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Omalizumab

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Asthma

Xolair® (Omalizumab) **may be considered medically necessary**, as add-on maintenance treatment, for moderate to severe asthma when **ALL** the following criteria are met:

1. It is prescribed by an asthma specialist (pulmonologist, allergist/immunologist); AND
2. Individual is at least 6 years of age or older; AND
3. There is documented and current use of an inhaled corticosteroid (ICS) in combination with a long acting beta2-agonist (LABA), leukotriene receptor antagonist [LTRA], theophylline or long-acting muscarinic antagonist (LAMA) for at least 3 months; AND
4. The individual has uncontrolled asthma while on control therapy as evidenced by two or more exacerbations requiring systemic glucocorticoids, frequent ER visits, or hospitalizations; AND

   NOTE 1: Individuals who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering off corticosteroids, will also meet this definition of moderate to severe asthma. For definition of uncontrolled asthma see Description section.
5. Baseline serum total IgE >30 IU/mL; AND
6. Body weight 150 kg or less; AND
7. There is written documentation of at least one perennial aeroallergen by a positive skin prick test or an in-vitro specific Immunoglobulin E (IgE) test, which correlated with the individual's clinical history; AND
8. Will not be used in combination with another antiasthmatic monoclonal antibody agent (e.g., reslizumab [Cinqair], benralizumab [Fasenra], mepolizumab [Nucala], ezepelumab-ekko [Tezspire]).

Chronic Spontaneous Urticaria

Xolair® (Omalizumab) **may be considered medically necessary** for the treatment of adults and adolescents (12 years of age and above) with chronic spontaneous urticaria (previously referred to as chronic idiopathic urticaria) (spontaneous urticaria lasting on most days of the week for >6 weeks) whose symptoms are inadequately controlled despite treatment with, or experience intolerant side effects, or have an FDA labeled contraindication to:

- Equal to or greater than 2 times the FDA labeled dose of a 2nd generation H1 antihistamine (i.e., cetirizine, levocetirizine, desloratadine, fexofenadine, loratadine).

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Xolair® (Omalizumab) **may be considered medically necessary**, as add-on maintenance treatment, for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) when the following criteria are met:

1. Individual is 18 years of age or older; AND
2. Confirmation of diagnosis by one of the following:
    a. Anterior rhinoscopy or endoscopy; or
    b. Computed tomography (CT) of the sinuses; AND
3. Inadequate response, intolerance or contraindication to intranasal corticosteroids; AND
4. Will be used in combination with standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids); AND
5. Will not be used in combination with other monoclonal antibodies for the treatment of nasal polyps (e.g., mepolizumab [Nucala], dupilumab [Dupixent]).

Xolair® (Omalizumab) **is considered not medically necessary** for the off-label use of allergic rhinitis as clinical outcomes have not demonstrated Xolair as superior to established, less costly treatment options.

IgE-Mediated Food Allergy

Xolair® (Omalizumab) **may be considered medically necessary** for the reduction of allergic reactions to food when **ALL** the following criteria are met:

- Individual has a diagnosis of IgE-mediated food allergy confirmed by an allergy diagnostic test (e.g., skin prick test, serum specific IgE test); AND
- Individual is at least 1 year of age or older.

Xolair® (Omalizumab) **is considered experimental, investigational and/or unproven** for other allergies, acute bronchospasm, status asthmaticus, eosinophilic gastroenteritis, eosinophilic esophagitis, and other forms of urticaria not addressed above.

NOTE 2: Spirometry results (particularly % predicted values) should not be adjusted for race or, if race was included in the calculations, results should be recalculated without the race-based adjustment.

Self-Administration

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional) after a minimum of three initial doses are given in a health care setting prepared to manage anaphylaxis, and therapy has safely been established. Therefore, coverage of a formulation that cannot be self-administered **may be considered medically necessary** when:

- The patient is receiving the initial three doses of Xolair treatment; **OR**
- Patient specific factors are present including:
    - For asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and chronic spontaneous urticaria (CSU):
        - A history of anaphylaxis to Xolair or other agents, such as foods, drugs, biologics, etc.; OR

- For IgE-Mediated Food Allergy:
  - A history of anaphylaxis to Xolair or other agents (except foods), such as drugs, biologics, etc.; OR
- Patient received any of the 3 initial doses of Xolair under the guidance of a healthcare provider AND had a hypersensitivity reaction during any of the 3 initial doses; OR
- Patient or caregiver is unable to recognize symptoms of anaphylaxis; OR
- Patient or caregiver is unable to treat anaphylaxis appropriately; OR
- Patient or caregiver is unable to perform subcutaneous injections with a prefilled syringe or autoinjector with proper technique according to the prescribed dosing regimen and Instructions for Use; OR
- The patient has a physical or cognitive limitation that makes the utilization of a self-administered formulation unsafe or otherwise not feasible, as demonstrated by BOTH of the following:
  - Inability to self-administer the medication; and
  - Lack of caregiver or support system for assistance with administration of self-administered products.

Coverage of a formulation that cannot be self-administered **is considered not medically necessary** if the above criteria are not met.

Policy Guidelines

None.

Description

Xolair® (Omalizumab) is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE).

