

Xolair® (Omalizumab)

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[Instructions for Use](#)

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Community Plan Policy
• Xolair® (Omalizumab)

Coverage Rationale

➔ See [Benefit Considerations](#)

Moderate to Severe Persistent Asthma

Xolair (omalizumab) for subcutaneous use is proven for patients with moderate to severe persistent asthma who meet all of the following criteria:

- Have a positive skin test or in vitro reactivity to a perennial aeroallergen.
- Symptoms inadequately controlled with inhaled corticosteroids.
- Have a baseline plasma immunoglobulin E (IgE) level greater than or equal to 30 IU/mL and less than or equal to 1500 IU/mL.

Xolair is medically necessary when all of the following criteria are met:

- Diagnosis of moderate or severe asthma; and
- Classification of asthma as uncontrolled or inadequately controlled as defined by at least one of the following:
 - Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20); or
 - Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; or
 - Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); or
 - Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second [FEV1] less than 80% predicted [in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal])
 - Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma and
- One of the following:
 - Baseline (pre-omalizumab treatment) serum total IgE level greater than or equal to 30 IU/mL and less than or equal to 1500 IU/mL; or
 - Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma and
- Positive skin test or in vitro reactivity to a perennial aeroallergen; and

- Used in combination with one of the following:
 - One maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) product [e.g., Advair/AirDuo Respiclick (fluticasone propionate/salmeterol), Symbicort (budesonide/formoterol), Breo Ellipta (fluticasone furoate/vilanterol)]; or
 - Combination therapy including both of the following:
 - One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco[®]), mometasone furoate (Asmanex[®]), beclomethasone dipropionate (QVAR[®])]; and
 - One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi[®]) or indacaterol (Arcapta[®]); leukotriene receptor antagonist – montelukast (Singulair[®]); theophylline]
- and
- Patient is not receiving Xolair in combination with either of the following:
 - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
 - Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
- and
- Xolair dosing for moderate to severe persistent asthma is in accordance with the United States Food and Drug Administration approved labeling; and
- Prescribed by or in consultation with an allergist/immunologist or pulmonologist; and
- Initial authorization will be for no more than 6 months.

Reauthorization/Continuation of Care Criteria

For patients currently on Xolair for the treatment of moderate to severe persistent asthma, authorization for continued use will be approved based on all of the following criteria:

- Documentation of positive clinical response as demonstrated by at least one of the following:
 - Reduction in the frequency of exacerbations
 - Decreased utilization of rescue medications
 - Increase in percent predicted FEV1 from pretreatment baseline
 - Reduction in severity or frequency of asthma-related symptoms (e.g., wheezing, shortness of breath, coughing, etc.)
- and
- Used in combination with an ICS-containing controller medication; and
- Patient is not receiving Xolair in combination with either of the following:
 - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
 - Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
- and
- Xolair dosing for moderate to severe persistent asthma is in accordance with the United States Food and Drug Administration approved labeling; and
- Prescribed by or in consultation with allergist/immunologist or pulmonologist; and
- Reauthorization will be for no more than 12 months.

Chronic Urticaria

Xolair (omalizumab) for subcutaneous use is proven for patients with chronic urticaria who continue to remain symptomatic despite H1 antihistamine [e.g., cetirizine (Zyrtec), fexofenadine (Allegra)] treatment.

Xolair is medically necessary when all of the following criteria are met:

- Diagnosis of chronic urticaria; and
- One of the following:
 - Patient remains symptomatic despite at least a 2-week trial of, or history of contraindication or intolerance to, two H1-antihistamines [e.g., Allegra (fexofenadine), Benadryl (diphenhydramine), Claritin (loratadine)]*; or
 - Patient remains symptomatic despite at least a 2-week trial of, or history of contraindication or intolerance to both of the following taken in combination:
 - A second generation H1-antihistamine [e.g., Allegra (fexofenadine), Claritin (loratadine), Zyrtec (cetirizine)]; and
 - One of the following:
 - Different second generation H1-antihistamine [e.g., Allegra (fexofenadine), Claritin (loratadine), Zyrtec (cetirizine)]
 - First generation H1-antihistamine [e.g., Benadryl (diphenhydramine), Chlor-Trimeton (chlorpheniramine), Vistaril (hydroxyzine)]*

- H2-antihistamine [e.g., Pepcid (famotidine), Tagamet HB (cimetidine), Zantac (ranitidine)]
- Leukotriene modifier [e.g., Singulair (montelukast)]

and

- Xolair dosing for chronic urticaria is in accordance with the United States Food and Drug Administration approved labeling; and
- Prescribed by or in consultation with an allergist/immunologist or dermatologist; and
- Initial authorization will be for no more than 6 months.

Reauthorization/Continuation of Care Criteria

For patients currently on Xolair for the treatment of chronic urticaria, authorization for continued use will be approved based on all of the following criteria:

- Documentation of positive clinical response (e.g., reduction in exacerbations, itch severity, hives); and
- Xolair dosing for chronic urticaria is in accordance with the United States Food and Drug Administration approved labeling; and
- Prescribed by or in consultation with allergist/immunologist or dermatologist; and
- Reauthorization will be for no more than 12 months.

