XOLAIR® (omalizumab)

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INSTRUCTIONS FOR USE
This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines 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.

COVERAGE RATIONALE

Omalizumab (Xolair®) for subcutaneous use is proven for:

1. Adults and adolescents with moderate to severe persistent asthma who meet all of the following criteria:3,9
   a. Age 12 years or older
   b. Have a positive skin test or in vitro reactivity to a perennial aeroallergen
   c. Symptoms inadequately controlled with inhaled corticosteroids. Refer to Benefit Considerations for specific state guidance.
   d. Have a baseline plasma immunoglobulin E (IgE) level between 30 and 1500 IU/mL
Additional information to support medical necessity review where applicable:
Omalizumab is medically necessary for treatment of adults and adolescents with moderate to severe persistent asthma when all of the following criteria are met:^3,25,40,41
A. Age 12 years or older
   -AND-
B. Diagnosis of moderate to severe persistent uncontrolled asthma as defined by one of the following:
   1. Daily asthmatic symptoms
   2. Daily use of inhaled short-acting beta2-agonist
   3. Exacerbations affect/limit activity
   4. Exacerbations (requiring oral systemic corticosteroids) ≥ 2 times a year
   5. Nighttime awakening more than once per week
   6. Forced expiratory volume in one second (FEV1) or peak expiratory flow (PEF) ≤ 80% of predicted level
   7. Measures of asthma control indicate uncontrolled asthma (e.g., Asthma Control Test (ACT) score ≤ 19)
   -AND-
C. Baseline (pre-omalizumab treatment) serum total IgE level ≥ 30 IU/mL and ≤ 1500 IU/mL
   -AND-
D. Positive skin test or in vitro reactivity to a perennial aeroallergen
   -AND-
E. Documented failure (e.g., emergency room visit or hospitalization for asthma exacerbation, need for oral steroid burst) of at least 3 months to regular/routine treatment with one of the following (refer to Benefit Considerations for specific state guidance):
   1. One combination inhaled corticosteroid/long-acting beta2-agonist product [e.g., fluticasone propionate/salmeterol (Advair®), mometasone/formoterol (Dulera®), budesonide/formoterol (Symbicort®)]
      -OR-
   2. Combination therapy including both of the following:
      a. One inhaled corticosteroid at the maximum dosage [e.g., fluticasone propionate (Flovent®), budesonide (Pulmicort®), beclomethasone dipropionate (QVAR®)]
         -AND-
      b. One long-acting beta2-agonist [e.g., formoterol fumarate (Foradil®), salmeterol xinafoate (Serevent®)]
         -AND-
F. Prescribed by or in consultation with an allergist/immunologist or pulmonologist

2. Omalizumab is proven and medically necessary as add-on therapy in children with severe persistent allergic asthma when all of the following criteria are met:^3,7,9,25
A. Age 6 years to less than 12 years
   -AND-
B. Diagnosis of severe persistent uncontrolled asthma as defined by one of the following:
   a. Frequent daytime symptoms
   b. Nighttime awakenings
   c. Use of short-acting beta2-agonist several times per day for symptom control
   d. Exacerbations limit/affect daily activity
   e. Exacerbations (requiring use of oral systemic corticosteroids) ≥ 2/year
      -AND-
C. Baseline (pre-omalizumab treatment) serum total IgE level ≥ 30 IU/mL and ≤ 1500 IU/mL
      -AND-
D. Documented failure (e.g., emergency room visit or hospitalization for asthma exacerbation, need for oral steroid burst) of at least 3 months to regular/routine treatment with one of the following (refer to Benefit Considerations for specific state guidance):
   a. One combination inhaled corticosteroid/long-acting beta2-agonist product [e.g., fluticasone propionate/salmeterol (Advair®), mometasone/formoterol (Dulera®), budesonide/formoterol (Symbicort®)]
      -OR-
   b. Combination therapy including both of the following:
      (1) One inhaled corticosteroid at the maximum dosage [e.g., fluticasone propionate (Flovent®), budesonide (Pulmicort®), beclomethasone dipropionate (QVAR®)]
      -AND-
      (2) One long-acting beta2-agonist [e.g., formoterol fumarate (Foradil®), salmeterol xinafoate (Serevent®)]
   -AND-

E. Prescribed by or in consultation with an allergist/immunologist or pulmonologist

3. Omalizumab is proven in chronic urticaria in adults and adolescents who meet both of the following criteria:
   A. Age 12 years or older
   -AND-
   B. Continues to remain symptomatic despite H1 antihistamine [e.g., cetirizine (Zyrtec), fexofenadine (Allegra)] treatment. Refer to Benefit Considerations for specific state guidance.

Additional information to support medical necessity review where applicable:
Omalizumab is medically necessary for treatment of chronic urticaria in adults and adolescents when all of the following criteria are met:
   A. Age 12 years or older
   -AND-
   B. One of the following: (Refer to Benefit Considerations for specific state guidance.)
      a. 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-
      b. 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:
         i. Second generation H1-antihistamine [e.g., Allegra (fexofenadine), Claritin (loratadine), Zyrtec (cetirizine)]
         -AND-
         ii. One of the following:
             1. Different second generation H1-antihistamine [e.g., Allegra (fexofenadine), Claritin (loratadine), Zyrtec (cetirizine)]
             2. First generation H1-antihistamine [e.g., Benadryl (diphenhydramine), Chlor-Trimeton (chlorpheniramine), Vistaril (hydroxyazine)]*
             3. H2-antihistamine [e.g., Pepcid (famotidine), Tagamet HB (cimetidine), Zantac (ranitidine)]
             4. Leukotriene modifier [e.g., Accolate (zafirlukast), Singulair (montelukast), Zyflo (zileuton)]
      -AND-
C. Prescribed by or in consultation with an allergist/immunologist

*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.