Allergic Asthma
Asthma is a common condition in which the airways in the lungs become narrowed, making it difficult to breathe. Asthma caused by allergies results from the immune system's over-reaction to inhaled allergen, and this immune system reaction prompts inflammation that causes the airway narrowing and other symptoms (i.e., wheezing, chest tightness, and cough).

The severity of asthma varies from mild intermittent to severe persistent. Most asthma is effectively treated based on the National Heart, Lung and Blood Institute (NHLBI) clinical guidelines. Xolair can be beneficial as adjunctive therapy in patients whose symptoms are inadequately controlled despite the regular use of maximum dose inhaled corticosteroids.

Xolair inhibits the binding of Immunoglobulin E (IgE) to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells

limits the degree of release of mediators of the allergic response. Treatment with Xolair also reduces the number of FcεRI receptors on basophils in atopic patients.

Xolair is administered subcutaneously once or twice a month, and in some cases more than one injection at a time.

Definition of Uncontrolled Asthma

At least one of the following:

- Asthma Control Questionnaire (ACQ) score consistently >1.5, Asthma Control Test (ACT) score <20 (or ''not well controlled'' by National Asthma Education and Prevention Program (NAEPP) /Global Initiative for Asthma (GINA) guidelines);
- Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids (CS) (>3 days each) in the previous year;
- Serious exacerbations: at least 1 hospitalization, intensive care unit (ICU) stay, or mechanical ventilation in the previous year;
- Airflow limitation: after appropriate bronchodilator withhold, forced expiratory volume in 1 second (FEV_1) <80% predicted (in the face of reduced FEV_1/forced vital capacity (FVC) defined as less than the lower limit of normal). (6)

Chronic Spontaneous Urticaria (CSU)

In the treatment of CSU, Xolair binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate. The mechanism by which these effects of omalizumab result in an improvement of CSU symptoms is unknown.

The appropriate duration of therapy for CSU has not been evaluated and should be periodically reassessed for the need for continued therapy.

Nasal Polyps

Nasal polyps are benign growths in the nasal cavity thought to originate from the ethmoid sinuses. They tend to be present in both sides of the nasal cavity. Symptoms can include nasal drainage, nasal congestion, facial pressure or pain, and a decreased sense of smell lasting for more than 12 weeks.

In the treatment of nasal polyps, Xolair treatment led to a reduction in serum free IgE and an increase in serum total IgE levels, similar to the observations in asthma patients.

IgE-Mediated Food Allergies

Immunoglobulin E (IgE)-mediated food allergic reactions are referred to as immediate or acute allergic reactions because they are rapid in onset, typically beginning within seconds to minutes from the time of ingestion, although reactions up to two hours or more after exposure can occur. One exception is the IgE-mediated reaction to carbohydrate allergens in meats, which usually begin four to six hours after ingestion. Signs and symptoms can involve the skin, respiratory and gastrointestinal tracts, and cardiovascular system, and are caused by mediator release from tissue mast cells and circulating basophils.

Regulatory Status
Xolair, a recombinant deoxyribonucleic acid (DNA)-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE), received U.S. Food and Drug Administration (FDA) approval in June 2003 and is the first anti-IgE agent for the treatment of patients at high risk from their allergy related asthma. Xolair was approved in March 2014 for chronic spontaneous urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment. The FDA approved Xolair for the treatment of nasal polyps in adults ages 18 years and older with inadequate response to nasal corticosteroids, as an add-on maintenance, in November 2020. In February 2024, the FDA approved Xolair for IgE-mediated food allergies in adult and pediatric patients aged 1 and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. It is to be used in conjunction with food allergen avoidance. (2)

Rationale

This medical policy was originally developed in 2004 and has been regularly updated using searches of the PubMed database as well as the U.S. Food and Drug Administration (FDA) prescribing information. The most recent update is through July 22, 2024.

Asthma
Adult and Adolescent Patients 12 Years of Age and Older
The safety and efficacy of Xolair were evaluated in three randomized, double-blind, placebo-controlled, multicenter trials.

The trials enrolled patients 12 to 76 years old, with moderate to severe persistent (NHLBI – National Heart, Lung and Blood Institute criteria) asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. In all trials, Xolair dosing was based on body weight and baseline serum total Immunoglobulin E (IgE) concentration. All patients were required to have a baseline IgE between 30 and 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of Xolair or a matching volume of placebo over each 4-week period. The maximum Xolair dose per 4 weeks was 750 mg. (2)

In all three trials an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline inhaled corticosteroids (ICS) dose. Most exacerbations were managed in the outpatient setting and the majority was treated with systemic steroids. Hospitalization rates were not significantly different between Xolair and placebo-treated patients; however, the overall hospitalization rate was small. Among those patients who experienced an exacerbation, the distribution of exacerbation severity was similar between treatment groups. (2)

Asthma Trials 1 and 2

At screening, patients in Asthma Trials 1 and 2 had a forced expiratory volume in one second (FEV1) between 40% and 80% predicted. All patients had a FEV1 improvement of at least 12% following beta2-agonist administration. All patients were symptomatic and were being treated with ICS and short acting beta2-agonists. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded. Each trial was comprised of a run-in period to achieve a stable conversion to a common ICS (beclomethasone dipropionate), followed by randomization to Xolair or placebo. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 weeks during which ICS dose reduction was attempted in a step-wise manner. (2)

The distribution of the number of asthma exacerbations per patient in each group during a study was analyzed separately for the stable steroid and steroid-reduction periods.