*Note: Patients 65 years of age and older in whom first generation H1-antihistamines are considered high risk medications to be avoided (e.g., Beers criteria, HEDIS) should be directed to try alternatives that are not considered high risk.

Unproven

Xolair is unproven and not medically necessary in the following:

- Seasonal allergic rhinitis
- Perennial allergic rhinitis
- Atopic dermatitis
- Peanut allergy
- Acute bronchospasm or status asthmaticus

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J2357	Injection, omalizumab, 5 mg

Diagnosis Code	Description
J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation
J44.9	Chronic obstructive pulmonary disease, unspecified
J45.40	Moderate persistent asthma, uncomplicated
J45.41	Moderate persistent asthma with (acute) exacerbation
J45.50	Severe persistent asthma, uncomplicated
J45.51	Severe persistent asthma with (acute) exacerbation
J45.909	Unspecified asthma, uncomplicated
J45.998	Other asthma
L50.0	Allergic urticaria
L50.1	Idiopathic urticaria

Diagnosis Code	Description
L50.8	Other urticaria

Maximum Dosage Requirements

Maximum Allowed Quantities by HCPCS Units

This section provides information about the maximum dosage per administration for omalizumab administered by a medical professional.

Medication Name		Diagnosis	Maximum Dosage per Administration	HCPCS Code	Maximum Allowed
Brand	Generic				
Xolair	omalizumab	Moderate to Severe Asthma	375 mg	J2357	90 HCPCS units (5 mg per unit)
		Chronic Urticaria	300 mg	J2357	60 HCPCS units (5 mg per unit)

Maximum Allowed Quantities by National Drug Code (NDC) Units

The allowed quantities in this section are calculated based upon both the maximum dosage information supplied within this policy as well as the process by which NDC claims are billed. This list may not be inclusive of all available NDCs for each drug product and is subject to change.

Medication Name		Diagnosis	How Supplied	National Drug Code	Maximum Allowed
Brand	Generic				
Xolair	omalizumab	Moderate to Severe Asthma	150 mg vials	50242-0040-62	3 vials
		Chronic Urticaria	150 mg vials	50242-0040-62	2 vials

Background

Asthma is a common chronic inflammatory disease of the airways that affects an estimated 24 million adults and children and is associated with significant morbidity and mortality. Omalizumab is a monoclonal antibody that binds to human immunoglobulin E (IgE)'s high affinity Fc receptor, thereby preventing the binding of IgE to a variety of cells associated with the allergic response. Preventing the bridging between IgE and cells associated with allergic response prevents degranulation of such cells and, thereby, the release of inflammatory mediators. Omalizumab has been found in clinical trials to reduce free serum IgE concentrations by more than 90%, considerably suppress eosinophils in induced sputum, and blunt both early and late phase allergic reactions.³³⁻³⁴

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

Proven

Allergic Asthma

Omalizumab is indicated for treatment of adults and adolescents 6 years of age and older, who have moderate to severe persistent asthma and a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.³

Deschildre et al evaluated omalizumab efficacy and safety in a real-life setting in children aged 6 to 18 years (n=104) with severe asthmas followed up in pediatric pulmonary tertiary care centers.²⁸ Asthma control levels, exacerbations, inhaled corticosteroid dose, lung function and adverse events were evaluated over 1 year. Children were characterized by allergic sensitization to three or more allergens (66%), high IgE levels (mean 1125 kU · L(-1)), high rate of exacerbations (4.4 per year) and healthcare use during the previous year, and high inhaled corticosteroid dose (mean 703 µg equivalent fluticasone per day). Asthma control levels defined as good, partial or poor, improved from 0%, 18% and 82% at entry to 53%, 30% and 17% at week 20, and to 67%, 25% and 8% at week 52, respectively (p<0.0001). Reported exacerbation and hospitalization rates decreased by 72% and 88.5%, respectively. At 12 months, forced expiratory volume in 1 s (FEV1) improved by 4.9% (p=0.023), and inhaled corticosteroid dose decreased by 30% (p<0.001). Six patients stopped omalizumab for related significant adverse events. Omalizumab improved asthma control in children with severe allergic asthma and was generally well tolerated. Authors concluded that the observed benefit was greater than that reported in clinical trials.

