Drug and Biologic Coverage Policy

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Coverage Policy Number 4026

Omalizumab

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Related Coverage Resources

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The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Omalizumab (Xolair®) is considered medically necessary when ONE of the following criteria is met:

- **Treatment of moderate to severe, persistent allergen-related asthma when ALL of the following criteria are met:**
  - Individual is 6 years of age or older
  - Positive skin test or in vitro reactivity to a perennial aeroallergen
  - Inadequately controlled with (or not a candidate for) a moderate dose of inhaled corticosteroids (ICS) plus long-acting beta-agonists or leukotriene receptor antagonist for at least 3 months
  - Continued use of an ICS AND another controller therapy such as a long-acting beta agonist or leukotriene receptor antagonist with add-on omalizumab (Xolair)
  - Laboratory data reflecting IgE levels greater than 30

- **Treatment of chronic idiopathic urticaria (CIU) when ALL of the following criteria are met:**
  - Individual is 12 years of age or older
  - Symptoms for greater than 6 weeks
  - Failure or inadequate response, contraindication per FDA label, documented intolerance, or not a candidate for a second generation H1 antihistamines (for example, cetirizine, desloratadine, fexofenadine), including a trial at twice recommended dose for at least 4 weeks

- Failure or inadequate response, contraindication per FDA label, documented intolerance, or not a candidate for an H2 antagonist (for example famotidine, ranitidine) used concurrently with a high dose second generation H1 antihistamine

Xolair will not be approved in combination with other monoclonal antibodies (for example: benralizumab [Fasenra], dupilumab [Dupixent], mepolizumab [Nucala], reslizumab [Cinqair]).

Initial authorization is up to 12 months.

Reauthorization of Xolair is considered medically necessary for allergen-related asthma, omalizumab (Xolair) when ALL of the following criteria are met:
- Pretreatment clinical condition met the initial criteria
- Documented evidence of continued beneficial clinical response to Xolair
- Continued use of an ICS AND another controller therapy such as a long-acting beta agonist or leukotriene receptor antagonist with add-on omalizumab (Xolair)

Reauthorization of Xolair is considered medically necessary for chronic idiopathic urticaria, omalizumab (Xolair) when ALL of the following are met:
- Pretreatment clinical condition met the initial criteria
- Documented evidence of continued beneficial clinical response to Xolair (for example, reduced exacerbations)
- Continued concomitant therapy with a second generation H1 antihistamine

Reauthorization for up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Omalizumab (Xolair®) is considered experimental, investigational, or unproven for ANY other use including the following:
- Non-allergic asthma
- Seasonal allergic rhinitis (SAR)
- Perennial allergic rhinitis (PAR)
- Food allergy

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

FDA Approved Indications

FDA Approved Indication

Asthma

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

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

Limitations of Use:
- Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus.
- Xolair is not indicated for treatment of other allergic conditions.

Chronic Idiopathic Urticaria (CIU)

Xolair is also indicated for the treatment of adults and adolescents 12 years of age and above with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment.

Limitation of Use:

- Xolair is not indicated for treatment of other forms of urticaria.

Recommended Dosing

FDA Recommended Dosing

Asthma

Administer Xolair 150 to 375 mg by subcutaneous (SC) injection every 2 or 4 weeks. Determine doses (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg).

Adjust doses for significant changes in body weight during treatment (see Tables 1 and 2).

Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination.

- Interruptions lasting less than one year: Dose based on serum IgE levels obtained at the initial dose determination.
- Interruptions lasting one year or more: Re-test total serum IgE levels for dose determination using Table 1 or 2, based on the patient's age.

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

Adult and adolescent patients 12 years of age and older: Initiate dosing according to Table 1.

Table 1. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Patients 12 Years of Age and Older with Asthma

Pre-treatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight			
		30-60 kg	> 60-70 kg	> 70-90 kg	> 90-150 kg
		Dose (mg)			
≥ 30-100	Every 4 weeks	150	150	150	300
> 100-200		300	300	300	225
> 200-300		300	225	225	300
> 300-400	Every 2 weeks	225	225	300	
> 400-500		300	300	375	
> 500-600		300	375	**Insufficient Data to Recommend a Dose**	
> 600-700		375			

Pediatric patients 6 to <12 years of age: Initiate dosing according to Table 2.