In both Asthma Trials 1 and 2 the number of exacerbations per patient was reduced in patients treated with Xolair compared with placebo (Table 1).

Measures of airflow (FEV1) and asthma symptoms were also evaluated in these trials. The clinical relevance of the treatment-associated differences is unknown. Results from the stable steroid phase Asthma Trial 1 are shown in Table 2. Results from the stable steroid phase of Asthma Trial 2 and the steroid reduction phases of both Asthma Trials 1 and 2 were similar to those presented in Table 2. (2)

Table 1. Frequency of Asthma Exacerbations per Patient by Phase in Trials 1 and 2 (2)

Stable Steroid Phase (16 weeks)				
	Asthma Trial 1		**Asthma Trial 2**	
Exacerbations per patient	**Xolair N=268**	**Placebo N=257**	**Xolair N=274**	**Placebo N=272**
0	85.8%	76.7%	87.6%	69.9%
1	11.9%	16.7%	11.3%	25.0%
≥2	2.2%	6.6%	1.1%	5.1%
p-Value	0.005		<0.001	
Mean number of exacerbations/patient	0.2	0.3	0.1	0.4
Steroid Reduction Phase (12 weeks)				
Exacerbations per patient	**Xolair N=268**	**Placebo N=257**	**Xolair N=274**	**Placebo N=272**
0	78.7%	67.7%	83.9%	70.2%
1	19.0%	28.4%	14.2%	26.1%
≥2	2.2%	3.9%	1.8%	3.7%
p-Value	0.004		<0.001	

Mean number of exacerbations/patient	0.2	0.4	0.2	0.3

Table 2. Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Trial 1 (2)

	Xolair N=268[a]		**Placebo N=257[a]**	
Endpoint	**Mean Baseline**	**Median Change (Baseline to Week 16)**	**Mean Baseline**	**Median Change (Baseline to Week 16)**
Total asthma symptoms score	4.3	-1.5[b]	4.2	-1.1[b]
Nocturnal asthma score	1.2	-0.4[b]	1.1	-0.2[b]
Daytime asthma score	2.3	-0.9[b]	2.3	-0.6[b]
FEV1 % predicted	68	3[b]	68	0[b]

Asthma symptom scale: total score from 0 (least) to 9 (most); nocturnal and daytime scores from 0 (least) to 4 (most symptoms).

[a] Number of patients available for analysis ranges 255-258 in the Xolair group and 238-239 in the placebo group.

[b] Comparison of Xolair versus placebo ($p<0.05$).

Asthma Trial 3

In Asthma Trial 3, there was no restriction on screening FEV1, and unlike Asthma Trials 1 and 2, long-acting beta2-agonists were allowed. Patients were receiving at least 1000 µg/day fluticasone propionate and a subset was also receiving oral corticosteroids. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded. (2)

The trial was comprised of a run-in period to achieve a stable conversion to a common ICS (fluticasone propionate), followed by randomization to Xolair or placebo. Patients were stratified by use of ICS-only or ICS with concomitant use of oral steroids. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 16 weeks during which ICS or oral steroid dose reduction was attempted in a step-wise manner. (2)

The number of exacerbations in patients treated with Xolair was similar to that in placebo-treated patients (Table 3). The absence of an observed treatment effect may be related to differences in the patient population compared with Asthma Trials 1 and 2, study sample size, or other factors. (2)

Table 3. Percentage of Patients with Asthma Exacerbations by Subgroup and Phase in Trial 3 (2)

	Stable Steroid Phase (16 weeks)			
	Inhaled Only		**Oral plus Inhaled**	
	Xolair N=126	**Placebo N=120**	**Xolair N=50**	**Placebo N=45**

% Patients with ≥1 exacerbations	15.9%	15.0%	32.0%	22.2%
Difference (95% CI)	0.9 (-9.7, 13.7)		9.8 (-10.5, 31.4)	
	Steroid Reduction Phase (16 weeks)			
	Xolair N=126	**Placebo N=120**	**Xolair N=50**	**Placebo N=45**
% Patients with ≥1 exacerbations	22.2%	26.7%	42.0%	42.2%
Difference (95% CI)	-4.4 (-17.6, 7.4)		-0.2 (-22.4, 20.1)	

CI: confidence internal.

In all three of the trials, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV1 >80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy. (2)

Pediatric Patients 6 to <12 Years of Age

The safety and efficacy of Xolair in pediatric patients 6 to <12 years of age with moderate to severe asthma is based on one randomized, double-blind, placebo controlled, multi-center trial (Trial 4) and an additional supportive study (Trial 5). (2)

Trial 4 was a 52-week study that evaluated the safety and efficacy of Xolair as add-on therapy in 628 pediatric patients ages 6 to <12 years with moderate to severe asthma inadequately controlled despite the use of ICS (fluticasone propionate dry powder inhaler ≥200 mcg/day or equivalent) with or without other controller asthma medications. Eligible patients were those with a diagnosis of asthma >1 year, a positive skin prick test to at least one perennial aeroallergen, and a history of clinical features such as daytime and/or night-time symptoms and exacerbations within the year prior to study entry. During the first 24 weeks of treatment, steroid doses remained constant from baseline. This was followed by a 28-week period during which ISC adjustment was allowed. (2)