Sorkness et al conducted a post-hoc analyses which examined patient characteristics of those eligible and ineligible for omalizumab; described onset of effect after initiation of omalizumab and offset of treatment effect after stopping therapy; and determined whether the efficacy differs by age, asthma severity, dosing regimen, and pre-specified biomarkers.²⁷ Inner-city children and adolescents with persistent allergic asthma enrolled in the Inner-City Anti-IgE Therapy for Asthma (ICATA) trial that compared omalizumab with placebo added to guidelines-based therapy for 60 weeks were eligible for the evaluation (a significant portion of children and adolescents particularly suited for omalizumab because of asthma severity status were ineligible due to IgE >1300 IU/mL). Two hundred ninety-three of 889 participants (33%) clinically suitable for omalizumab were ineligible for dosing according to a modified dosing table specifying IgE level and body weight criteria. Baseline symptoms were comparable among those eligible and ineligible to receive omalizumab, but other characteristics (rate of health care utilization and skin test results) differed. Patients receiving biweekly injections experienced a greater reduction in both exacerbations (OR = 2.54) and inhaled corticosteroids (ICS) usage (-204.8 µg/day) compared to patients receiving monthly injections (1.42 and -50.2 µg/day; p=0.08 and p=0.02, respectively). Omalizumab efficacy for symptom days per 2 weeks did not differ by dosing regimen (p=0.62). Patients with total IgE ≥700 IU/mL had the greatest reduction in ICS usage (-504.6 µg/day) because of treatment with omalizumab. The time of onset of omalizumab effect was <30 days and time of offset was between 30 and 120 days. No difference in efficacy was noted by age or asthma severity, but high exhaled nitric oxide, blood eosinophils, and body mass index predicted efficacy. Researchers concluded that results of this analysis showed that efficacy for exacerbations and ICS treatment was comparable in children 6 to 12 years of age compared with older children (>12 years). Additionally, the data suggested that omalizumab may be efficacious in both severe disease (steps 5-6 treatments) and more moderate disease (steps 1-4). Certain subgroups of persons, for example, those with higher exhaled nitric oxide, blood eosinophils, and BMI were more likely to benefit from omalizumab according to the secondary analysis.

The Inner-City Anti-IgE Therapy for Asthma (ICATA) Study was a 60-week, randomized, double-blind, placebo-controlled, parallel-group trial (n=419) which evaluated the effectiveness of omalizumab (75-375 mg subcutaneously every 2-4 weeks), as compared with placebo, when added to guidelines-based therapy.²¹ The primary outcome was reduction in symptoms and exacerbations of asthma. Inner-city patients 6 to 20 years of age with persistent asthma (receiving long-term therapy for disease control and having symptoms of persistent asthma or evidence of uncontrolled disease as indicated by hospitalization or unscheduled urgent care in the 6 to 12 months preceding study entry), at least one positive skin test for a perennial allergen, weight between 20 and 150 kg, and having total serum levels of IgE between 30 and 1300 IU per milliliter were eligible for enrollment. Additionally, patients not receiving long-term control therapy were eligible for enrollment only if they had both persistent symptoms and uncontrolled asthma. The primary outcome defined as reduction in symptoms (number of days with symptoms during the previous two weeks) and exacerbations of asthma was evaluated every 4 weeks. Omalizumab as compared with placebo significantly reduced the number of days with asthma symptoms, from 1.96 to 1.48 days per 2-week interval, a 24.5% decrease (p<0.001). Similarly, the percentage of participants with exacerbations (one or more) during the study was 48.8% in the placebo group as compared with 30.3% in the omalizumab group (p<0.001), and the percentage who

were hospitalized because of asthma was 6.3% as compared with 1.5%, respectively ($p=0.02$). Improvements occurred with omalizumab despite reductions in the use of inhaled glucocorticoids and long-acting beta-agonists.

In a further pre-specified, subgroup [Lanier 2009] analysis, Kulus et al. evaluated efficacy and safety of omalizumab as compared to placebo in children ($n=235$) with severe, persistent allergic asthma.²⁴ Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline inhaled corticosteroid dose and/or systemic steroids) by 34% versus placebo (0.42 vs 0.63, $p=0.047$). Over 52 weeks, the exacerbation rate was reduced by 50% ($p<0.001$). The overall incidence of adverse events (AEs) was similar in both omalizumab and placebo groups (93.4% vs 95.0%, $p=0.779$), serious AEs were less frequent in the omalizumab group (3.6% vs 10.0%, $p=0.073$), and no new safety concerns were evident. Researchers noted that the sample size was not based on providing statistical power in the severe subgroup, and no corrections were made for multiple comparisons; however, outcomes consistently favored omalizumab.

Milgrom et al. evaluated the safety of omalizumab in children ($n=926$) ages 6-12 with allergic (IgE-mediated) asthma in a pooled analysis of two double-blind, placebo controlled studies [Milgrom 2001 and Lanier 2009].²² Children on optimized asthma care were randomized (2:1) to omalizumab (75-375 mg every 2 or 4 weeks) or placebo. Adverse events (AEs) were more frequently reported in the placebo (91.7%) than omalizumab (89.7%) group. The most common AEs were nasopharyngitis, upper respiratory tract infection and headache. Suspected treatment-related AEs included headache, erythema and urticaria; none of which were reported by $\geq 2\%$ of patients receiving omalizumab. Serious adverse effects were reported by 3.4% and 6.6% of patients receiving omalizumab and placebo, respectively; the most common were appendicitis, pneumonia and bronchitis; no deaths were reported.

