



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Omalizumab (Xolair®)**

Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	6
References	6
Policy History.....	7

Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), 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 participant'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 participant's benefit plan document **always supercedes** 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 group 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. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers omalizumab (Xolair®) as medically necessary for the treatment of moderate to severe, persistent allergen-related asthma when ALL of the following criteria are met:

- age 12 years or older
- positive skin test or in vitro reactivity to a perennial aeroallergen
- inadequate control with inhaled corticosteroids
- regular use of an inhaled corticosteroid **AND** another controller therapy such as a long-acting beta agonist or leukotriene receptor antagonist

Subsequent authorizations of 12 months each require evidence of continued beneficial clinical response to Xolair.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to omalizumab (Xolair®) therapy for the condition being addressed.

CIGNA does not cover omalizumab (Xolair®) for ANY of the following indications because it is considered experimental, investigational, or unproven (this list may not be all-inclusive):

- non-allergic asthma
 - seasonal allergic rhinitis (SAR)
 - perennial allergic rhinitis (PAR)
 - food allergy
-

FDA Approved Indications

Xolair (Omalizumab) is indicated for adults and adolescents (12 years of age and above) 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. Xolair is not indicated for treatment of other allergic conditions. Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus. Xolair is not indicated for use in pediatric patients less than 12 years of age.

FDA Recommended Dosing

Xolair (omalizumab) 150 to 375 mg is administered SC every 2 or 4 weeks. Because the solution is slightly viscous, the injection may take 5-10 seconds to administer. Doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). Doses of more than 150 mg are divided among more than one injection site to limit injections to not more than 150 mg per site. The need for continued therapy should be periodically reassessed based upon the patient's disease severity and level of asthma control.

Black Box Warning

Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur.

Drug Availability

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

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.

Omalizumab is slowly absorbed after subcutaneous injection. Peak omalizumab concentrations are reached approximately 7–8 days after injection. The formation of omalizumab-IgE complexes results in an extended serum elimination half-life. Omalizumab's pharmacokinetics is not affected by age, race, ethnicity or gender; however, apparent rate of clearance is directly related to body weight.

Clinical Efficacy

The primary outcomes for omalizumab efficacy in moderate to severe allergic asthma include asthma symptom scores, an asthma quality of life questionnaire (AQLQ) with corresponding pediatric questionnaire (PAQLQ), number of asthma exacerbations, number of beta-2 agonist rescue doses, discontinuation of inhaled steroids, and standard pulmonary function tests.

Soler and colleagues (2001) also analyzed the effect of omalizumab on 546 patients with moderate to severe allergic asthma requiring inhaled corticosteroid use for control. Patients age 12 to 76 with serum IgE concentrations between 30 and 700 IU/mL received either seven monthly doses of placebo or omalizumab ~0.016 mcg/kg/IgE concentration in IU/mL given subcutaneously. The doses were rounded to the schedule of doses currently prescribed in the approved product labeling for administration every 2–4 weeks. All patients required inhaled steroids, which were held steady for 16 weeks and then tapered over 12 weeks with the intention of stopping inhaled steroids. The primary outcomes of asthma exacerbations were significantly reduced in the omalizumab group, $p < 0.001$, for both the steroid-stable and steroid-reduction phases. Statistical significance was also found for the number of patients who could cut their inhaled corticosteroid dose in half or more, reduce the number of albuterol rescue doses, reduce their asthma symptom score, and improved morning peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV₁) (all p -values < 0.05). Also, no statistically significant difference in the rate of adverse events was noted between placebo and omalizumab.

Buhl et al (2002) published an analysis of quality of life using the AQLQ tool at 0, 16, 28, and 52 weeks of omalizumab therapy. Overall, many patients had increased composite scores on the AQLQ, with a detectable improvement considered to be ≥ 0.5 point increase and a large clinical improvement defined as a ≥ 1.5 point increase in the scores. For both a “detectable” and a “large clinical” improvement, omalizumab produced significant increases with p -values < 0.05 at all time points. The categories with the largest impact in the AQLQ were the activities and symptoms scales. Overall, more patients and physicians rated effectiveness to be either excellent or good with omalizumab over placebo, $p < 0.001$. These humanistic outcomes suggest a benefit of adding omalizumab to the treatment regimen for allergic asthma.