Table 2. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Pediatric Patients with Asthma Who Begin XOLAIR Between the Ages of 6 to <12 Years

Pre-treatment Serum IgE (IU/ml)	Dosing Freq.	Body Weight									
		20-25 kg	>25-30 kg	>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	>125-150 kg
		Dose (mg)									
30-100		75	75	75	150	150	150	150	150	300	300
>100-200		150	150	150	300	300	300	300	300	225	300
>200-300		150	150	225	300	300	225	225	225	300	375

>300-400	**Every 4 weeks**	225	225	300	225	225	225	300	300
>400-500		225	300	225	225	300	300	375	375
>500-600		300	300	225	300	300	375	Insufficient Data to Recommend a Dose	
>600-700		300	225	225	300	375			
>700-800	**Every 2 weeks**	225	225	300	375				
>800-900		225	225	300	375				
>900-1000		225	300	375					
>1000-1100		225	300	375					
>1100-1200		300	300						
>1200-1300		300	375						

Chronic Idiopathic Urticaria
Administer Xolair 150 or 300 mg by subcutaneous injection every 4 weeks. Dosing of Xolair in CIU patients is not dependent on serum IgE (free or total) level or body weight. The appropriate duration of therapy for CIU has not been evaluated. Periodically reassess the need for continued therapy.

Dosage (12 years of age and older) for Second Generation Antihistamines
Allegra (fexofenadine): Tablets: 180 mg once daily or 60 mg twice daily
Claritin (loratadine): 10 mg once daily
Zyrtec (cetirizine): 5 to 10 mg once daily

Drug Availability

Injection: Xolair injection is a clear to slightly opalescent and colorless to pale brownish-yellow solution available as:

- 75 mg/0.5 mL in a single-dose prefilled syringe with blue needle shield
- 150 mg/mL in a single-dose prefilled syringe with purple needle shield

For injection: 150 mg white lyophilized powder in a single-dose vial for reconstitution.

General Background

Pharmacology

Omalizumab is a monoclonal antibody that interferes with allergic response by binding to immunoglobulin E (IgE). Omalizumab binds to the receptor-binding portion of IgE, eliminating IgE's ability to bind to receptors on mast cells, basophils, B cells, macrophages, and platelets. Because omalizumab only binds to freely circulating IgE, it lacks the ability to induce inflammatory responses by crosslinking cell-bound IgE molecules. Free IgE levels decrease dramatically during omalizumab treatment. Total IgE levels increase during omalizumab treatment, and may persist for up to a year after discontinuation.

Professional Societies/Organizations

Asthma
Global Initiative for Asthma
Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention in 2018 and in November 2018, GINA released a guideline on the diagnosis and management of severe and difficult to treat asthma. GINA provided criteria for establishing a diagnosis of severe asthma and the criteria requires multiple interventions before a diagnosis can be made. For those patients with a diagnosis of severe asthma and uncontrolled on Step 4 treatment (for example: 2 or more controllers plus as-needed reliever medication or taking maintenance oral corticosteroids), phenotyping for Type 2 inflammation into categories (such as severe allergic, aspirin-exacerbated or eosinophilic asthma) is recommended. Treatment with omalizumab is recommended for patients greater than or equal to 6 years of age with severe allergic asthma that is uncontrolled on Step 4 (for example, medium to high dose inhaled corticosteroid with a long acting beta agonist). Add-on treatment that is phenotype guided is recommended with severe asthma that is not controlled

on Step 4 and patients who are 6 years of age and older with severe allergic asthma with elevated level of IgE may benefit with Omalizumab treatment (Evidence A) (GINA 2018a, GINA 2018b)

National Heart, Lung, and Blood Institute (NHLBI)
The 2007 NHLBI guidelines state that signs of lack of asthma control may include any of the following:

- At least 2 or more exacerbations per year requiring oral corticosteroid bursts
- Symptoms greater than 2 days per week
- Reliever medication required more than 2 days per week
- Nighttime awakenings 1 to 3 times per week
- FEV_1 or peak flow at 60% to 80% predicted/personal best
- Limited participation in normal activities
- Needing urgent medical care, including hospitalization

The NHLBI expert panel (2007) recommends that omalizumab may be considered as adjunctive therapy in step 5 or 6 care for adults and adolescents 12 years of age and older:

- Step 5 Care – Preferred: High-dose ICS and long-acting beta-agonist (LABA). Consider omalizumab for patients who have sensitivity to relevant perennial allergens.
- Step 6 Care – Preferred: High-dose ICS and LABA and oral corticosteroid. Consider omalizumab for patients who have allergies.

(NHLBI, 2007)

International European Respiratory Society (ERS)/American Thoracic Society (ATS)
The 2014 ERS/ATS Guidelines on Definition, Evaluation, and Treatment of Severe Asthma suggest a therapeutic trial of omalizumab both in adults and children with severe allergic asthma (conditional strength; quality of evidence low (adults) and very low (children)). Guidelines further states those adults and children greater than or equal to 6 years with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacologic and non-pharmacologic management and appropriate allergic avoidance if their total IgE level is 30-700IUml^{-1}. 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 therapy, it is unlikely that further administration of omalizumab will be beneficial. (ERS/ATS, 2014)

