric studies in children with asthma\(^{22,24}\), the Xolair prescribing information\(^1\) includes the following statement:

**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 trials 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.**

Regarding pediatric use in CIU, the prescribing information states:

**Clinical studies with Xolair have not been conducted in patients < 12 years of age with CIU. Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥ 12 years of age, the risk-benefit assessment does not support the use of Xolair in patients < 12 years of age. Therefore, the use of Xolair in this patient population is not recommended.**

**References**

1. Xolair® subcutaneous injection [prescribing information]. South San Francisco, CA and East Hanover, NJ: Genentech, Inc. and Novartis Pharmaceuticals Corporation; December 2015.


34. Joint Task Force on Practice Parameters: American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol.* 2008;122(2):S1-S84.


65. Seidman

**Other References Utilized**


**Billing Coding/Physician Documentation Information**

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**Additional Policy Key Words**

5.02.503

**Policy Implementation/Update Information**

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