Omalizumab is **unproven** in the following:
1. Seasonal allergic rhinitis
2. Perennial allergic rhinitis
3. Atopic dermatitis
4. Peanut allergy
5. Acute bronchospasm or status asthmaticus

**Centers for Medicare and Medicaid Services (CMS):**
Medicare does not have a National Coverage Determination (NCD) for Xolair (Omalizumab). Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Xolair (Omalizumab).

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. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at [http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf](http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf)

(Updated April 15, 2014)

**BENEFIT CONSIDERATIONS**

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit 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. 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.

The State of New Jersey prohibits requiring failed prior therapy or intolerance to therapy as a requirement for coverage.

**CLINICAL EVIDENCE**

**Proven Asthma**

In a 48-week, prospective, randomized, parallel-group, double-blind trial (n=850) omalizumab-treated patients experienced a significant 25% relative reduction in the asthma exacerbation rate compared with placebo in patients with severe allergic asthma inadequately controlled on high dose inhaled corticosteroids (ICS) and long acting beta agonists (LABAs) with or without other controllers, including oral corticosteroids (OCS). Patients with an age range of 12 to 75 years, a history of severe allergic asthma for at least one year prior to screening, and at least one documented asthma exacerbation during that year were randomized to receive either placebo...
(n=423) or a minimum dose of omalizumab 0.008 mg/kg/IgE [IU/mL] subcutaneously every 2 weeks or 0.016 mg/kg/IgE [IU/mL] subcutaneously every 4 weeks (n=427). All patients also received high dose ICS equivalent to fluticasone 500 mcg twice daily and either salmeterol 50 mcg or formoterol 12 mcg twice daily. Long-term maintenance OCS were permitted with equivalent dose of prednisone 2 to 40 mg/day or 5 to 80 mg every other day. In an analysis of the primary endpoint, the asthma exacerbation rate (worsening of asthma symptoms requiring treatment with systemic corticosteroids for at least 3 days, or an exacerbation requiring at least 20 mg increase in the average daily dose of oral prednisone) was significantly lower in the omalizumab group compared with placebo, 0.66 vs 0.88, representing a 25% relative reduction (incidence rate ratio, 0.75 [95% CI, 0.61 to 0.92; p=0.006]). In secondary endpoint analysis, compared with the placebo group, omalizumab-treated patients had greater decreases in the mean asthma symptom score (-0.26; 95% CI, -0.42 to -0.1), mean daily albuterol puffs (-0.27 puffs/day; 95% CI, -0.49 to -0.04), and greater increase in asthma quality of life questionnaire (AQLQ) score (0.29 point; 95% CI, 0.15 to 0.43). The incidence of adverse effects (80.4% vs 79.5%) and serious adverse effects (9.3% vs 10.5%) was similar in the omalizumab and the placebo groups, respectively. Researchers concluded that omalizumab provided additional clinical benefit for patients with severe allergic asthma that is inadequately controlled with high dose inhaled corticosteroids and long acting beta agonists.

Omalizumab labeling includes 3 double-blind, placebo-controlled trials (n=1,368) of allergic asthmatic patients. Patients (12 to 76 years of age) were randomized to receive either subcutaneous placebo or omalizumab every 2 or 4 weeks. Omalizumab doses were based on body-weight and on baseline IgE levels. Inhaled corticosteroid doses were kept stable over the initial 16-weeks of study treatment. After the stable-steroid phase, inhaled corticosteroids were tapered during a 12-week treatment period. In two of the studies (n=542), 86% to 88% experienced no asthma exacerbations compared to 70% to 77% of placebo treated patients in the stable-steroid phase. During the 12-week steroid taper phase, 79% to 84% of omalizumab treated patients experienced no exacerbations in comparison with 68% to 70% of placebo treated patients.1,2 In the third study, the percentage of patients with one or more exacerbations was similar in the omalizumab and placebo groups.3

Chronic Urticaria

In a phase III trial, Kaplan et al evaluated the safety and efficacy of 24 weeks of treatment with omalizumab in patients with persistent chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU) despite treatment with H₁-antihistamines at up to 4 times the approved dose plus H₂-antihistamines, leukotriene receptor antagonists, or both.33 Of the 480 patients screened, 360 patients aged 12 to 75 years were randomized to receive 6 subcutaneous injections at 4-week intervals of either 300 mg of omalizumab or placebo, followed by a 16-week observation period. The primary objective of the study was to evaluate the overall safety of omalizumab compared with placebo. Efficacy (itch severity, hive, and urticaria activity scores) was evaluated at weeks 12 and 24. The reported mean change from baseline in weekly itch severity score (ISS) at week 12 (primary efficacy end point) showed improvement in the omalizumab group compared with that in the placebo group (−8.6 vs −4.0, p<0.001). This efficacy benefit with omalizumab was sustained to week 24 (−8.6 vs −4.0; LSM treatment difference, −4.5 [95% CI, −6.1 to −3.0]; p<0.001). After week 24 and until week 40, the mean weekly ISS in the omalizumab group gradually increased to values similar to those in the placebo group but did not return to baseline values throughout the follow-up period; however, there were no statistical differences noted between the omalizumab and placebo groups at week 40. The overall incidence and severity of adverse events and serious adverse events were similar between omalizumab and placebo recipients; the safety profile was consistent with omalizumab in patients with allergic asthma. Researchers concluded that omalizumab was well tolerated and reduced the signs and symptoms of CIU/CSU in patients who
remained symptomatic despite the use of H₁-antihistamines (up to 4 times the approved dose) plus H₂-antihistamines, leukotriene receptor antagonists, or both.