The primary efficacy variable was the rate of asthma exacerbations during the 24-week, fixed steroid treatment phase. An asthma exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline ICS dose for at least 3 days and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days. At 24 weeks, the Xolair group had a statistically significantly lower rate of asthma exacerbations (0.45 vs. 0.64) with an estimated rate ratio of 0.69 (95% CI: 0.53, 0.90). (2)

The Xolair group also had a lower rate of asthma exacerbations compared to placebo over the full 52-week double-blind treatment period (0.78 vs. 1.36; rate ratio: 0.57; 95% CI: 0.45, 0.72). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and measures of airflow (FEV1) were not significantly different in Xolair-treated patients compared to placebo. (2)

Trial 5 was a 28-week randomized, double blind, placebo-controlled study that primarily evaluated safety in 334 pediatric patients, 298 of whom were 6 to <12 years of age, with moderate to severe asthma who were well-controlled with ICS (beclomethasone dipropionate

168-420 mcg/day). A 16-week steroid treatment period was followed by a 12-week steroid dose reduction period. Patients treated with Xolair had fewer asthma exacerbations compared to placebo during both the 16-week fixed steroid treatment period (0.18 vs. 0.32; rate ratio: 0.58; 95% CI: 0.35, 0.96) and the 28-week treatment period (0.38 vs. 0.76; rate ratio: 0.50; 95% CI: 0.36, 0.71). (2)

According to a study by Maselli et al., Xolair (omalizumab) was as effective in patients with an IgE level greater than 700 IU/mL compared with patients with levels of 30 to 700 IU/mL. (3) In this study, twenty-six (26) patients with an IgE level greater than 700 IU/mL (group 1) were matched by age, sex, and severity of asthma to patients with an IgE of 30-700 IU/mL (group 2). Both groups had an improvement in asthma control based on the mean Asthma Control Test (ACT) score before and after treatment (15.6 vs 18.9 [P = .02] and 15.4 vs 19 [P = .006], respectively). There was also a significant reduction in the frequency of systemic corticosteroid use during the 6 months before and after treatment (2.58 vs 0.96 [P < .001] and 2.62 vs 1.23 [P < .001] systemic steroid treatments, respectively).

Vennera et al. (4) reported in the Spanish registry on 266 patients with uncontrolled severe asthma receiving high-dose ICS plus long-acting β2-agonist (LABA). Asthma exacerbation rate (AER) was reduced from 3.6 (3.6) in previous year to 0.67 (1.2) at 4 months ($p < .05$) and to 1.04 (1.8) at 2 years ($p < .05$). Asthma control test (ACT) increased significantly from 14.3 (4.7) at baseline to 18.4 (4.4) at 4 months ($p < .05$) and to 20.3 (4.0) ($p < .05$) at 2 years. After 4 months, 74.6% of patients had reached a good or excellent rate on the global evaluation of treatment effectiveness (GETE) scale ($p < .05$). This rate continued increasing up to 81.6% at 2 years. These efficacy results were similar for patients with "off-label" IgE > 700 IU/mL.

Zielen et al. (5) evaluated the potential of high omalizumab doses to block allergen-induced bronchoconstriction in patients with higher IgE levels. Asthmatic adults ages 18-65 years, with body weights from 40-150 kg, were divided into groups according to screening IgE (group 1: 30-300 IU/mL; group 2: 700-2,000 IU/mL; and then randomized 2:1 to omalizumab/placebo every 2 or 4 weeks for 12-14 weeks. Serum free IgE was determined as a pharmacodynamic endpoint. The primary efficacy endpoint, the early-phase allergic response (EAR), was defined as the maximum percentage drop in FEV1 during the first 30 min after allergen bronchoprovocation (ABP). The exhaled fractional concentration of nitric oxide (FE(NO)) was an exploratory endpoint. Fifty patients were included in the study. Omalizumab improved EAR; at week 8, EAR was 23.1% for placebo, 9.3% in group 1 ($p = 0.018$ versus placebo) and 5.6% in group 2 ($p < 0.001$). At week 16, EAR was 20%, 11.8% ($p = 0.087$) and 5.1% ($p < 0.001$), respectively. Free IgE decreased in groups 1 and 2 and remained <50 ng/ml in all patients during weeks 6-16. Omalizumab completely suppressed FE(NO) increases after ABP in both groups. The authors concluded that Omalizumab blocked early asthmatic responses over a broad range of IgE/body weight combinations and extending the dosing tables enables omalizumab to benefit a wider range of patients.