Chronic Idiopathic Urticaria
Joint Task Force on Practice Parameters
The Joint Task Force on Practice Parameters (JTFPP) represents the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology and provides guidelines for the diagnosis and management of acute and chronic urticaria. Chronic urticaria is defined as urticaria that has been continuously or intermittently present for at least 6 weeks. (Bernstein, 2014)

The parameters provide summary statements regarding available therapies that include strength of recommendation based the category of evidence. An “A” recommendation is directly based on category I evidence (evidence from meta-analysis of randomized controlled trials or from at least 1 randomized controlled trial). A “B” recommendation is based on category II evidence (evidence from at least 1 controlled study without randomization or from at least 1 other type of quasiexperimental study) or is an extrapolated recommendation from category I evidence. A “C” recommendation is based on category III evidence (evidence from non-experimental descriptive studies, such as comparative studies) or is an extrapolated recommendation from category I or II evidence. A “D” recommendation is based on category IV evidence (evidence from expert committee reports or opinions or clinical experience of respected authorities or both) or is an extrapolated recommendation from category I, II, or III evidence. An “E” recommendation is based on consensus of the Joint Task Force on Practice Parameters. (Bernstein, 2014)

The parameters state that second-generation antihistamines are safe and effective therapies and are considered first-line agents (A). The authors also note that first-generation antihistamines have similar efficacy to second generation antihistamines, but are associated with more sedation and impairment (A). Regarding H2-

antihistamines, the authors state that combination use of H1-antihistamines and H2-antihistamines is more efficacious compared with H1-antihistamines alone (A). The authors also summarize that leukotriene receptor antagonists have demonstrated efficacy in several (but not all) randomized controlled trials and are generally well-tolerated (A). The parameters also describe treatment with hydroxyzine or doxepin for those patients who remain poorly controlled with dose advancement of second-generation antihistamines and the addition of H2-anthistamines, first-generation H1-antihistamines at bedtime, and/or antileukotrienes (D). Omalizumab can be considered for refractory chronic urticaria (A). (Bernstein, 2014)

The parameters provide a step-care approach for chronic urticaria and angioedema. Step 1 is monotherapy with a second generation antihistamine and avoiding triggers and relevant physical factors. Step 2 includes one or more of the following: increasing the dose of the second generation antihistamine used in Step 1; adding another second generation antihistamine; adding an H2-antagonist; adding a leukotriene receptor antagonist; or adding a first generation antihistamine to be taken at bedtime. Step 3 involves dose advancement of a potent antihistamine (for example, hydroxyzine or doxepin) as tolerated. Omalizumab is an option listed as an alternative agent in Step 4 (the final step) along with cyclosporine or other anti-inflammatory agents, immunosuppressants, or biologics. The parameters also advocate "stepping-down" at any step once consistent control is achieved. (Bernstein, 2014)

Joint guidelines by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization (EAACI/GA/LEN/EDF/WAO)
Joint guidelines for the definition, classification, diagnosis, and management of urticaria recommend omalizumab treatment in patients who have symptoms despite treatment with a 4-fold dose of modern second generation antihistamines. This represents a change from previous guidelines that recommended the use of either omalizumab or cyclosporine after failure of high-dose antihistamines. However, due to adverse effects and the lack of an approved indication, the new recommendation was that cyclosporine should be considered only if an adequate response was not achieved with omalizumab. (Zuberbier, 2018)

Therefore, the joint guidelines recommend modern 2nd generation H1-antihistamines at licensed doses for first-line treatment and for second line treatment, the guidelines recommend up-dosing (up to 4x) of the second generation H1-Antistamine (for 2-4 weeks or earlier, if symptoms are intolerable). The guidelines do not recommend the older first generation antihistamines (hydroxyzine) because they have a large effect on the anticholinergic system and sedative properties. The third step, which should be performed under the supervision of a specialist is add omalizumab to the second generation H1-Antihistamine. The fourth step is add-Cyclosporine to the second-generation H1-Antihistamines. (Zuberbier, 2018) Second generation H1-Antihistamines include certrizine, desloratadine, and fexofenadine.

Furthermore, H_2-antagonists and dapsone, which were recommended in the previous versions of the guideline, are now thought to have little evidence to have them remain as recommendable in the algorithm, however the joint guideline state that H_2-antagonists may still have relevance as they are very affordable in some more restricted healthcare systems. With regards to H2-antagonists, the joint guidelines do not make recommendations for or against their use in patients with urticarial. (Zuberbier, 2018)

With regards to leukotriene receptor antagonists, the joint guidelines state that there are randomized controlled trials that have assessed their use; however these studies are difficult to compare due to different populations that were studied. In general, leukotriene receptor antagonists efficacy in urticaria is low but the guidelines state it is best for montelukast. Therefore, the joint guidelines state that they cannot make a recommendation with respect to using montelukast as an add-on treatment to H1-Antihistamines in CIU patients unresponsive to H-Antihistamines. (Zuberbier, 2018)

