Drug Coverage Policy

Effective Date.....9/1/2024
Coverage Policy Number.....IP0487
Policy Title.....Xolair

Immunologicals – Xolair

- Xolair® (omalizumab subcutaneous injection - Genentech/Novartis)

INSTRUCTIONS FOR USE
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. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. 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.

Cigna Healthcare Coverage Policy

OVERVIEW

Xolair, an anti-immunoglobulin (Ig)E monoclonal antibody, is indicated for the following uses:[1]

- **Asthma,** in patients ≥ 6 years of age with moderate to severe persistent disease who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICSs). 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. It is also not indicated for the treatment of other allergic conditions.

- **Chronic idiopathic urticaria**, in patients ≥ 12 years of age who remain symptomatic despite H1 antihistamine treatment. Limitation of Use: Xolair is not indicated for the treatment of other forms of urticaria.
- **Chronic rhinosinusitis with nasal polyps** (CRSwNP), as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids.
- **IgE-mediated food allergy**, in patients ≥ 1 year of age, for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. Xolair is to be used in conjunction with food allergen avoidance. Limitation of Use: Xolair is not indicated for the emergency treatment of allergic reactions, including anaphylaxis.

Dosing of Xolair for the treatment of asthma or nasal polyps is based on body weight and the serum total IgE level measured before the start of treatment.[1] Dosing for these indications is only provided for patients with a pretreatment serum IgE level ≥ 30 IU/mL. Dosing of Xolair in patients with chronic idiopathic urticaria is not dependent on serum IgE level or body weight.

Clinical Efficacy

Timing of efficacy assessments varied by indication across the numerous pivotal studies in which Xolair demonstrated benefit. In the majority of the asthma trials, efficacy with Xolair was assessed as early as 16 weeks.[1-11] In chronic idiopathic urticaria, one of the studies included a 12-week double-blind treatment period, while the other was longer with 24 weeks of double-blind treatment.[12,13] Across both studies evaluating Xolair in nasal polyps, efficacy was evaluated at Week 24.[14] Patients continued treatment with intranasal corticosteroids throughout the study. In the pivotal study of Xolair for food allergy, patients were required to have a positive skin prick test response to a food and to have a positive IgE test to food.[15] Patients were provided with an epinephrine auto-injector throughout the study.

Guidelines

Asthma Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2023) proposes a step-wise approach to asthma treatment.[16] Xolair is listed as an option for add-on therapy in patients ≥ 6 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., patients with symptoms and/or exacerbations despite medium- or high-dose ICS/long-acting beta2-agonist [LABA] or who require maintenance oral corticosteroid). Allergy-driven symptoms and childhood-onset asthma may predict a good asthma response to Xolair.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[17,18] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

Chronic Urticaria Guidelines
Guidelines for the definition, classification, diagnosis, and management of urticaria have been published by the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/Asia Pacific Association of Allergy, Asthma and Clinical Immunology (2022).[19] The American Academy of Dermatology was involved in the development of these guidelines and endorses their recommendations. Chronic spontaneous urticaria is defined as the appearance of wheals, angioedema, or both for > 6 weeks due to known or unknown causes. Signs and symptoms may be present daily/almost daily or have an intermittent recurrent course. Second generation H1-antihistamines taken regularly are the recommended first-line treatment for all types of urticaria following elimination of possible underlying causes. If standard doses do not eliminate urticaria signs and symptoms, the dose of the antihistamine should be increased up to 4-fold. If symptoms persist following 2 to 4 weeks of antihistamine therapy, the addition of Xolair may be considered. For patients with refractory chronic urticaria, the addition of Xolair may be considered. Short courses of rescue systemic corticosteroids are recommended for treatment of patients with acute exacerbations of chronic urticaria. However, guidelines recommend against the long-term use of systemic steroids.

Chronic Rhinosinusitis with Nasal Polyps Guidelines
The Joint Task Force on Practice Parameters (JTFPP) published a focused guideline update for the medical management of CRSwNP (2023), which updated recommendations regarding intranasal corticosteroids and biologic therapies.[20] Intranasal corticosteroids are recommended for the treatment of CRSwNP. Use of biologics (e.g., Xolair) are also recommended. However, in patients who derived a sufficient benefit from other therapies such as intranasal corticosteroids, surgery, or aspirin therapy after desensitization, biologics may not be preferred. Conversely, biologics may be preferred over other medical treatment options in patients who continue to have a high burden of disease despite receiving at least 4 weeks of treatment with an intranasal corticosteroid.