In a phase III, multicenter, randomized, double-blind, placebo-controlled study, researchers evaluated the efficacy and safety of omalizumab over 28 weeks in adult and adolescent (≥12 years) patients with moderate-to-severe chronic idiopathic urticaria who remained symptomatic despite H₁ antihistamine therapy. Patients were eligible for inclusion in the study if they were between the ages of 12 and 75 years and met all the following criteria: a history of at least 6 months of chronic idiopathic urticaria, the presence of hives associated with itching for at least 8 consecutive weeks at any time before enrollment despite current use of H₁-antihistamines, an urticaria activity score (UAS) during a 7-day period (UAS7) of 16 or more (on a scale ranging from 0 to 42, with higher scores indicating greater activity and a minimally important difference [MID] of 9.5 to 10.5), 24 a weekly itch-severity score of 8 or more (on a scale ranging from 0 to 21, with higher scores indicating more severe itching and an MID of ≥5) during the 7 days before randomization (week 0), a score of 4 or more on the UAS (ranging from 0 to 6, with higher scores indicating greater activity) as assessed by a clinician on at least one of the screening-visit days, and receipt of a licensed dose of a second-generation H₁-antihistamine for chronic idiopathic urticaria for at least 3 consecutive days immediately preceding the screening visit 14 days before randomization, and no missing electronic-diary entries for the 7 days before randomization. After a 2-week screening period, 323 patients were randomly assigned to four groups in a 1:1:1:1 ratio to receive three subcutaneous injections of omalizumab (at doses of 75 mg, 150 mg, or 300 mg) or placebo at 4 week intervals. After the 12-week treatment period, patients were observed for an additional 16 weeks. Patients continued to receive stable doses of H₁-antihistamine throughout the treatment period. During the follow-up period, patients were allowed to use a licensed dose of one additional H₁-antihistamine. For the duration of the study, all patients were provided with diphenhydramine (25 mg) as rescue medication for itch relief (up to a maximum of three doses in 24 hours on the basis of local regulations). The primary efficacy outcome was the change from baseline in a weekly itch-severity score (ranging from 0 to 21, with higher scores indicating more severe itching). The baseline weekly itch-severity score was approximately 14 in all four study groups. At week 12, the mean (SD) change from baseline to week 4 in the weekly itch-severity score reported was -5.1±5.6 in the placebo group, -5.9±6.5 in the 75-mg group (p=0.46), -8.1±6.4 in the 150-mg group (p=0.001), and -9.8±6.0 in the 300-mg group (p<0.001). Most prespecified secondary outcomes at week 12 showed similar dose-dependent effects. Similar to the weekly itch-severity scores, the weekly score for number of hives decreased with all three doses of omalizumab to a greater extent than with placebo throughout the 12-week treatment period, with the largest difference observed in the 300-mg group. During the follow-up period starting after week 12, the mean weekly score for the number of hives for all omalizumab groups increased to reach values similar to those in the placebo group and did not return to baseline values for the duration of follow-up. The percentages of patients with at least one adverse event were similar across the treatment groups: 61% in the placebo group, 59% in those receiving 75 mg of omalizumab, 67% in those receiving 150 mg of omalizumab, and 65% in those receiving 300 mg of omalizumab. The frequency of serious adverse events was low, although the rate was higher in the 300-mg group (6%) than in the placebo group (3%) or in either the 75-mg or 150-mg group (1% for each). Researchers concluded that omalizumab diminished clinical symptoms and signs of chronic idiopathic urticaria in those patients that had remained symptomatic despite the use of approved doses of H(1)-antihistamines.

In a phase II, prospective, double-blind, placebo-controlled, dose-ranging multicenter trial, 90 patients (ages 12 to 75 years) with persistent moderate-to-severe chronic urticaria (CU) despite antihistamine use were treated with a single administration of placebo or omalizumab (75, 300 or 600 mg) subcutaneously and monitored for 16 weeks. The primary efficacy outcome was a change from baseline to week 4 in urticaria activity scores (UAS7). Patients were followed for an...
additional 12 weeks to monitor safety. Both the 300 mg omalizumab group (-19.9 vs -6.9, 
p<0.001) and the 600-mg omalizumab group (-14.6 vs -6.9, p=0.047) showed greater 
 improvement versus the placebo group in UAS7. Secondary efficacy outcomes demonstrated a 
 mean change from baseline to week 4 in the weekly itch score was 29.2 (SD, 5.98) points for the 
 300 mg omalizumab group (23.5 points for placebo, p< 0.001) and 26.5 (SD, 5.63) points for the 
 600 mg omalizumab group (23.5 for placebo, p=5.056). During the same time period, the mean 
 change in weekly hive score was 10.7 (SD, 6.75) points for the 300 mg omalizumab group 
 (p<0.001) and 8.1 (SD, 6.0) points for the 600 mg omalizumab group (p=5.02) compared with 3.5 
 (SD, 5.2) points for the placebo group. No meaningful difference was observed for the 75 mg 
 omalizumab group in both primary and secondary outcomes. During the treatment period (day 0 
 to week 4), 44.0% of patients experienced at least one adverse event (47.6% placebo; 34.8% 
 omalizumab 75mg; 48.0% omalizumab 300mg; 47.6% omalizumab 600mg). During the follow-up 
 period (week 4 to week 16), 40.7% of patient experienced at least one adverse event (35.0% 
 placebo; 50.0% omalizumab 75 mg; 52.2% omalizumab 300 mg; 25.0% omalizumab 600 mg). 
 Researchers concluded that a fixed dose of 300 or 600 mg of omalizumab provides rapid and 
 effective treatment of CU in patients who are symptomatic despite treatment with antihistamines. 