Allergic Asthma with IgE Levels > 700 IU/ml

A retrospective study evaluated the response of asthmatic patients treated with omalizumab with IgE levels greater than 700 IU/mL.²⁹ Emergency department (ED) visits, hospitalizations, change in forced expiratory volume in 1 second (FEV1), corticosteroid bursts, and Asthma Control Test (ACT) scores were recorded for a period of 6 months before and after treatment with omalizumab in patients with elevated IgE levels or treatment length of ≥ 6 months. Twenty-six patients with an IgE level > 700 IU/mL (group 1) were matched by age, sex, and severity of asthma to patients with an IgE of 30 to 700 IU/mL (group 2). The mean numbers of ED visits before and after treatment was 0.96 vs 0.23 ($p=0.008$) in group 1 and 0.65 vs 0.15 ($p=0.02$) in group 2. Both groups had an improvement in asthma control based on the mean ACT score before and after treatment (15.6 vs 18.9 [$p=0.02$] and 15.4 vs 19 [$p=0.006$], respectively). Additionally, there was a significant reduction in the frequency of systemic corticosteroid use during the 6 months before and after treatment (2.58 vs 0.96 [$p < 0.001$] and 2.62 vs 1.23 [$p < 0.001$] systemic steroid treatments, respectively). Researchers concluded that omalizumab was just as effective in reducing ED visits, controlling asthma symptoms, and reducing the need for systemic corticosteroids in patients with IgE levels > 700 IU/mL compared with patients with levels within 30 to 700 IU/mL.

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study evaluated use of high dose omalizumab in adult patients with IgE levels > 700 IU/ml.²⁵ Fifty asthmatic patients (pre-bronchodilator forced expiratory volume in 1 second (FEV1) $\geq 65\%$ predicted; had been asthma exacerbation-free for ≥ 4 weeks; and skin reactivity to a specific allergen within 2 years before screening) with an age range of 18 to 65 years and a body weight range of 40 to 150 kg were divided into two groups according to IgE levels (group 1: 30-300 IU/ml and group 2: 700-2000 IU/ml) and randomized 2:1 to receive either omalizumab or placebo every 2 or 4 weeks. Allergen bronchoprovocation (ABP) testing was performed at baseline, week 8 and week 16. The primary efficacy endpoint measured was the early-phase allergic response (EAR; defined as the maximum percentage drop in forced expiratory volume in 1 second during the first 30 minute after ABP). Secondary outcome evaluated with the late-phase allergic response (LAR; defined as maximum percentage drop in FEV1 over 3-8 hours after ABP). Additional outcomes assessed included serum free IgE (as a pharmacodynamic endpoint) and the exhaled fractional concentration of nitric oxide (FENO; as an exploratory endpoint). At week 8, EAR was 23.1% for placebo and treatment with omalizumab reduced it to 9.3% in in group 1 ($p=0.018$ vs placebo) and 5.6% in group 2 ($p<0.001$ vs placebo). Additionally, at week 16, reported EAR was 20%, 11.8% ($p=0.087$) and 5.1% ($p<0.001$), respectively. LAR analysis was not performed due to the small number of patients studied. Serum free IgE levels decreased in groups 1 and 2 and remained <50 ng/ml in all patients during weeks 6-16. Treatment with omalizumab suppressed FENO increases after ABP in both groups. Authors conclude that the outcomes of this study demonstrated that the protective effects of omalizumab against allergen-induced bronchoconstriction in patients with allergic asthma and baseline IgE up to 2000 IU/ml.

Researchers conducted a post-marketing observational surveillance trial to evaluate the efficacy and tolerability of omalizumab in a real-life setting in Spain, particularly in those patients with immunoglobulin E (IgE) levels out of range.²⁶ Patients were recruited if they had a diagnosis of uncontrolled severe, persistent, allergic asthma while on high-dose inhaled corticosteroids (ICSs) plus long-acting β 2-agonist (LABA); had an age \geq 12 years; and had received at least one dose of omalizumab between May 2006 and November 2009. Main efficacy outcomes evaluated included asthma exacerbation rate (AER), asthma control test (ACT), and global evaluation of treatment effectiveness (GETE). Of the 266 patients enrolled, 7 patients had IgE levels $<$ 30 IU/ml and 46 patients had IgE levels $>$ 700 IU/ml. Average AER reported for all groups showed a reduction from 3.6 in previous year to 0.67 at 4 months ($p < 0.05$) and to 1.04 at 2 years ($p < 0.05$). Average ACT increased from 14.3 at baseline to 18.4 at 4 months ($p < 0.05$) and to 20.3 $p < 0.05$ at 2 years. After 4 months, 74.6% of patients had reached a good or excellent rate on the GETE scale ($p < 0.05$) and this rate continued to increase to 81.6% at 2 years. Similarly, in the IgE $>$ 700 IU/ml group, researchers reported an increased ACT from 13.6 at baseline to 20.9 at the 2-year visit ($p < 0.05$) and a decrease in exacerbations from 3.58 at baseline to 0.72 at the 2-year visit ($p < 0.05$). At follow-up, maintenance treatment with oral steroids was reduced from 89 patients to 19 patients ($p < 0.05$). Omalizumab was discontinued because of lack of efficacy in 28/266 (10.5%) patients and 30 patients (11.4%) reported adverse events (none were severe). Researchers conclude that this observational study confirms that omalizumab is efficacious and well tolerated in patients with uncontrolled severe asthma, including those patients with IgE levels $>$ 700 IU/ml.