A study by Busse et al. (2001) compared omalizumab to placebo in 525 patients ages 12–75 years with allergic asthma meeting similar criteria and following the same study design and that used by Soler. Omalizumab dosing is the same as that recommended in the package insert given either every 2–4 weeks based upon the patient's weight and IgE concentrations. All patients underwent a corticosteroid-stable and then reduction phase. During both phases, asthma exacerbations occurred statistically less frequently than those receiving placebo, $p \leq 0.003$. Secondary outcomes, including reduced or discontinued corticosteroid use, decreased rescue doses of albuterol, improved asthma symptom scores, improved PEF and FEV₁, and both patient and physician's efficacy scores had statistically significant improvements with omalizumab over placebo. No serious adverse effects were noted with omalizumab, and fewer patients receiving omalizumab withdrew from the study than those receiving placebo. Omalizumab is shown to be both safe and effective as compared to placebo in the treatment of severe allergic asthma in patients requiring inhaled corticosteroids.

A single pediatric study of the effect of omalizumab on moderate to severe allergic asthma was performed by Milgrom and colleagues in 2001. In this trial, 334 children age 6-12 years received omalizumab at the standard dose of 0.016 mg/kg/ IgE concentration in IU/mL given subcutaneously every four weeks. The outcomes of this trial showed statistical benefit of omalizumab therapy over placebo for the following measures: asthma exacerbations at 28 weeks, hospitalizations, unscheduled physician visits, use of rescue medication, discontinuation of inhaled corticosteroids, missed school days, and global evaluation scores. No difference was noted between omalizumab and placebo for parent days lost from work, patient asthma symptoms scores, and pulmonary function values (ie PEF rates and FEV₁). Fewer patients withdrew from the treatment group than the placebo group with only one subject in each group withdrawing for an adverse event. This trial demonstrated the safety and efficacy of omalizumab in improving markers of asthma control in children.

Berger and colleagues (2003) published an open-label extension of the Milgrom 2001 trial after a total of 52 weeks exposure to omalizumab. This study was an open-label extension that examined safety as the primary outcome in children who received the medication for a total of 52 weeks. It does not have a placebo-treated group to compare the rate of adverse effects or continued efficacy. Safety is loosely compared with baseline and the end of the 28-week, placebo-controlled study. Promising outcomes at the end of the trial included 81.4% of patients discontinuing all other asthma medications and 55% of patients never experiencing exacerbations with one year of omalizumab. The authors conclude that safety and efficacy did not change over the course of the remaining 24 weeks of therapy; however, a placebo-controlled trial extension would have provided a more reliable conclusion.

Overall, data showed a statistically significant reduction in asthma exacerbations before and after tapering inhaled corticosteroids, unscheduled outpatient visits, and hospitalizations for patients treated with omalizumab,

$p < 0.01$. The values that did not reach statistical significance were emergency room treatments and average number of hospital days per visit, although there were trends toward improvements with the use of omalizumab. Overall, the pooled data add strength to the conclusion that omalizumab is superior to placebo for the management of allergic asthma in patients, particularly in patients 12 years and older.

In summary, omalizumab is only indicated for the treatment of allergic asthma in patients 12 years and older. Sufficient data are published to demonstrate the benefit in clinical and humanistic outcomes with the use of omalizumab for moderate to severe allergic asthma in adolescents and adults. Improvements for up to one year are identified in quality of life surveys, and both reduced asthma exacerbations and corticosteroid use with omalizumab treatment. Published information on the effect of omalizumab in children age 6–12 years suggests improved clinical benefit; however, no improvements in the quality of life analyses are noted with omalizumab. Placebo-controlled trials beyond 28 weeks are needed to ensure the safety and continued efficacy of omalizumab for chronic allergic asthma symptoms.