Maurer et al. investigated the efficacy of omalizumab treatment in patients with CU whom had 
demonstrable IgE autoantibodies to thyroid peroxidase (TPO) in a 24 week randomized, double-
blind, placebo-controlled trial. Patients (ages 18-70 years) were randomized to receive 
omalizumab (dosed according to weight and total IgE level; range 75-375 mg) or placebo 
 subcutaneously once every 2 or 4 weeks for 24 weeks. The primary endpoint was the change in 
 weekly UAS7 scores after 24 weeks. Compared with placebo, omalizumab therapy was 
 associated with a significantly greater reduction in UAS7 scores from baseline (-17.9 versus -7.9 
 points; p=0.089) and a significantly higher rate of complete control of CU including wheal 
 development (70% versus 5%). The incidence of suspected drug-related adverse events was 
 similar between those receiving omalizumab and placebo (22.2% and 22.7%, respectively). 
 Researchers concluded that omalizumab is an effective treatment option for patients with CU; 
 however potential side effects should be evaluated (including risk for anaphylaxis) should be 
 evaluated thoroughly before initiating therapy. Additional studies are warranted to determine 
 optimal omalizumab dose and duration including evaluation of long-term disease-modifying 
 effects and comparison to current treatments.

Allergic Asthma in Children < 12 Years of Age
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. 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 he 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 

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offset of treatment effect after stopping therapy; and determined whether the efficacy differs by age, asthma severity, dosing regimen, and pre-specified biomarkers.36 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.27 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.

A double blind, randomized, placebo controlled trial evaluated the safety, steroid sparing effects, and impact on disease exacerbations of omalizumab in the treatment of stable pediatric allergic asthma patients.4 Children were randomized to subcutaneously administered placebo (n=109) or omalizumab (n=225) at a dose based on body weight and initial serum IgE (0.016 mg/kg/IgE [IU/mL] per 4 weeks). Doses of beclomethasone dipropionate (BDP; initial range 168-420) was

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kept stable for 16 weeks (stable-steroid phase), reduced over 8 weeks to the minimum effective
dose (steroid-reduction phase), and maintained constant for the final 4 weeks. Patients were
allowed to use albuterol 2 puffs as needed (maximum 8 puffs per day) at any time during the
study. However, except as necessary for treatment of asthma exacerbation, all other asthma
medications were excluded. More participants in the omalizumab group decreased their BDP
dose, and their reduction was greater than that of the placebo group (median reduction 100% vs.
66.7%). BDP was withdrawn completely in 55% of the omalizumab group versus 39% of the
placebo group. The incidence and the frequency of asthma exacerbations requiring treatment
with doubling of BDP dose or systemic corticosteroids were lower in the omalizumab group. The
treatment differences were statistically significant during the steroid-reduction phase, during which
fewer participants in the omalizumab group had asthma exacerbation episodes (18.2% vs.
38.5%), and the mean number of episodes per patient was smaller than with placebo (0.42 vs.
2.72). Five asthma exacerbations requiring hospitalization all occurred in the placebo group.
Participants’ and investigators’ global evaluations of treatment effectiveness were more favorable
for omalizumab than placebo. Investigators rated effectiveness excellent for 31.5% of the
omalizumab group versus 16.3% of the placebo group and good for 44.7% of the omalizumab
group versus 32.7% of the placebo group. There was little change in asthma symptom scores or
spirometry measurements during either the stable-steroid or steroid dose-reduction phase, with
minimal differences between the treatment groups. The requirement for rescue medication in the
omalizumab group during both the stable-steroid and steroid dose-reduction phases was
consistently lower than at baseline. At week 28, the median number of puffs of rescue medication
taken daily was zero in the omalizumab group and 0.46 in the placebo group. The change from
baseline was significant in favor of omalizumab. Omalizumab treatment was well tolerated. There
were no serious treatment-related adverse events. The frequency and types of all adverse events
were similar in the omalizumab and placebo groups. Study-drug-related adverse events occurred
more frequently in the omalizumab group than in the placebo group (6.2% vs. 0.9%). Urticaria
was reported in 9 omalizumab patients (4%) compared with 1 (0.9%) placebo patient and was
mild or moderate in nearly all cases. The investigators concluded that treatment with omalizumab
is safe in children with asthma and reduces the requirement for inhaled corticosteroids while
protecting against disease exacerbation although additional studies are needed.

In a separate report of the Milgrom trial, the effects of treatment with omalizumab on asthma-
related quality of life were measured. The Pediatric Asthma Quality of Life Questionnaire
(PAQQLQ) was administered at baseline, week 16, and week 28. Baseline demographics, PAQQLQ
scores, and other data were comparable for the 2 treatment groups. At the end of the steroid-
reduction phase, patients in the omalizumab-treated group reported significant improvements in
the "activities" and "symptoms" domain scores as well as overall PAQQLQ compared with placebo.
More patients in the omalizumab group achieved clinically relevant changes (defined as an
increase in domain or overall score of greater than or equal to 0.5 points) in PAQQLQ scores
during the course of the study. This difference was significant for activities and overall PAQQLQ.