Chronic Spontaneous Urticaria (CSU)

Adult and Adolescent Patients 12 Years of Age and Older

The safety and efficacy of Xolair for the treatment of CSU was assessed in two placebo-controlled, multiple-dose clinical trials of 24 weeks' duration (CSU Trial 1; n= 319) and 12 weeks' duration (CSU Trial 2; n=322). Patients received Xolair 75 mg, 150 mg, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. A total of 640 patients (165 males, 475 females) were included for the efficacy analyses. Most patients were white (84%) and the median age was 42 years (range 12–72). (2)

Disease severity was measured by a weekly urticaria activity score (UAS7, range 0–42), which is a composite of the weekly itch severity score (range 0–21) and the weekly hive count score (range 0–21). All patients were required to have a UAS7 of ≥16, and a weekly itch severity score of ≥8 for the 7 days prior to randomization, despite having used an H1 antihistamine for at least 2 weeks. (2)

The mean weekly itch severity scores at baseline were fairly balanced across treatment groups and ranged between 13.7 and 14.5 despite use of an H1 antihistamine at an approved dose. The reported median durations of CSU at enrollment across treatment groups were between 2.5 and 3.9 years (with an overall subject-level range of 0.5 to 66.4 years). (2)

In both CSU Trials 1 and 2, patients who received Xolair 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at Week 12. Representative results from CSU Trial 1 are shown (Table 4); similar results were observed in CSU Trial 2. The 75-mg dose did not demonstrate consistent evidence of efficacy and is not approved for use. (2)

Table 4. Change from Baseline to Week 12 in Weekly Itch Severity Score and Weekly Hive Count Score in CSU Trial 1[a] (2)

	Xolair 75mg	**Xolair 150mg**	**Xolair 300mg**	**Placebo**
N	77	80	81	80
Weekly Itch Severity Score				
Mean Baseline Score (SD)	14.5 (3.6)	14.1 (3.8)	14.2 (3.3)	14.4 (3.5)
Mean Change Week 12 (SD)	-6.46 (6.14)	-6.66 (6.28)	-9.40 (5.73)	-3.63 (5.22)
Difference in LS means vs. placebo	-2.96	-2.95	-5.80	
95% CI for difference	-4.71, -1.21	-4.72, -1.18	-7.49, -4.10	-
Weekly Hive Count Score[b]				
Mean Baseline Score (SD)	17.2 (4.2)	16.2 (4.6)	17.1 (3.8)	16.7 (4.4)

Mean Change Week 12 (SD)	-7.36 (7.52)	-7.78 (7.08)	-11.35 (7.25)	-4.37 (6.60)
Difference in LS means vs. placebo	-2.75	-3.44	-6.93	
95% CI for difference	-4.95, -0.54	-5.57, -1.32	-9.10, -4.76	-

SD: standard deviation; CI: confidence interval.

[a] Modified intent-to-treat (mITT) population: all patients who were randomized and received at least one dose of study medication.

[b] Score measured on a range of 0-21.

The appropriate duration of therapy for CSU with Xolair has not been determined.

In CSU Trial 1, a larger proportion of patients treated with Xolair 300 mg (36%) reported no itch and no hives (UAS7=0) at Week 12 compared to patients treated with Xolair 150 mg (15%), Xolair 75 mg (12%), and placebo group (9%). Similar results were observed in CSU Trial 2. (2)

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) (2)

Adult Patients 18 Years of Age and Older

The safety and efficacy of Xolair was evaluated in two, randomized, multicenter, double-blind, placebo-controlled clinical trials that enrolled patients with nasal polyps with inadequate response to nasal corticosteroids (Nasal Polyps Trial 1, n=138; Nasal Polyps Trial 2, n=127). Patients received Xolair or placebo SC every 2 or 4 weeks for 24 weeks followed by a 4-week follow-up period. All patients received background nasal mometasone therapy during both the treatment period and during a 5-week run-in period. Prior to randomization, patients were required to have evidence of bilateral polyps as determined by a nasal polyp score (NPS) ≥ 5 with NPS ≥ 2 in each nostril, despite use of nasal mometasone during the run-in period. NPS was measured via endoscopy and scored (range 0-4 per nostril: 0= no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity) for a total NPS (range 0-8).

Patients were furthermore required to have a weekly average of nasal congestion score (NCS) > 1 prior to randomization, despite use of nasal mometasone. Nasal congestion was measured by a daily assessment on a 0 to 3-point severity scale (0=none, 1=mild, 2=moderate, 3=severe). Prior sino-nasal surgery or prior systemic corticosteroid usage were not required for inclusion in the trials and sinus CT scans were not performed to evaluate for sinus opacification. Demographics and baseline characteristics, including allergic comorbidities, are described in Table 5.

Table 5. Demographics and Baseline Characteristics of Nasal Polyps Trials 1 and 2

Parameter	Nasal Polyps Trial 1 (n=138)	Nasal Polyps Trial 2 (n=127)
Mean age (years (SD)	51 (13)	50 (12)
% Male	64	65
Patients with systemic corticosteroid use in the previous year (%)	19	26
Patients with prior surgery for nasal polyps (%)	79 (57)	79 (62)
Mean bilateral endoscopic NPS (SD), range 0-8	6.2 (1.0)	6.3 (0.9)
Mean nasal congestion score (SD) range 0-3	2.4 (0.6)	2.3 (0.7)
Mean sense of smell score (SD) range 0-3	2.7 (0.7)	2.7 (0.7)
Mean post-nasal drip score (SD) range 0-3	1.8 (0.9)	1.7 (0.9)
Mean runny nose score (SD) range 0-3	2.0 (0.8)	1.9 (0.9)
Mean blood eosinophils (cells/mcL) (SD)	346 (284)	335 (188
Mean total IgE IU/mL (SD)	161 (140)	190 (201)
Asthma (%)	54	61
Aspirin exacerbated respiratory disease (%)	20	35

SD: standard deviation; NPS: nasal polyp score; IgE: Immunoglobulin E; IU: International units; mcL: microliter.
For NPS, NCS (nasal congestion score), sense of smell, post-nasal drip, and runny nose, higher scores indicate greater disease severity.