Chronic Urticaria

Omalizumab is indicated for treatment of chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.³

Saini et al conducted a 40-week, randomized, double-blind, placebo-controlled trial (ASTERIA I) to evaluate the efficacy and safety of subcutaneous omalizumab as add-on therapy for 24 weeks in patients ($n=319$) with chronic idiopathic urticaria/spontaneous urticaria (CIU/CSU) who remained symptomatic despite H₁ antihistamine treatment.¹ Eligible patients aged 12–75 years with CIU/CSU who remained symptomatic despite treatment with approved doses of H₁ antihistamines were randomized (1:1:1:1) in a double-blind manner to subcutaneous omalizumab 75 mg ($n=78$), 150 mg ($n=80$), or 300 mg ($n=81$) or placebo ($n=80$) every 4 weeks for 24 weeks followed by 16 weeks of follow-up. The primary outcome measured was change from baseline in weekly itch severity score (ISS) at week 12. Secondary outcomes evaluated at week 12, included changes from baseline in UAS7 and weekly number of hives score; time to MID response (≥ 5 -point decrease) in weekly ISS; the proportion of patients with UAS7 ≤ 6 ; the proportion of weekly ISS MID responders; changes from baseline in weekly size of largest hive score and overall DLQI score; the proportion of angioedema-free days during weeks 4 to 12; and the proportion of patients with complete response (UAS7=0). Compared with placebo mean weekly ISS was reduced from baseline to week 12 by an additional 2.96 points (95% confidence interval (CI): -4.71 to -1.21; $p=0.0010$), 2.95 points (95% CI: -4.72 to -1.18; $p=0.0012$), and 5.80 points (95% CI: -7.49 to -4.10; $p < 0.0001$) in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively. The omalizumab 300-mg group met all nine secondary end points, including a significant decrease in the duration of time to reach minimally important difference response (≥ 5 -point decrease) in weekly ISS ($p < 0.0001$) and higher percentages of patients with well-controlled symptoms (urticaria activity score over 7 days (UAS7) ≤ 6 : 51.9% vs. 11.3% $p < 0.0001$) and complete response (UAS7=0: 35.8% vs. 8.8% $p < 0.0001$) versus placebo. During the 24-week treatment period, the proportions of patients who experienced one or more treatment-emergent adverse events (AEs) ranged from 57 to 69% in the omalizumab groups versus 51% in the placebo group. Additionally, 2 (2.9%), 3 (3.4%), 0, and 4 (5.0%) patients in the omalizumab 75-mg, 150-mg, 300-mg, and placebo groups, respectively, experienced a serious adverse event. Omalizumab 300 mg administered every 4 weeks reduced weekly ISS and other symptom scores versus placebo in CIU/CSU patients who remained symptomatic despite treatment with approved doses of H₁ antihistamines. Additionally, the results of this study showed a sustained treatment effect of omalizumab 300 mg for up to 24 weeks on CIU/CSU symptom scores in patients with H1 antihistamine-refractory CIU/CSU. The safety profile for omalizumab over 24 weeks of treatment in patients with CIU/CSU receiving approved doses of H1 antihistamines was consistent with the established safety profile in allergic asthma and with previous observations in CIU/CSU.

Unproven

Seasonal Allergic Rhinitis

Researchers conducted a systemic review and meta-analysis of the efficacy and safety of omalizumab in poorly controlled allergic rhinitis in randomized controlled trials dating through 2013.¹⁶ Eleven studies that assessed 2870 randomized patients were included. A statistically significant reduction in the daily nasal symptom severity score (standardized mean difference -0.67 [95% CI, -1.3 to -0.31]; $p < .0001$; I(2), 92%) and a statistically significant reduction in daily nasal rescue medication score (-0.22 [95% CI, -0.39 to -0.05; $p=0.01$; I(2), 58%) were observed. There was not a statistically significant difference in the occurrence of

any adverse event (relative risk 1.06 [95% CI, 0.94-1.19; I(2), 55%). The meta-analysis showed that, in seasonal and perennial allergic rhinoconjunctivitis, treatment with omalizumab provided an improvement of the daily nasal symptom severity score (DNSSS) and a reduction of antiallergic medication use compared with placebo. The rhinosinusitis-related quality of life (rQoL) appeared to be improved in the limited randomized evidence available. The observed safety profile indicated an adequate tolerability and a comparable overall AEs pattern. The potential benefits of omalizumab need to be considered in the context of costs of therapy and rare AEs. Larger clinical trials and economic studies are needed to address issues of rare events occurrence and cost-effectiveness, respectively.

Several studies have evaluated the use of omalizumab therapy in children, adolescents and adults with seasonal allergic rhinitis. Though results appear to be promising, additional trials are warranted to establish long-term efficacy and safety, as well as appropriate dosage and timing.⁶⁻¹¹

Perennial Allergic Rhinitis

Corren et al. assessed 19 patients (ages 18-65 years) with perennial allergic rhinitis in a 26 week open-label study of intravenous (IV) omalizumab 0.015-0.03mg/kg/IgE [IU/mL] every 2 weeks.¹² Serum free IgE concentrations decreased by up to 99%. Nasal allergen challenge symptom scores (e.g. sneezing, rhinorrhea) decreased significantly.