In a 24-week open-label extension of the Milgrom study, patients were evaluated for long-term
safety of omalizumab. Patient safety was evaluated in 202 patients during the 28-week double-
blind trial, plus the 24-week open-label trial, for a total duration of evaluation of 1 year. Most of
the adverse events reported were rated as mild or moderate and were not considered treatment-
related. About 7% of patients experienced an adverse event suspected to be caused by
omalizumab and 1 of these events was considered severe (urticaria). The most common adverse
events reported were similar for the 52-week evaluation compared with the 28-week double-blind
phase and included upper respiratory tract infection (47.1%), headache (42.7%), pharyngitis
(34.7%), and viral infection (31.6%). Urticaria occurred in 11 patients (4.9% of 225) throughout
the 52-week evaluation, but only 1 patient required corticosteroid therapy. One patient did
discontinue therapy because of hives, which occurred after the seventh and eighth injections, but
the reaction resolved completely with the administration of an antihistamine. Overall, adverse events were similar not only during the double-blind treatment phase and in the open-label extension but also between omalizumab- and placebo-treated groups. While some of the studies already completed are promising, additional long-term studies are needed with omalizumab in treating the pediatric population diagnosed with allergic asthma.

Children (n=627) ages 6-12 with moderate-to-severe persistent allergic asthma and total serum IgE 30-1300 IU/mL who were inadequately controlled with medium-dose or high-dose inhaled corticosteroids were randomized 2:1 to omalizumab (75-375 mg every 2 or 4 weeks) or placebo for 52 weeks. The study period included a 24-week fixed-steroid phase followed by a 28-week adjustable-steroid phase. Omalizumab reduced the rate of clinically significant asthma exacerbations versus placebo during the fixed-steroid phase (0.45 vs. 0.64, p=0.007). Over the 52 weeks, omalizumab reduced the exacerbation rate by 43% (p<0.001).

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. 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]. 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 ≥ 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. 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.
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. Fifty asthmatic patients (pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≥ 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. Patients were recruited if they had a diagnosis of uncontrolled severe, persistent, allergic asthma while on high-dose inhaled corticosteroids (ICSs) plus long-acting β2-agonist (LABA); had an age ≥ 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 has 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.
Unproven
Seasonal Allergic Rhinitis

Casale et al. evaluated 536 patients aged 12 to 75 years with at least a 2-year history of moderate to severe ragweed-induced seasonal allergic rhinitis and a baseline IgE level between 30 and 700 IU/mL. Moderate to severe ragweed-induced symptoms were defined as a score of 2 or more in 4 of 8 symptom categories, such as, sneezing, itchy nose, running nose, stuffy nose, watery eyes, red eyes, itchy eyes, or itchy throat. This was a self-reported scale, in which patients were required to recall the previous allergy season, which was on a scale of 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms). Patients were randomly assigned to receive omalizumab, 50 mg (n=137), 150 mg (n=134), or 300 mg (n=129), or placebo (n=136) subcutaneously just prior to ragweed season and repeated during the pollen season every 3 weeks in patients with baseline IgE levels of 151 to 700 IU/mL (4 total treatments) and every 4 weeks in patients with baseline IgE levels of 30 to 150 IU/mL (3 total treatments). The primary efficacy endpoint was the average daily nasal symptom severity score (range 0 to 3). Nasal symptom severity scores were statistically significantly lower in patients who received 300 mg of omalizumab than in those who received placebo (0.75 versus 0.98, respectively (confidence interval (CI) -0.38 to -0.08; p=0.002). A significant association was observed between IgE reduction and nasal symptoms and rescue antihistamine use. Rhinitis-specific quality of life scores were consistently better in patients who received 300 mg of omalizumab than in those who received lower dosages or placebo and did not decline during peak season. The frequency of adverse events was not significantly different among the omalizumab and placebo groups. Although this study was statistically significant in the primary efficacy endpoint, clinical significance was not defined. Additionally, the large placebo effect makes the true effect of omalizumab in treating seasonal allergic rhinitis difficult to determine.

Nayak et al. conducted an open-label, 12-week study designed to assess the safety and tolerability of retreatment with omalizumab during a second ragweed pollen season in 287 patients who participated in the trial by Casale et al. Omalizumab 300 mg was administered subcutaneously every 4 weeks (three injections) to patients with IgE levels ≤ 150 IU/mL (n=182) and every 3 weeks (four injections) to patients with IgE levels > 150 IU/mL (n=105) at screening before retreatment. The overall incidence and pattern of adverse events were similar to those reported in the primary study. There were no severe or serious adverse events related to omalizumab treatment and no anti-omalizumab antibodies were detected in any patient. Two patients withdrew from treatment because of adverse events (skin rash and nausea; facial erythema and edema) related to study treatment. In summary, retreatment during a second pollen season with omalizumab, 300 mg every 3 or 4 weeks, was well tolerated and was not associated with any significant immunologic reactions. Longer studies are needed in order to determine the safety of omalizumab in this population.

A randomized, double-blind, placebo-controlled trial was conducted in Germany to compare the efficacy of single and combined treatment with specific immunotherapy (SIT) and omalizumab in reducing symptom severity and rescue medication use in seasonal allergic rhinoconjunctivitis. A total of 221 patients with birch and grass pollen allergic rhinoconjunctivitis for at least 2 years and aged 6-17 years were analyzed during the grass pollen season to compare the efficacy of single and combined treatment with SIT and omalizumab. Patients were randomized into 4 groups. Group A, served as a reference group in which there was no effective treatment (SITbirch + placebo). Group B received omalizumab monotherapy during grass pollen season, group C received SIT grass pollen monotherapy and group D received the combined treatment of SIT and omalizumab. Patients recorded their daily symptoms using a 4-point scale (0 = no symptoms to 3 = severe symptoms). Patients were allowed to use the following rescue medications: levocabastine eye drops and nasal spray, inhaled salbutamol, cetirizine tablets and oral prednisolone. Rescue medications were assessed using a 4 point scale to the daily maximal
score (0 = no rhinitis medication, 1 = topical nasal, ocular or lung treatment apart from corticosteroids; 2 = systemic antihistamines, 3 = topical or systemic corticosteroids for nose or lung). Variables of symptom severity and rescue medication scores were further categorized to greater or equal to 1 during the grass season, in order to point out clinical relevance. Preseasonal treatment with grass pollen SIT alone did not reduce symptoms or rescue medication use. Omalizumab monotherapy (group B) did not show a reduction in the percentage of patients with symptoms severity scores greater than or equal to 1 during the grass pollen season compared to the reference group (group A). However, three patients receiving omalizumab monotherapy had a rescue medication score greater than or equal to 1 compared with 10 patients in the reference group (A versus B: median score 0.27 versus 0.08, p<0.001). The combined treatment with SIT and omalizumab showed superior efficacy on symptom severity compared with omalizumab alone (group B versus group D: p=0.04).