The co-primary endpoints in Trials 1 and 2 were NPS and average daily NCS at Week 24. In both trials, patients who received Xolair had a statistically significant greater improvement from baseline at Week 24 in NPS and weekly average NCS, than patients who received placebo. Results from Nasal Polyps Trials 1 and 2 are shown in Table 6. The greater improvements in NPS and NCS in the Xolair group compared to the placebo group were observed as early as the first assessment at Week 4 in both studies.

Table 6. Change from Baseline at Week 24 in Nasal Polyp Score and 7-day Average of Daily Nasal Congestion Score in Nasal Polyps Trials 1 and 2

	Trial 1		**Trial 2**	
	Placebo	**Xolair**	**Placebo**	**Xolair**
Number of patients	65	72	65	62
Nasal Polyp Score				
Mean Baseline Score	6.3	6.2	6.1	6.4
LS Mean Change From Baseline at Week 24	0.1	-1.1	-0.3	-0.9
Difference in LS Mean vs. Placebo	-1.1		-0.6	
95% CI for difference	-1.6, -0.7		-1.1, -0.1	
p-value	<0.0001		0.0140	
7-day Average of Daily Nasal Congestion Score				
Mean Baseline Score	2.5	2.4	2.3	2.3

LS Mean Change From Baseline at Week 24	-0.4	-0.9	-0.2	-0.7
Difference in LS Mean vs. Placebo	-0.6		-0.5	
95% CI for difference	-0.8, -0.3		-0.8, -0.2	
p-value	0.0004		0.0017	

LS: least-square; CI: confidence interval. Change from baseline was analyzed using a mixed-effect model of repeated measures (MMRM) model with baseline score, baseline score/timepoint (week) interaction as covariates, and the following factors: geographic region, asthma/aspirin sensitivity comorbidity status, timepoint, treatment group, treatment/timepoint interaction.

Xolair had statistically significant improvements on sense of smell score compared to placebo. Sense of smell was measured by a daily assessment on a 0 to 3-point severity scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). The LS mean difference for change from baseline at Week 24 in sense of smell score in Xolair compared to placebo was -0.3 (95% CI: -0.6, -0.1) in Trial 1 and -0.5 (95% CI: -0.7, -0.2) in Trial 2.

Xolair had statistically significant improvements on post-nasal drip compared to placebo. The LS mean difference for change from baseline at Week 24 in post-nasal drip score in Xolair compared to placebo was -0.6 (95% CI: -0.8, -0.3) in Trial 1 and -0.5 (95% CI: - 0.8, -0.3) in Trial 2.

Xolair had statistically significant improvements on runny nose compared to placebo. The LS mean difference for change from baseline at Week 24 in runny nose score in Xolair compared to placebo was -0.4 (95% CI: -0.7, -0.2) in Trial 1 and -0.6 (95% CI: - 0.9, -0.4) in Trial 2.

In a pre-specified pooled analysis of systemic corticosteroid use during the 24-week treatment period, there was no significant reduction in systemic corticosteroid use between the treatment arms. The proportion of patients taking systemic corticosteroid in Xolair was 2.3% compared to 6.2% in placebo. The odds-ratio of systemic corticosteroid use with Xolair compared to placebo was 0.4 (95% CI: 0.1, 1.5).

There were no sino-nasal surgeries reported, in either placebo or Xolair arms, in either Trial.

IgE-Mediated Food Allergy (2)

The safety and efficacy of Xolair was evaluated in a multi-center, randomized, double-blind, placebo-controlled Food Allergy (FA) trial [NCT03881696] in 168 adult patients and pediatric patients 1 year of age to less than 56 years who were allergic to peanut and at least two other foods, including milk, egg, wheat, cashew, hazelnut, or walnut (i.e., studied foods). The FA trial enrolled patients who experienced dose-limiting symptoms (e.g., moderate to severe skin, respiratory or gastrointestinal symptoms) to a single dose of ≤100 mg of peanut protein and ≤300 mg protein for each of the other two foods (milk, egg, wheat, cashew, hazelnut, or walnut) during the screening double-blind placebo-controlled food challenge (DBPCFC). Patients with a history of severe anaphylaxis (defined as neurological compromise or requiring intubation) were excluded from the study. Patients were randomized 2:1 to receive a

subcutaneous dosage of Xolair or placebo based on serum total IgE level (IU/mL), measured before the start of treatment, and by body weight for 16 to 20 weeks. After 16 to 20 weeks of treatment, each patient completed a DBPCFC consisting of placebo and each of their 3 studied foods. Following the DBPCFC, the first 60 patients that included 59 pediatric patients and one adult patient who completed the double-blind, placebo-controlled phase of the study could continue to receive Xolair in a 24 to 28 week open-label extension.

Efficacy of Xolair is based on 165 pediatric patients who were included in the efficacy analyses provided below. The mean age of the pediatric patients was 8 years (age range: 1 to 17 years); 37% were less than 6 years of age, 38% were 6 to less than 12 years of age, and 25% were 12 to less than 18 years of age. Patient population were 56% male, 63% White, 13% Asian, 7% Black, 16% Other, and 55% of patients had a history of asthma.