In another study, 40 patients with perennial allergic rhinitis receiving open-label omalizumab 0.015-0.030 mg/kg/IgE [IU/mL] IV every 2 weeks for 28 weeks showed up to 99% decrease in serum free IgE and decreased reaction to wheal-and-flare skin tests at day 98.¹³ However, upon decreased dosage to 0.0015-0.005mg/kg/IgE [IU/mL] for another 18 weeks, serum free IgE and skin test reactivity increased significantly and returned to baseline upon discontinuation.

Chervinsky et al. studied the efficacy, safety, and tolerability of omalizumab in the short-term treatment of patients 12 to 70 years of age with perennial allergic rhinitis with moderate to severe symptoms in a randomized, double-blind trial.¹⁴ The patients completed 16 weeks of either placebo (n=145) or at least 0.016 mg/kg/IgE [IU/mL] subcutaneous omalizumab every four weeks (n=144). Patients maintained a diary of their daily symptoms including nasal severity scores throughout the study period, which was based on a 4-point scale (0 = no symptoms to 3 = severe symptoms). Patients in the omalizumab group had a 69% reduction in the average daily nasal severity score from baseline compared to 49% of the placebo treated patients (p=0.001). Symptoms were controlled, which was defined as a score of less than 0.75 on a 4 point scale, in 28% (40/143) of patients in the omalizumab group compared to 10% (14/145) of patients in the placebo group. In both study groups, antihistamine use was low, however omalizumab significantly decreased antihistamine use per month more than placebo (omalizumab; 4.5 to 1.5 days per month, placebo: 3.6 to 2.7 days per month, p=0.005). Three patients in each group dropped out due to intolerance of study medication or placebo, but no severe safety concerns were noted throughout the study. In this study, there was a large placebo effect making the true effect of omalizumab difficult to determine. Additional and larger studies are needed in this population.

Atopic Dermatitis

Heil et al. investigated the effects of omalizumab or placebo on the expression of IgE and its receptors on cells and on serum components of patients with atopic dermatitis (AD).²⁵ Additional evaluation included whether omalizumab would revert preexisting lesions in patients with long lasting and ongoing AD. Twenty patients were randomized 2:1 in a placebo-controlled, double blind study for 16 weeks. Male and female patients (ages 12-60 years) with a clinical diagnosis of AD and a serum IgE between 30 and 1300 IU/ml were included. Patients in the omalizumab treatment had reduced serum levels of free IgE and decreased surface-bound IgE. However, omalizumab treatment did not significantly alter several measures of clinical disease activity (i.e., atopy patch test results in single patients). Researchers conclude that a therapeutic benefit of omalizumab treatment, if present at all, would be seen in patients with acute rather than chronic forms of AD.

Peanut Allergy

In a phase II, double-blind, randomized clinical trial, omalizumab was evaluated in patients with a hypersensitivity reaction to peanut and compared with placebo.¹⁷⁻¹⁹ During screening, patients underwent a double-blind oral food challenge with either peanut flour or wheat flour. Patients who reacted to less than or equal to 250 mg of peanut flour and not wheat flour were randomized to omalizumab (minimum 0.016 mg/kg/IgE [IU/mL] every 4 weeks or 0.008 mg/kg/IgE [IU/mL] every 2 weeks) or placebo for 20 to 22 weeks. At 24 weeks, patients were to receive a second double-blind oral challenge to either peanut or wheat flour. However, due to safety concerns of the oral food challenge, an external data and safety monitoring committee terminated the trial early.

Acute Bronchospasm or Status Asthmaticus

The US Food and Drug Administration (FDA) has required the manufacturer of omalizumab to state in its labeling that Xolair cannot be used to treat acute bronchospasm or status asthmaticus.³

Professional Societies

Allergic Asthma

The Global Initiative for Asthma (GINA, 2020) recommends that for Step 5 treatment, patients 6 years and older may be treated with omalizumab as follows:²

- Consider add-on for those with moderate or severe allergic asthma that is uncontrolled on Step 4-5 treatment including high dose ICS/LABA, add on long-acting muscarinic antagonist, or LTRA.
- Step 5: Refer for phenotypic investigation and/or add-on treatment. Patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be referred to a specialist with expertise in investigation and management of severe asthma.
- Add-on treatments for moderate or severe allergic asthma, anti-IgE treatment (subcutaneous omalizumab for patients aged ≥ 6 years) that is uncontrolled on Step 4-5 treatment.