A double-blind clinical study included 221 children and adolescents (6-17 years old) with seasonal allergic rhinitis. After at least 14 weeks of SIT prior to the start of pollen season, they were randomized to 24 weeks of SIT-birch + placebo, SIT-birch + omalizumab, SIT-grass + placebo, or SIT-grass + omalizumab. Omalizumab was dosed at 2 or 4 week intervals to provide at least 0.016 mg/kg/IgE [IU/mL]. Symptom load (sum of daily symptom severity score and rescue medication score during pollen season) was significantly lower with combination therapy vs. SIT alone.

Similar results were shown in a randomized, double-blind, placebo-controlled trial of omalizumab vs. placebo in combination with depigmented SIT in 140 patients (ages 11-46) with seasonal allergic rhinoconjunctivitis who also have co-morbid seasonal allergic asthma not completely controlled by conventional pharmacotherapy. The trial consisted of a 2 week run-in phase, a pre-seasonal 10 week treatment phase, and an 8 week seasonal maintenance treatment phase. Omalizumab or placebo was given every 2 to 4 weeks based on omalizumab dosing tables. Combination therapy statistically reduced symptom load by 39% (p = 0.0464) vs. SIT alone.

Adult patients with ragweed allergic rhinitis were evaluated in a 9 week, double-blind, parallel-group, placebo-controlled trial evaluating omalizumab prior to rush immunotherapy (RIT). Subjects (n = 159) received either monthly omalizumab (0.016 mg/kg/IgE [IU/mL] or placebo, followed by 1-day RIT or placebo, so that the trial contained 4 arms. Ragweed-specific IgG levels increased >11-fold in the RIT patients. Free IgE levels declined >10-fold in the omalizumab group. The addition of omalizumab to RIT resulted in a 5-fold decrease in the risk of RIT-associated anaphylaxis. Those patients receiving omalizumab plus RIT had a significant (p = 0.044) improvement in severity scores during ragweed season compared with those receiving only RIT. Additional trials are required to establish long-term efficacy, as well as appropriate dosage and timing.

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. 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. 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.

Xolair Policy: Drug Policy (Effective 09/1/2014)

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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. 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). 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.

Twenty-one patients (ages 14-64 years) with moderate to severe persistent allergic asthma and atopic dermatitis were assessed according to a Global Assessment index. The mean IgE level prior to therapy was 1521 IU/mL (range 18.2 to 8396). In this 9 month study, all patients showed statistically significant improvement of their atopic dermatitis.

Omalizumab was not beneficial in 3 adult patients with a medical history of chronic severe lichenified atopic dermatitis. Omalizumab 450 mg was administered as a subcutaneous injection every other week for 4 months. All patients had received previous medication therapies for this condition. Patient 1 was a 34-year-old male with a history of asthma and an IgE level of 23,000 IU/mL. Prior medications included topical and systemic steroids, PUVA, azathioprine, mycophenolate mofetil, thalidomide and methotrexate. Patient 2 was a 48-year-old male with comorbid conditions of allergic rhinitis and hypertension and an IgE level of 5,440 IU/mL with a prior medication history of topical and systemic steroids and mycophenolate mofetil. Patient 3 was a 36-year-old female with severe asthma and allergic rhinitis with an IgE level of 24,400 IU/mL and a history of receiving topical and systemic steroids. There was no reduction in symptomatic flares and there was no improvement in their chronic lichenified eczema in any of the 3 patients.