The diagnosis of CRSwNP was not addressed in this focused guideline update. Previous guidelines have noted that the presence of two or more signs and symptoms of chronic rhinosinusitis (e.g., rhinorrhea, postnasal drainage, anosmia, nasal congestion, facial pain, headache, fever, cough, and purulent discharge) that persist for an extended period of time makes the diagnosis of chronic rhinosinusitis likely.[21-24] However, this requires confirmation of sinonasal inflammation, which can either be done via direct visualization or computed tomography (CT) scan. Oral corticosteroids and surgical intervention were not specifically addressed in this update. Prior guidelines recommend short courses of oral corticosteroid as needed and consideration of surgical removal as an adjunct to medical therapy in patients with CRSwNP that is not responsive or is poorly responsive to medical therapy.[21,22,24]

Medical Necessity Criteria

Xolair is considered medically necessary when ONE of the following is met (1, 2, 3, or 4):

FDA-Approved Indications

1) Asthma. Approve Xolair for the duration noted if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
  - **i.** Patient is ≥ 6 years of age; AND

ii. Patient has a history of ONE of the following (a or b):
- **a)** Patient meets BOTH of the following (1 and 2):
  - **(1)** Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; AND
    Note: The reduced FEV_1 should not be due to smoking-related chronic obstructive pulmonary disease.
  - **(2)** Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
- **b)** Patient meets ONE of the following (1, 2, 3, 4, or 5)
  - **(1)** Increase of > 12% and > 200ml in FEV_1 following administration of a standard dose of a short-acting bronchodilator; OR
  - **(2)** Increase of > 12% and > 200ml in FEV_1 between prescriber visits; OR
  - **(3)** Increase of > 12% and > 200ml in FEV_1 from baseline to after at least 4 weeks of asthma treatment; OR
  - **(4)** Positive exercise challenge testing; OR
  - **(5)** Positive bronchial challenge testing; AND

Note: Patients 6 to 11 years of age would only be required to have an increase of > 12% in FEV_1 in each of the respective criteria above (i.e., they would not be required to have an increase > 200 mL)
Note: The above lung function criteria may be met at anytime prior to or during asthma treatment.

iii. Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
Note: "Baseline" is defined as prior to receiving any treatment with Xolair or another monoclonal antibody therapy that may lower IgE levels (e.g., Dupixent [dupilumab subcutaneous injection], Tezspire [tezepelumab-ekko subcutaneous injection]).

iv. Patient has a baseline positive skin test or *in vitro* test (i.e., a blood test) for allergen-specific immunoglobulin E (IgE) for one or more perennial aeroallergens and/or for one or more seasonal aeroallergens; AND
Note: "Baseline" is defined as prior to receiving any Xolair or another monoclonal antibody therapy that may interfere with allergen testing (e.g., Dupixent and Tezspire). Examples of perennial aeroallergens are house dust mite, animal dander, cockroach, feathers, and mold spores. Examples of seasonal aeroallergens are grass, pollen, and weeds.

v. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
- **a)** An inhaled medium- or high-dose corticosteroid; AND
- **b)** At least one additional asthma controller or asthma maintenance medication; AND
  Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting $beta_2$-agonists, inhaled long-acting muscarinic antagonists, , and monoclonal antibody therapies for asthma (e.g., Xolair, Cinqair [reslizumab intravenous infusion], Dupixent, Fasenra [benralizumab subcutaneous injection], Nucala [mepolizumab subcutaneous injection], and Tezspire). Use of a combination inhaler containing both a medium- or high-dose inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.

vi. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, or c):
Note: "Baseline" is defined as prior to receiving Xolair or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Cinqair, Dupixent, Fasenra, Nucala, Tezspire, and Xolair.
- **a)** Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
- **b)** Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR

c) Patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND

vii. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Xolair. Approve Xolair for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has already received at least 4 months of therapy with Xolair; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with Xolair should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Xolair therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department/urgent care, or medical clinic visits due to asthma; decreased reliever/rescue medication use; and improved lung function parameters.