In April 2013, The National Institute for Health and Care Excellence (NICE) published a technology appraisal guidance addressing use of omalizumab in children aged 6 to 11 years with severe, persistent asthma.⁴ In the assessment, NICE noted the 'life-changing' effect of omalizumab reported by patients and concluded that omalizumab as an add-on to optimised standard therapy is more clinically effective in treating severe persistent allergic asthma than optimised standard therapy alone, leading to a reduction in total emergency visits (including hospital admissions, A&E visits and unscheduled general physician visits) in adults, reduced hospital admissions in children, improved lung function in adults and a reduction in the frequency and use of rescue medication and oral corticosteroids. The committee recommended that omalizumab be used as follows:

- Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimized standard therapy [defined - as a full trial of (and, if tolerated, documented compliance with) inhaled high-dose corticosteroids, long-acting β_2 -agonists, leukotriene receptor antagonists, theophylline, oral corticosteroids and smoking cessation if clinically appropriate].
- In people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)
 - Optimized standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

In June 2015, NICE published an additional technology appraisal guidance addressing use of omalizumab in children and adults aged 12 years and over for the treatment of spontaneous urticaria.³² The committee recommended that omalizumab be used as follows:

- Omalizumab is recommended as an option as add-on therapy for treating severe chronic spontaneous urticaria in adults and young people aged 12 years and over only if:
 - the severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more
 - the person's condition has not responded to standard treatment with H₁-antihistamines and leukotriene receptor antagonists
 - omalizumab is stopped at or before the fourth dose if the condition has not responded
 - omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded, to establish whether the condition has gone into spontaneous remission, and is restarted only if the condition relapses
 - omalizumab is administered under the management of a secondary care specialist in dermatology, immunology or allergy

European Respiratory Society (ERS)/American Thoracic Society (ATS)

The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines define severe asthma as that which requires treatment with high-dose ICSs plus a second controller (or systemic corticosteroids) to prevent progression to uncontrolled disease status or continuing uncontrolled disease status despite this therapy.³ The guidelines recommend omalizumab in adults and children with severe allergic asthma (Recommendation: Conditional, Low for adults, Very Low in

children). This recommendation places higher value on the clinical benefits from omalizumab in some patients with severe allergic asthma and lower value on increased resource use.

The guidelines remark:

- Those adults and children aged ≥ 6 years with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance if their total serum IgE level is 30–700 IU/mL (in three studies the range was wider: 30–1300 IU/mL).
- Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare utilization, and improvement in quality of life.
- If a patient does not respond within 4 months of initiating treatment, it is unlikely that further administration of omalizumab will be beneficial.

Chronic Urticaria

In 2014, the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology updated the practice parameter for the diagnosis and management of acute and chronic urticaria (CU). The practice parameter established a step-care approach to the treatment of chronic urticaria and angioedema. The task force recommended the following step-care treatment approach:²⁰

- Monotherapy with second-generation antihistamines: H1-antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients.
- Dose advancement of H1-antihistamine therapy, combining first- and second-generation agents and adding an H2-antihistamine and/or an antileukotriene agent: Higher doses of second-generation antihistamines can provide greater efficacy when control is not achieved with conventional doses of these agents.
- Therapeutic trial of potent antihistamine (e.g., hydroxyzine or doxepin): First-generation antihistamines should be prescribed cautiously in the elderly or patients with occupations (e.g., machine operators, airline pilots, or alpine skiers) for which alertness is essential.
- Add an immunosuppressant or biologic agent: Omalizumab and cyclosporine have the greatest published experience documenting efficacy in patients with CU compared with all other alternative agents.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage

Xolair is approved by the U.S. Food and Drug Administration (FDA) for use in adults and adolescents 6 years of age and older, who have moderate to severe persistent asthma and a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair is not indicated for acute bronchospasm or status asthmaticus. Xolair is also approved for chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H₁ antihistamine treatment. It is not indicated for other allergic conditions or other forms of urticaria. Because of the risk of anaphylaxis, healthcare providers administering Xolair should observe patients closely for an appropriate period of time and be prepared to manage anaphylaxis that can be life-threatening.³

On September 26, 2014, the U.S. FDA released a drug safety alert entitled: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events.¹⁶ An FDA review of safety studies suggests a slightly increased risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the asthma drug Xolair (omalizumab) than in those who were not treated with Xolair. As a result, FDA has added information about these potential risks to the drug label. Additionally, reviewers found no difference in the rates of cancer between those patients being treated with Xolair and those who were not being treated with Xolair. However, due to limitations in the 5-year study, FDA cannot rule out a potential risk of cancer with Xolair, so this information was added to the Warnings and Precautions section of the drug label.

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for Xolair® (omalizumab). Local Coverage Determinations (LCDs) exist; see the LCDs for [Omalizumab](#) and [Drugs and Biologicals, Coverage of, for Label and Off-Label Uses](#).

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the [Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals](#). (Accessed June 25, 2020)