Omalizumab was beneficial in 3 pediatric patients with a medical history of refractory atopic dermatitis. Patient 1 was a 10-year-old girl with recalcitrant atopic dermatitis with an initial IgE level of 1,990 IU/mL. Prior medication therapies included topical and systemic corticosteroids,
topical tacrolimus, bland emollients, repeated oral antibiotic courses, sedating and non-sedating H1-blocking antihistamines, montelukast and cyclosporine. This patient was also positive for methicillin-resistant *Staphylococcus aureus* and had a positive radioallergosorbent (RAST) test for 7 aeroallergens. The patient was treated with subcutaneous omalizumab 300 mg every 2 weeks. The patient continued receiving trimethoprim-sulfamethoxazole, topical tacrolimus and triamcinolone ointment, montelukast and hydroxyzine during treatment with omalizumab. The omalizumab dose was eventually increased to 450 mg every 2 weeks. During the first 2 weeks of treatment, the patient noticed improvement and continued to improve during omalizumab treatment. All monthly laboratory examinations such as comprehensive chemistry panel, complete blood cell count with differential and urinalysis were all within normal parameters throughout omalizumab therapy. The second pediatric patient presented by Lane et al., was a 13-year-old male with atopic dermatitis. The child had an initial IgE level of 6,120 IU/ml with a RAST test positive for 12 aeroallergens. The patient’s prior medication regimen consisted of bland emollients, topical corticosteroids, antihistamines, montelukast, topical tacrolimus, trimethoprim-sulfamethoxazole, oral prednisone and cyclosporine. This patient was refractory to all therapies. Subcutaneous omalizumab was started at 150 mg every 2 weeks. After there was no improvement in symptoms, omalizumab was increased to 300 mg and 450 mg on the third and fourth dose, respectively. After the fourth omalizumab treatment, there was a 50% improvement by patient and physician global assessment. The child continued to improve with omalizumab 450 mg every 2 weeks and continued to receive other medications such as, trimethoprim-sulfamethoxazole, topical triamcinolone and tacrolimus, montelukast and antihistamines. All monthly laboratory results were within normal parameters. The third pediatric patient presented by Lane et al., was a 12-year-old male with chronic atopic dermatitis, which involved about 80% of body surface area. The patient had an initial IgE level of 2,890 IU/mL with a RAST test positive for 15 aeroallergens. The child had a medical history of asthma, which had been treated with multiple doses of oral prednisone and inhaled corticosteroids. The atopic dermatitis only mildly improved with topical tacrolimus, montelukast, and hydroxyzine. Subcutaneous omalizumab was initiated at 150 mg every 2 weeks and then alternated with a 300 mg dose, depending on severity. Upon cutaneous examination, the patient markedly improved and the patient was able to taper his daily inhaled and nebulized corticosteroids. All monthly laboratory results were within normal parameters. Additional studies are needed to assess omalizumab’s efficacy for treating atopic dermatitis.

**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. 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.
professional societies
the Global Initiative for Asthma (GINA, 2012) guidelines state that omalizumab has proven efficacy in children ages 6 to 12 years with moderate to severe and severe persistent allergic (IgE mediated) asthma. the GINA guidelines note that trials involving these children have shown similar efficacy to adolescents and adults. European Medicines Agency (EMEA) labeling for Xolair indicates omalizumab for children ages 6 years older, as well as for adolescents and adults, with IgE mediated asthma.

section 3, component 1: Measures of Asthma Assessment and Monitoring of the U.S. Department of Health and Human Services National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI) 2007 Guidelines for the Diagnosis and Management of Asthma provides information on classifying asthma severity. These guidelines recommend that omalizumab may be considered as adjunctive therapy for patients ages 12 and older who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose inhaled corticosteroid and long-acting beta-agonist. The Expert Panel also states that the beneficial effects of long-acting beta-agonist (LABAs) in combination therapy for the great majority of patients who require more therapy than low-dose inhaled corticosteroid alone to control asthma (i.e., require step 3 care or higher) should be weighed against the increased risk of severe exacerbations, although uncommon, associated with the daily use of LABAs. Figure 1 shows how to establish asthma severity classification for children >/= 12 years of age and adults, and recommends a step for initiating therapy. Figure 3 details how to assess asthma control in children >/= 12 years and adults.
### FIGURE 4–6. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications.

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity ≥12 years of age</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Persistent</td>
<td>Mild</td>
</tr>
<tr>
<td>Intermittent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≥2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤5x/month</td>
<td>3–4x/month</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8–19 yr</td>
<td>85%</td>
<td>80%</td>
</tr>
<tr>
<td>20–39 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–59 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–80 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control (not prevention of EIB)</td>
<td>≥2 days/week bit not daily, and not more than 1x on any day</td>
<td>Daily</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
</tr>
<tr>
<td>Lung function</td>
<td>• Normal FEV₁ between exacerbations, FEV₁ &gt;80% predicted</td>
<td>• FEV₁ &gt;80% predicted</td>
</tr>
<tr>
<td></td>
<td>• FEV₁/FVC normal</td>
<td>• FEV₁/FVC normal</td>
</tr>
<tr>
<td>Risk</td>
<td>0–1 year (see note)</td>
<td>≥2 year (see note)</td>
</tr>
</tbody>
</table>

**Recommended Step for Initiating Treatment**

(See figure 4–5 for treatment steps.)

- In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.

**Key:** FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

**Notes:**
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient’s/caregiver’s recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

**FIGURE 4-7. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS**

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma Control (≥12 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
</tr>
<tr>
<td>Impairment</td>
<td>≥2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≥3x/month</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control (not prevention of EIB)</td>
<td>≥2 days/week</td>
</tr>
<tr>
<td>FEV1 or peak flow</td>
<td>&gt;80% predicted/ personal best</td>
</tr>
<tr>
<td>VATSified questionnaires</td>
<td>ATAQ ≥7.75* ACQ ≥10</td>
</tr>
<tr>
<td>Risk</td>
<td>Exacerbations requiring oral systemic corticosteroids</td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term followup care</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>Medication side effects vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
</tr>
</tbody>
</table>

**Recommended Action for Treatment**

(see figure 4-5 for treatment steps)

- Maintain current step
- Regular followup every 1–6 months to maintain control
- Consider step down if well controlled for at least 3 months
- Step up 1 step and reevaluate in 2–6 weeks
- For side effects, consider alternative treatment options
- Consider short course of oral systemic corticosteroids
- Step up 1–2 steps, and reevaluate in 2 weeks
- For side effects, consider alternative treatment options

*ACQ values of ≥7.75–1.4 are indeterminate regarding well-controlled asthma.