Dosing. Approve up to a maximum dose of 375 mg administered subcutaneously not more frequently than once every 2 weeks.

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2) Chronic Idiopathic Urticaria (Chronic Spontaneous Urticaria). Approve Xolair for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 12 years of age; AND

ii. Patient has/had urticaria for > 6 weeks (prior to treatment with Xolair), with symptoms present > 3 days per week despite daily non-sedating H_1 antihistamine therapy with doses that have been titrated up to a maximum of four times the standard FDA-approved dose; AND
Note: Examples of non-sedating H_1 antihistamine therapy are cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine.

iii. The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

B) Patient is Currently Receiving Xolair. Approve Xolair for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has already received at least 4 months of therapy with Xolair; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with Xolair should be considered under criterion 2A (Chronic Idiopathic Urticaria, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Xolair therapy are decreased severity of itching, decreased number and/or size of hives.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 150 mg administered subcutaneously once every 4 weeks; OR

B) 300 mg administered subcutaneously once every 4 weeks.

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3) Chronic Rhinosinusitis with Nasal Polyps. Approve Xolair for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):

i. Patient is ≥ 18 years of age; AND
ii. Patient has chronic rhinosinusitis with nasal polyps as evidenced by direct examination, endoscopy, or sinus computed tomography (CT) scan; AND
iii. Patient has experienced two or more of the following symptoms for at least 6 months: nasal congestion, nasal obstruction, nasal discharge, and/or reduction/loss of smell; AND
iv. Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
Note: "Baseline" is defined as prior to receiving any treatment with Xolair or another monoclonal antibody therapy that may lower IgE levels (e.g., Dupixent [dupilumab subcutaneous injection], Tezspire [tezepelumab-ekko subcutaneous injection]).
v. Patient meets BOTH of the following (a and b):
a) Patient has received at least 4 weeks of therapy with an intranasal corticosteroid; AND
b) Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Xolair; AND
vi. Patient meets ONE of the following (a, b, or c):
a) Patient has received at least one course of treatment with a systemic corticosteroid for 5 days or more within the previous 2 years; OR
b) Patient has a contraindication to systemic corticosteroid therapy; OR
c) Patient has had prior surgery for nasal polyps; AND
vii. The medication is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose, and throat [ENT] physician specialist).

B) Patient is currently receiving Xolair. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient has already received at least 6 months of therapy with Xolair; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Xolair should be considered under criterion 3A (Nasal Polyps, Initial Therapy).
ii. Patient continues to receive therapy with an intranasal corticosteroid; AND
iii. Patient has responded to Xolair therapy as determined by the prescriber.
Note: Examples of a response to Xolair therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, and/or improved sense of smell.

Dosing. Approve up to a maximum dose of 600 mg administered subcutaneously not more frequently than once every 2 weeks.

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4) Immunoglobulin (Ig)E-Mediated Food Allergy. Approve Xolair for 1 year if the patient meets ALL of the following (A, B, C, D, E, F, and G):
A) Patient is ≥ 1 year of age; AND
B) Patient has a baseline immunoglobulin (Ig)E level ≥ 30 IU/mL; AND
Note: "Baseline" is defined as prior to receiving any treatment with Xolair or another monoclonal antibody therapy that may lower IgE levels (e.g., Dupixent [dupilumab subcutaneous injection], Tezspire [tezepelumab-ekko subcutaneous injection]).
C) Patient meets BOTH of the following (i and ii):
i. Patient has a positive skin prick test (SPT) response to one or more foods; AND
ii. Patient has a positive *in vitro* test (i.e., a blood test) for IgE to one or more foods; AND
D) According to the prescriber, the patient has a history of an allergic reaction to a food that met each of the following (i, ii, and iii):
i. Patient demonstrated signs and symptoms of a significant systemic allergic reaction; AND
Note: Signs and symptoms of a significant systemic allergic reaction include hives, swelling, wheezing, hypotension, and gastrointestinal symptoms.

ii. This reaction occurred within a short period of time following a known ingestion of the food; AND

iii. The prescriber deemed this reaction significant enough to require a prescription for an epinephrine auto-injector; AND
Note: Examples of epinephrine auto-injectors include EpiPen, EpiPen Jr., Auvi-Q, and generic epinephrine auto-injectors.