The primary efficacy endpoint was the percentage of patients who were able to consume a single dose of ≥600 mg of peanut protein without dose-limiting symptoms (e.g., moderate to severe skin, respiratory or gastrointestinal symptoms) during DBPCFC. Table 7 shows Xolair treatment led to a statistically higher response rate (68%) than placebo (5%).

The secondary efficacy endpoints were the percentage of patients who were able to consume a single dose of ≥1000 mg of cashew, milk, or egg protein without dose-limiting symptoms during DBPCFC. The study met the secondary endpoints and demonstrated that Xolair treatment led to statistically higher response rates than placebo for all three foods. See Table 7 for details.

Table 7. DBPCFC Response Rates in Pediatric Patients for Single Dose of Peanut, Cashew, Milk, or Egg Protein in FA Trial

Food, Challenge Dose	Response Rate[a] (%) (n/N)		Treatment Difference (%) (Xolair-Placebo) (95% CI)
	Xolair	Placebo	
Peanut, ≥600 mg	68% (75/110)	5% (3/55)	63% (50%, 73%)
Peanut, ≥1000 mg[b]	65% (72/110)	0% (0/55)	65% (56%, 74%)
Cashew, ≥ 100 mg	42% (27/64)	3% (1/30)	39% (20%, 53%)
Milk, ≥1000 mg	66% (25/38)	11% (2/19)	55% (29%, 73%)
Egg, ≥1000 mg	67% (31/46)	0% (0/19)	67% (49%, 80%)

CI: Confidence interval; DBPCFC: Double-blind placebo-controlled food challenge; n: Number of responders; N: Total number of patients receiving food, challenge dose.

[a] Response defined as consumption of a single dose of the specified amount of food without dose-limiting symptoms.

[b] Consumption of a single dose of ≥1000 mg of peanut protein was an additional secondary endpoint. The key secondary efficacy endpoints were the percentage of patients who were able to consume a single dose of ≥1000 mg of cashew, milk, or egg protein.
Notes: Subjects without an exit DBPCFC or evaluable exit DBPCFC were counted as non-responders; P-values from two-sided Fisher's exact tests were <0.0001 for all the food challenge doses

Seventeen percent of Xolair treated patients were not able to consume >100 mg of peanut protein without moderate to severe dose-limiting symptoms. Eighteen, 22, and 41 percent of Xolair-treated patients were not able to consume >300 mg of milk, egg, or cashew protein, respectively, without moderate to severe dose-limiting symptoms.

Additional secondary analyses included the percentage of patients who were able to consume at least two or all three foods during DBPCFC. For two foods, 71% of Xolair treated patients were able to consume a single dose of ≥600 mg versus 5% in the placebo group and 67% were able to consume a single dose of ≥1000 mg versus 4% in the placebo group. For a single dose of ≥600 mg of three foods, the response rates were 48% in the Xolair group versus 4% in the placebo group and for a single dose of ≥1000 mg of three foods, the response rate in the Xolair group was 39% while none of the placebo patients were able to consume the challenge dose without symptoms.

The effectiveness of Xolair in adults is supported by the adequate and well-controlled trial of Xolair in pediatric patients, disease similarity in pediatric and adult patients, and pharmacokinetic (PK) similarity.

While efficacy cannot be established from uncontrolled, open-label studies, for 38 pediatric patients who continued Xolair for 24-28 weeks in an open-label extension, the percentage of patients who were able to consume ≥600 mg of peanut protein and ≥1000 mg of egg, milk, and/or cashew protein without moderate to severe dose-limiting symptoms was maintained.

Summary of Evidence
For the treatment of asthma in adult and adolescent patients 12 years of age and older, the studies provided to the U.S. Food and Drug Administration (FDA) consists of three double-blinded, placebo-controlled multicenter clinical trials. The number of asthma exacerbations per patient was reduced in patients treated with Xolair compared with placebo in two of the three trials. The number of exacerbations in patients treated with Xolair in the third trial was similar to that in placebo-treated patients. The absence of an observed treatment effect may be related to differences in the patient populations, study sample size or other factors. There is support in the literature for the use of Xolair in patients with a baseline serum IgE level of <1500 IU/mL.

The studies provided to the FDA for Xolair for the treatment of children ages 6 to 12 years of age included one randomized, double-blind, placebo controlled, multi-center trial and an additional supportive study. Both studies showed fewer exacerbations of asthma than placebo.

For the treatment of chronic spontaneous urticaria in adult and adolescent patients 12 years of age and older, the studies provided to the FDA includes two placebo-controlled, multiple-dose clinical trials of 24 weeks and 12 weeks duration. In both trials patients receiving Xolair 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75-mg dose did not demonstrate consistent evidence of efficacy and is not approved for use.

For the treatment of nasal polyps in adults 18 years of age and older, the studies provided to the FDA include two, randomized, multicenter, double-blind, placebo-controlled trials of 24 weeks followed by a 4-week follow-up period. In both trials, Xolair showed statistically significant improvements in sense of smell score, post-nasal drip, and runny nose compared to placebo.