Key: EIB, exercise-induced bronchospasm; ICU, intensive care unit

**Notes:**
- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient’s recall of previous 2–4 weeks and by spirometry or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient’s asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain)
  - ATAQ = Asthma Therapy Assessment Questionnaire® (See sample in “Component 1: Measures of Asthma Assessment and Monitoring.”)
  - ACQ = Asthma Control Questionnaire® (user package may be obtained at www.qoltech.co.uk or juniper@qoltech.co.uk)
  - ACT = Asthma Control Test™ (See sample in “Component 1: Measures of Asthma Assessment and Monitoring.”) Minimal Important Difference: 1.0 for the ATAQ 0.5 for the ACQ; not determined for the ACT.
- Before step up in therapy:
  - Review adherence to medication, inhaler technique, environmental control, and comorbid conditions.
  - If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step.

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. 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 optimised standard therapy [defined as a full trial of (and, if tolerated, documented compliance with) inhaled high-dose corticosteroids, long-acting β2-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)
  - Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting β2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Xolair (omalizumab) is approved by the U.S. Food and Drug Administration (FDA) for use in adults and adolescents 12 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

APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2357</td>
<td>Injection, omalizumab, 5 mg</td>
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</table>

<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>493.00</td>
<td>Extrinsic asthma, unspecified</td>
</tr>
<tr>
<td>493.02</td>
<td>Extrinsic asthma, with (acute) exacerbation</td>
</tr>
<tr>
<td>493.10</td>
<td>Intrinsic asthma, unspecified</td>
</tr>
<tr>
<td>493.12</td>
<td>Intrinsic asthma, with (acute) exacerbation</td>
</tr>
<tr>
<td>493.20</td>
<td>Chronic obstructive asthma, unspecified</td>
</tr>
<tr>
<td>493.22</td>
<td>Chronic obstructive asthma, with (acute) exacerbation</td>
</tr>
<tr>
<td>493.90</td>
<td>Asthma, unspecified, unspecified</td>
</tr>
<tr>
<td>493.92</td>
<td>Asthma, unspecified, with (acute) exacerbation</td>
</tr>
</tbody>
</table>

Xolair Policy: Drug Policy (Effective 09/1/2014)

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ICD-10 Codes (Preview Draft)
In preparation for the transition from ICD-9 to ICD-10 medical coding on October 1, 2015, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.*

<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Code (Effective 10/01/15)</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>J44.1</td>
<td>Chronic obstructive pulmonary disease with (acute) exacerbation</td>
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<tr>
<td>J44.9</td>
<td>Chronic obstructive pulmonary disease, unspecified</td>
</tr>
<tr>
<td>J45.20</td>
<td>Mild intermittent asthma, uncomplicated</td>
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<tr>
<td>J45.21</td>
<td>Mild intermittent asthma with (acute) exacerbation</td>
</tr>
<tr>
<td>J45.30</td>
<td>Mild persistent asthma, uncomplicated</td>
</tr>
<tr>
<td>J45.31</td>
<td>Mild persistent asthma with (acute) exacerbation</td>
</tr>
<tr>
<td>J45.40</td>
<td>Moderate persistent asthma, uncomplicated</td>
</tr>
<tr>
<td>J45.41</td>
<td>Moderate persistent asthma with (acute) exacerbation</td>
</tr>
<tr>
<td>J45.50</td>
<td>Severe persistent asthma, uncomplicated</td>
</tr>
<tr>
<td>J45.51</td>
<td>Severe persistent asthma with (acute) exacerbation</td>
</tr>
<tr>
<td>J45.901</td>
<td>Unspecified asthma with (acute) exacerbation</td>
</tr>
<tr>
<td>J45.909</td>
<td>Unspecified asthma, uncomplicated</td>
</tr>
<tr>
<td>J45.998</td>
<td>Other asthma</td>
</tr>
<tr>
<td>L50.8</td>
<td>Other urticaria</td>
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</tbody>
</table>

REFERENCES


**POLICY HISTORY/REVISION INFORMATION**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
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<tbody>
<tr>
<td>4/1/2013</td>
<td>Policy updated per annual review, approved by National Pharmacy and Therapeutics Committee on 2/19/2013. Added medical necessity</td>
</tr>
<tr>
<td>Date</td>
<td>Event Description</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>9/1/2012</td>
<td>Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/14.</td>
</tr>
<tr>
<td>8/1/2011</td>
<td>Clarified drug policy. Moved IgE level to proven indication under coverage rationale. Removed “to support medical necessity review where applicable” from Additional Information. Moved Additional Information section to under proven indications. Removed all unproven ICD-9 codes from the policy because standard policy format is to list only proven ICD-9 codes [477.0, 477.1, 477.2, 477.8, 477.9, 493.01, 493.11, 493.21, 493.91, 519.11, 691.0, 691.8, 692.9, V15.01].</td>
</tr>
<tr>
<td>6/7/2011</td>
<td>Policy updated per annual review, approved by National Pharmacy and Therapeutics Committee on 3/8/2011. Created an Additional Information section within the Coverage Rationale to address the IgE level upon which dosing is calculated. Added acute bronchospasm and status asthmaticus to the list of unproven uses. Added Benefits Consideration section. Updated Clinical Evidence. Removed deleted CPT codes 90769 and 90772. Moved 493.01, 493.11, 493.21 and 493.91 to unproven codes. Added 519.11 to unproven codes. Updated references. Policy 2011D0033D archived.</td>
</tr>
<tr>
<td>12/30/2009</td>
<td>Added ICD-9s 493.00, 493.10, and 493.90. Removed ICD-9 495.9</td>
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<tr>
<td>8/24/2009</td>
<td>Added in vitro reactivity to criteria for allergen response</td>
</tr>
<tr>
<td>3/11/2008</td>
<td>Diagnosis list updated per instructions from Coding and Integrity.</td>
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<tr>
<td>3/10/2008</td>
<td>New Policy</td>
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