British Society for Allergy and Clinical Immunology (BSACI)
This BSCAI guidance for the management of patients with chronic urticaria and angioedema has been prepared by the Standards of Care Committee of the This guidance for the management of patients with chronic urticaria and angioedema states that pharmacological treatment should start with a standard dose of a non-sedating H1-antihistamine (grade of recommendation = A). BSACI further states that higher than normal doses of

antihistamines may be required to control severe urticaria/angioedema (grade of recommendation = B); and that updosing with a single antihistamine is preferred to mixing of different antihistamines. (Powell, 2015)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative:
No recommendations are available for omalizumab (Xolair).

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
There are no CMS National Coverage Determinations for omalizumab (Xolair).

Clinical Efficacy

Allergic Asthma
FDA approval was based on the results of three multicenter randomized, double-blind, placebo-controlled trials conducted in patients at least 12 years of age with moderate to severe asthma for at least one year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between the values 30 and 700 IU/mL. The studies comprised of a run-in period to achieve a stable conversion to a common inhaled corticosteroid which was followed by randomization to omalizumab or to placebo.

In the first study, by Busse et al (N = 525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations per subject (0.28 versus 0.54) and decreased mean duration of exacerbations (7.8 versus 12.7 days) compared to placebo. During the steroid reduction phase, omalizumab was associated with fewer exacerbations per subject (0.39 vs 0.66) and a shorter mean duration for exacerbations (9.4 versus 12.6 days). (Busse, 2001)

In the second study, by Solèr et al (N=546), asthma exacerbations per patient decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 versus 0.66) and steroid reduction phases (0.36 versus 0.75). (Solèr, 2001)

In the third study, by Holgate et al (N=246), the percentage reduction in inhaled corticosteroid dose was greater among patients treated with omalizumab than among patients treated with placebo. In addition, percentages of patients with at least one asthma exacerbation were similar between omalizumab and placebo groups during the stable steroid and steroid reduction phases. (Holgate, 2004)

Chronic Idiopathic or Spontaneous Urticaria
Three phase III clinical trials using omalizumab for the treatment of chronic idiopathic or spontaneous urticaria have been conducted.

ASTERIA II evaluated 323 patients with a minimum 6 month duration of moderate-to-severe chronic idiopathic urticaria or chronic spontaneous urticaria (CIU/CSU). Patients were randomized to either omalizumab at doses of 75 mg, 150 mg, or 300 mg every 4 weeks or placebo for a treatment period of 12 weeks and a follow-up period of 16 weeks. Patients remained on their baseline licensed doses of H1-antihistamines throughout the trial. The primary endpoint was the change in a weekly itch-severity score from baseline to week 12 and significantly improved in the omalizumab 150 mg and 300 mg treatment groups compared to placebo. Following completion of the active treatment phase, patients in the omalizumab groups had increases in their mean weekly score for the number of hives that reached a similar value to placebo, but did not reach their baseline score. Serious adverse events were more common in the omalizumab 300 mg every 4 weeks group (8%) compared to omalizumab 75 mg every 4 weeks (5%) and 150 mg every 4 weeks (6%); the placebo group rate was similar at 9% to the 300 mg group. (Maurer, 2013)

GLACIAL evaluated the safety as the primary endpoint and efficacy of omalizumab 300 mg every 4 weeks compared to placebo for a treatment period of 24 weeks, followed by a 16-week observation period. Patients enrolled had a minimum 6 month duration of CIU/CSU despite treatment with H1-antihistamines (up to 4 times the licensed dose) with H2-antihistamines, leukotriene receptor antagonists, or both. Efficacies were evaluated using weekly itch severity scores, hives, and urticaria activity scores at weeks 12 and 24 and were statistically significantly in favor of omalizumab. The number of adverse events was similar between the omalizumab and

placebo groups during the treatment phase and the number of serious adverse events was 7.1% in the omalizumab compared to 6% in the placebo group. (Kaplan, 2013)

The third phase III trial is only available in abstract form (ASTERIA I). Safety and efficacy for use of omalizumab in CIU/CSU have not been established beyond 24 weeks of therapy.

Experimental, Investigational, Unproven Uses

Xolair has been evaluated for use in seasonal allergic rhinitis (Casale, 2001; Kamin, 2009), perennial allergic rhinitis (Chervinsky, 2003), and solar urticaria (Aubin, 2016). At this time, however, there is insufficient published data in terms of safety and efficacy to support the use of Xolair for these indications. Xolair has not been found efficacious in cow's milk allergy. (Wood, 2016) There is insufficient evidence in the peer-reviewed published scientific literature to support safety and efficacy of omalizumab for food allergies.

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J2357	Injection, omalizumab, 5 mg

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