References

1. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol*. 2015 Jan;135(1):67-75.
2. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention - revised 2019. Accessed June 24, 2020.
3. Xolair® [package insert]. South San Francisco, CA: Genentech, Inc., May 2019.
4. National Institute for Health and Care Excellence (NICE). Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201). London (UK): National Institute for Health and Care Excellence (NICE); 2013 Apr. 64 p. (Technology appraisal guidance; no. 278).
5. Xolair Solution for Injection. Omalizumab. Annex I. Summary of Product Characteristics. Nuremberg, Germany: Novartis; October 25, 2010.
6. Casale TB, Condemi J, LaForce C, et al. Omalizumab Seasonal Allergic Rhinitis Trial Group. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA*. 2001;286(23):2956-67.
7. Nayak A, Casale T, Miller SD, et al. Tolerability of retreatment with omalizumab, a recombinant humanized monoclonal anti-IgE antibody, during a second ragweed pollen season in patients with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2003;24(5):323-9.
8. Rolinck-Werninghaus C, Hamelmann E, Keil T, et al. The co-seasonal application of anti-IgE after pre-seasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. *Allergy*. 2004;59(9):973-979.
9. Kuehr J, Brauburger J, Zielen S, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2002;109(2):274-80.
10. Kopp MV, Hamelmann E, Zielen S, et al. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhino-conjunctivitis and co-morbid seasonal allergic asthma. *Clin and Exp Allergy*. 2009;39(2):271-9.
11. Casale TB, Busse WW, Kline JN, et al. Immune Tolerance Network Group. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2006;117(1):134-40.
12. Corren J, Diaz-Sanchez D, Saxon A, et al. Effects of omalizumab, a humanized monoclonal anti-IgE antibody, on nasal reactivity to allergen and local IgE synthesis. *Ann Allergy Asthma Immunol*. 2004;93(3):243-8.
13. Corren J, Shapiro G, Reimann J, et al. Allergen skin tests and free IgE levels during reduction and cessation of omalizumab therapy. *J Allergy Clin Immunol*. 2008;121(2):506-11.
14. Chervinsky P, Casale T, Townley R, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. 2003;91(2):160-7.
15. FDA Drug Safety Communication. FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events. Updated September 26, 2014. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm414911.htm>. Accessed May 16, 2016.

16. Tsaouri S, Tseretopoulou X, Priftis K, et al. Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. *J Allergy Clin Immunol Pract*. 2014 May-Jun;2(3):332-40.
17. Sampson HA. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair® (omalizumab) in peanut allergy (TOPS). *J Allergy Clin Immunol*. 2007;119 (Supp 1): s117. Abstract.
18. Genentech, Inc. Synopsis of Abbreviated Clinical Study Report: A Phase II, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Oral Food Challenge Trial of Xolair® (Omalizumab) in Peanut Allergy. Accessed December 30, 2011.
19. Sampson HA, Leung DY, Burks AW, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *J Allergy Clin Immunol*. 2011 May;127(5):1309-10.
20. Bernstein JA, Lang DM, Khan DA, et al. Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology. Practice parameter: The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allerg Clin Immunol*. 2014; 133(5):1270-1277.
21. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med*. 2011 Mar 17;364(11):1005-15.
22. Milgrom H, Fowler-Taylor A, Vidaurre CF, et al. Safety and tolerability of omalizumab in children with allergic (IgE-mediated) asthma. *Curr Med Res Opin*. 2011 Jan;27(1):163-9.
23. Heil PM, Maurer D, Klein B, et al. Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course - a randomized, placebo-controlled and double blind pilot study. *J Dtsch Dermatol Ges*. 2010;8(12):990.
24. Kulus M, Hébert J, Garcia E, et al. Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma. *Curr Med Res Opin*. 2010 Jun;26(6):1285-93.
25. Zielen S, Lieb A, De La Motte S, et al. Omalizumab Protects against Allergen-Induced Bronchoconstriction in Allergic (Immunoglobulin E-Mediated) Asthma. *Int Arch Allergy Immunol*. 2013;160(1):102-10.
26. Vennera M del C, Pérez De Llano L, Bardagi S, et al. Omalizumab therapy in severe asthma: experience from the Spanish registry—some new approaches. *J Asthma*. 2012 May;49(4):416-22.
27. Sorkness CA, Wildfire JJ, Calatroni A, et al. Reassessment of omalizumab-dosing strategies and pharmacodynamics in inner-city children and adolescents. *J Allergy Clin Immunol Pract*. 2013 Mar;1(2):163-71.
28. Deschildre A, Marguet C, Salleron J, et al., Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Eur Respir J*. 2013 Nov;42(5):1224-33.
29. Maselli DJ, Singh H, Diaz J, Peters JI. Efficacy of omalizumab in asthmatic patients with IgE levels above 700 IU/mL: a retrospective study. *Ann Allergy Asthma Immunol*. 2013 Jun;110(6):457-61.
30. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014 May;133(5):1270-7.
31. The MCG™ Care Guidelines, Omalizumab [ACG: A-0315 (AC)]. <http://www.careguidelines.com/>. Accessed June 26, 2020.
32. National Institute for Health and Care Excellence (NICE). Omalizumab for previously treated chronic spontaneous urticaria. London (UK): National Institute for Health and Care Excellence (NICE); 2015 June. 52 p. (Technology appraisal guidance; no. 339).
33. Gold Standard, Inc. Omalizumab. Clinical Pharmacology [database online]. Available at <http://www.clinicalpharmacology.com>. Accessed June 24, 2020.
34. Centers for Disease Control and Prevention. Asthma. Available at <http://www.cdc.gov>. Accessed June 13, 2019.
35. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014 Feb;43(2):343-73.

Policy History/Revision Information

Date	Summary of Changes
09/01/2020	Supporting Information <ul style="list-style-type: none">Updated <i>Clinical Evidence</i>, <i>CMS</i>, and <i>References</i> sections to reflect the most current informationArchived previous policy version 2019D0033Q

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.