Investigational Uses

Seasonal Allergic Rhinitis (SAR)

Studies of omalizumab compared to placebo are published for seasonal or perennial allergic rhinitis with varying degrees of clinical efficacy. The first large-scale trial of omalizumab in the treatment of seasonal allergic rhinitis was published in 1997 by Casale and colleagues. A total of 240 adults were randomized to one of five groups—omalizumab 0.15 mg/kg given intravenously or subcutaneously, omalizumab 0.5 mg/kg given intravenously, placebo given intravenously, or placebo given subcutaneously. No dose or route of administration demonstrated clinical benefit over placebo during this trial for nasal symptoms, quality of life assessments, or use of rescue antihistamines. No power analysis was included to ensure sufficient confidence that no difference truly exists between omalizumab and placebo.

A study by Adelroth et al. (2000) described the efficacy of a standard dose of omalizumab (300 mg subcutaneously) against placebo for seasonal allergic rhinitis in adults. This study demonstrated superior efficacy with regard to nasal symptom scores, use of rescue medication use, and quality of life questionnaire (RQLQ), $p \leq 0.001$. Omalizumab showed significant benefits on the RQLQ, with a desired point increase of 0.5 or more. No scores increased by greater than 1.5 points, suggesting that a clinical difference was detectable, but a large difference was not noted. Unlike the first trial, the significant improvements in clinical and humanistic outcomes suggest a standard dose of 300 mg may be beneficial for reducing symptoms of seasonal allergic rhinitis.

In 2001, Casale and colleagues again published a dose-ranging trial in 536 adolescents and adults with seasonal allergic rhinitis who received doses of omalizumab 50 mg, 150 mg or 300 mg, or placebo subcutaneously. The results demonstrate a dose-dependent increase in clinical efficacy with regard to nasal symptom scores, reduced rescue medication or quality of life measures. Significant improvements with omalizumab 300 mg are seen over placebo, and trends toward improved outcomes are noted between the 300 mg dose and the 50 mg and 150 mg doses, although no p-values are provided.

An analysis of the effect of omalizumab in children age 6–17 was published initially with 225 children enrolled, and later with a 92-patient subgroup analysis of blood samples. The published trials compared the benefit of adding either omalizumab dosed to patient weight and IgE concentrations to placebo. All patients in the trial received grass pollen or birch pollen allergy shots, called specific immunotherapy (SIT) in the trial. In the larger published trial, omalizumab produced a significant benefit as evidenced by a general rhinoconjunctivitis symptom score when compared with placebo. No assessment of rescue medication or quality of life was included. The addition of omalizumab to targeted allergy shot therapy was beneficial in improving a single measure of clinical efficacy in children with allergic rhinitis during both grass and birch pollen seasons.

Substudies have been performed evaluating the effect of omalizumab on symptom severity scores and inflammatory markers of the allergic response. A randomized, double-blind, placebo-controlled trial was conducted by Rolinck-Werninghaus et al. (2004) to compare the efficacy of single and combined treatment with SIT and omalizumab in reducing symptom severity and rescue medication use in 221 patients ages 6–17 years with birch and grass pollen allergic rhinoconjunctivitis during the grass pollen season. Neither symptom severity score nor the use of rescue medication was significantly reduced in patients treated with grass SIT alone during the grass pollen season. Patients receiving monotherapy with omalizumab experienced significant reductions in

symptom severity scores and rescue medication use. The combination of grass SIT plus omalizumab was clinically superior to each treatment alone.