For the treatment of IgE-mediated food allergies in pediatric and adult patients at aged 1 year or older, the study provided to the FDA included a multi-center, randomized, double-blind, placebo-controlled trial consisting of 16 to 20 weeks of treatment. Everyone in the trial completed a double-blind placebo-controlled food challenge, and the first 60 patients (59 pediatric and one adult patient) could continue to receive Xolair in a 24 to 28 week open-label extension. Treatment with Xolair showed a statistically higher response rate for individuals who were able to consume ≥600 mg or peanut protein without dose-limiting symptoms than placebo (68% vs. 5%). Individuals who were able to consume ≥1000 mg of cashew, milk, or egg protein also had a statistically higher response rate than placebo for all three foods (cashew – 42% vs 3%; milk – 66% vs. 11%; egg – 67% vs 0%).

Based on the studies reviewed by the FDA for asthma and chronic spontaneous urticaria, as well as literature supporting the use of Xolair for allergic asthma in patients with baseline IgE levels <1500 IU/mL, Xolair may be considered medically necessary for adult and adolescent patients meeting the criteria outlined in this medical policy. Based on the studies reviewed by the FDA, Xolair may be considered medically necessary for adult patients ages 18 years and older with inadequate response to nasal corticosteroids as an add-on maintenance for the treatment of nasal polyps. Based on the study reviewed by the FDA, Xolair may be considered medically necessary for the reduction of allergic reactions to food when the individual has a diagnosis of IgE-mediated food allergy confirmed by an allergy diagnostic test (skin prick, serum specific IgE test) and the individual is at least 1 year of age or older.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J2357

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
04/15/2025	Document updated. The following change was made to Coverage: Added "The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage of a

	formulation that cannot be self-administered is considered not medically necessary unless the patient has a physical or cognitive limitation that makes the utilization of a self-administered formulation unsafe or otherwise not feasible, as demonstrated by BOTH of the following: Inability to self-administer the medication, AND lack of caregiver or support system for assistance with administration of self-administered products." No new references added.
08/15/2024	Document updated with literature review. Coverage revised to indicate Xolair may be considered medically necessary for the reduction of allergic reactions to food when the individual has a diagnosis of IgE-mediated food allergy confirmed by an allergy diagnostic test (e.g., skin prick test, serum specific IgE test); and is at least 1 year of age or older. Reference 2 updated.
05/15/2024	Document updated with literature review. The following changes were made to Coverage: 1) Modified conditional criteria related to the treatment of moderate to severe asthma; 2) Modified conditional criteria related to the treatment of chronic rhinosinusitis with nasal polyps; 3) Updated terminology for "chronic idiopathic urticaria" to "chronic spontaneous urticaria". Reference 2 updated.
06/01/2023	Document updated with literature review. The following change was made to Coverage: Modified conditional criteria related to the treatment of chronic idiopathic urticaria. No new references added; reference 2 updated.
06/15/2021	Document updated with literature review. The following change was made to Coverage: Modified conditional criteria related to the treatment of allergic asthma. No new references added.
02/15/2021	Document updated with literature review. Coverage revised to indicate Xolair may be considered medically necessary as add-on maintenance treatment, for nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids. References revised.
10/01/2020	Document updated with literature review. Coverage revised to remove authorization limits for allergic asthma. Rationale revised. References revised and renumbered; some removed.
06/01/2019	Document updated with literature review. The following change was made to Coverage: Patient's baseline serum total IgE revised to a range of >30 IU/ml and <1500 IU/ml; exception for patients 6 years of age to <12 can have baseline total IgE up to 1300 IU/mL removed. References 15, 16, and 17 added.
10/15/2017	Reviewed. No changes.
08/01/2016	Document updated with revised age requirement for Xolair for allergic asthma per the Food and Drug Administration (FDA) label. Specific coverage criterion changed from 12 years of age and older, to 6 years of age and older.
04/15/2016	Document updated with literature review. Coverage unchanged.
10/01/2015	Reviewed. No changes.

10/15/2014	Document updated with literature review. Idiopathic urticaria was removed as an experimental, investigational and/or unproven indication and replaced with the following medically necessary coverage statement: "Xolair may be considered medically necessary for the treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria (urticaria lasting > 6 weeks) who remain symptomatic despite treatment with: 1) two or more H1 antihistamines, or 2) one H1 antihistamine and one or more of the following: H2 antihistamines, OR leukotriene modifiers. The NMN statement was clarified for allergic rhinitis to include the following: "clinical outcomes have not demonstrated Xolair as superior to established, less costly treatment options'. Experimental, investigational and/or unproven statement clarified to add the following indications: other allergies, acute bronchospasm, status asthmaticus and other forms of urticaria not addressed in the MN statement.
11/01/2012	Document updated with literature review. The following was added to criteria for coverage: "Body weight is 150 kg or less". The following was added to authorization limits: "Recertification will be authorized for 12 months and annually thereafter if the patient demonstrates documented reduction or discontinuation of oral or inhaled steroids". The following was added to the listing of experimental, investigational and unproven indications: "urticaria, eosinophilic gastroenteritis, and eosinophilic esophagitis."
02/15/2010	Medical document updated with literature review. Coverage unchanged. Medically necessary when meeting coverage criteria based on FDA approved indications and considered experimental, investigational and unproven for all other indications.
03/01/2009	Coverage Revised
02/01/2009	Coverage Revised
09/15/2007	Revised/Updated Entire Document
10/01/2004	New Medical Document