E) Patient has been prescribed an epinephrine auto-injector; AND
Note: Examples of epinephrine auto-injectors include EpiPen, EpiPen Jr., Auvi-Q, and generic epinephrine auto-injectors.

F) According the prescriber, Xolair will be used in conjunction with a food allergen-avoidant diet; AND

G) The medication is prescribed by or in consultation with an allergist or immunologist.

Dosing. Approve up to a maximum dose of 600 mg administered subcutaneously not more frequently than once every 2 weeks.

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.

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

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Atopic Dermatitis.** One single-center, double-blind, placebo-controlled trial, Atopic Dermatitis Anti-IgE Pediatric Trial (ADAPT) evaluated the efficacy of Xolair in patients 4 to 19 years of age with severe atopic dermatitis (n = 62).[25] After 24 weeks of therapy, the difference in the objective Scoring Atopic Dermatitis [SCORAD] index with Xolair vs. placebo was -6.9 (P = 0.01). This was statistically significant; however, the clinical significance is unknown. Quality of life measurements were also improved with Xolair. Smaller studies have not shown benefit and case studies have yielded mixed results.[25-27] Additional larger, well-designed clinical trials are needed to determine if Xolair has a role in the treatment of atopic dermatitis. Atopic dermatitis guidelines from the American Academy Dermatology (2023) note that there are insufficient data to make a recommendation regarding the use of Xolair.[28]

2. **Concurrent use of Xolair with another Monoclonal Antibody Therapy.** The efficacy and safety of Xolair used in combination with other monoclonal antibody therapies have not been established. There are very limited case reports describing the combined use of Nucala and Xolair for severe asthma as well as off-label indications.[29-32] One limited case series also reported the use of Xolair and Dupixent in patients with asthma or chronic idiopathic urticaria.[33] Further investigation is warranted.
Note: Monoclonal antibody therapies are Adbry® (tralokinumab-ldrm subcutaneous injection), Cinqair® (reslizumab intravenous infusion), Dupixent® (dupilumab subcutaneous injection), Fasenra® (benralizumab subcutaneous injection), Nucala® (mepolizumab subcutaneous injection), or Teszpire® (tezepelumab-ekko subcutaneous injection).

3. **Eosinophilic Gastroenteritis, Eosinophilic Esophagitis, or Eosinophilic Colitis.** There are limited and conflicting data from very small studies and case series on the use of Xolair for the treatment of eosinophilic gastrointestinal conditions.[34-37] Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) recommend against the use of Xolair in patients with this condition.[38]

4. **Latex Allergy in Health Care Workers with Occupational Latex Allergy.** A small European study assessed the effects of Xolair treatment in health care workers (n = 18) with occupational latex allergy.[39] Xolair use in these patients resulted in a reduction in mean conjunctival challenge test scores as compared with placebo-treated patients after 16-weeks of therapy. Also, three patients who did not respond to Xolair treatment during the double-blind phase responded during the 16-week open-label phase. Thus, the overall ocular response rate for all patients in the open-label phase was 93.8% (n = 15/16). Also 11 of 15 patients in the open-label phase had a negative response to a latex glove challenge test (4 patients had a mild response). Well-controlled trials are needed.

Coding Information

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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Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** policy title from Omalizumab to Immunologicals – Xolair. **Asthma:** Updated diagnostic criteria requirements for confirmation of asthma. Updated initial authorization duration from 12 months to 4 months. **Chronic Idiopathic Urticaria (Chronic Spontaneous Urticaria):** Updated non-sedating H1 antihistamine requirements to add "with symptoms present > 3 days per week" and removed duration of "for at least 2 weeks, unless contraindicated or intolerant". Updated initial authorization duration from 12 months to 4 months. **Chronic Rhinosinusitis with Nasal Polyps:** Approval condition updated from "Nasal Polyps" to "Chronic Rhinosinusitis with Nasal Polyps". Duration of the intranasal corticosteroid requirement was changed from 3 months to 4 weeks. Updated initial authorization duration from 12 months to 6 months. **IgE-Mediated Food Allergy:** New approval criteria for this indication were added. **Conditions Not Recommended for Approval:** "Peanut and Other Food Allergies" was removed as a Condition Not Recommended for Approval.	9/1/2024

The policy effective date is in force until updated or retired.