Bez et al. (2004) evaluated the release of eosinophilic cationic protein (ECP), tryptase, IL-6, and IL-8 in the nasal secretions of 53 out of 225 children ages 6–17 years with a history of seasonal allergic rhinoconjunctivitis induced by birch and grass pollen. These children were randomized into four groups: either birch- or grass-pollen SIT in combination with either anti-IgE or placebo. A significant reduction in tryptase only was seen in omalizumab-treated group during birch- ($p < 0.05$) and pollen season and after the pollen season ($p < 0.05$) compared to the placebo group. Throughout the birch-pollen season and at the end of the study, a slight reduction in IL-6 levels was observed in both the omalizumab and placebo groups. Overall, results show that the combination of SIT and omalizumab is associated with prevention of nasal ECP increase and decreased tryptase levels in nasal secretions.

Perennial Allergic Rhinitis (PAR)

A single clinical trial for perennial rhinitis is published, with relevant clinical outcomes. Chervinsky and colleagues (2003) studied 289 patients ages 12–75 years old with documented allergies to dust mites, cat dander or dog dander and clinical symptoms for two or more years. Omalizumab 0.016 mg/kg/IgE{IU/mL} monthly was compared to placebo in a 16-week trial where patients received omalizumab once monthly or split twice monthly based upon baseline IgE concentrations; dosing is that recommended for use by the Xolair[®] package insert. The investigators employed several measures of clinical effectiveness in this trial, including the nasal severity score, RQLQ, patient global evaluation of treatment, use of rescue antihistamine tablets, and safety data. At weeks 4, 8, 12, and 16, omalizumab produced a significant improvement in the nasal severity score, $p < 0.01$. For the quality of life assessment, all factors except eye symptoms and emotions improved significantly with the use of omalizumab, $p = 0.001$. For patient's global evaluation of treatment, patients who considered therapy to provide complete control of symptoms was 53% of omalizumab-treated and 34% of placebo-treated patients, $p = 0.001$. Patients who considered the treatment to worsen symptoms included 1.4% of omalizumab-treated and 2.8% of placebo-treated patients. Omalizumab-treated patients used fewer rescue doses of oral antihistamines at 4, 12, and 16 weeks ($p < 0.05$) and at eight weeks ($p < 0.001$). Three patients in each group decided to drop out of the trial for inability to tolerate the study intervention, but no severe adverse reactions were correlated with the use of omalizumab overall. This trial provides promising evidence that omalizumab may significantly reduce symptoms of perennial allergic rhinitis; however, the short duration of the trial limits the understanding of how safe and effective long-term treatment with omalizumab would be.

In a parallel-group, randomized, double-blind, placebo-controlled European study, a total of 23 patients with allergic rhinitis received omalizumab ($n=12$) or placebo ($n=11$) for 2- or 4-week intervals. Before treatment, patients were challenged nasally with 16 weeks of exposure to cat dander, grass, house dust mite, or birch allergen. After 16 weeks, patients who were treated with omalizumab showed a significantly lower allergen challenge-induced nasal symptom score compared to the placebo group ($p < 0.01$), as well as significantly lower allergen challenge-induced increases in human serum albumin in the nasal lavage fluid (NAL), ($p < 0.01$). The sample size of this study is small; however, results show that omalizumab may provide a new strategy for the treatment of allergic rhinitis.

Adverse Reactions

The most serious adverse reactions occurring in clinical trials with Xolair were anaphylaxis and malignancies. Anaphylaxis was reported in 3 of 3507 patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient. In clinical trials the observed incidence of malignancy among Xolair-treated patients was numerically higher than among patients in control groups.

The adverse reactions most commonly observed among patients treated with Xolair in clinical studies included injection site reaction, viral infections, upper respiratory tract infection, sinusitis, headache, and pharyngitis. These events were observed at similar rates in Xolair-treated patients and control patients. These were also the most frequently reported adverse reactions resulting in clinical intervention (e.g. discontinuation of Xolair, or the need for concomitant medication to treat an adverse reaction).

Coding/Billing Information

Note: This section is not in use.

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	4/15/2009	4026	Omalizumab (Xolair®)
Great-West Healthcare	12/2006	P03.102.2	Xolair

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.