PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Xolair Prior Authorization Policy
- Xolair® (omalizumab injection for subcutaneous use – Genentech/Novartis)

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OVERVIEW

Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody that is indicated in the following conditions:[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.
- **Nasal polyps**, as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids.

Dosing of Xolair for the treatment of asthma or nasal polyps is based on body weight and the serum total immunoglobulin E (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

Asthma Clinical Efficacy

In general, the pivotal studies in which Xolair demonstrated its efficacy for the treatment of asthma included patients with moderate to severe allergic asthma who had a positive skin test to perennial aeroallergens.[1-11] Patients also had a baseline IgE level between 30 and 700 IU/mL and were experiencing asthma symptoms despite ICS therapy (with or without a second controller such as an inhaled long-acting beta$_2$-agonist [LABA]). There are data to support the use of Xolair in patients ≥ 6 years of age. In the majority of the Xolair trials, efficacy was assessed as early as 16 weeks.

Chronic Idiopathic Urticaria Clinical Efficacy

Efficacy and safety of Xolair in the treatment of chronic idiopathic urticaria was established in two pivotal studies in patients 12 to 75 years of age who had symptomatic chronic idiopathic urticaria despite having used an H1-receptor antagonist for ≥ 2 weeks.[1,12,13] Chronic idiopathic urticaria was defined as a patient having hives, angioedema, or both that recur for > 6 weeks and have no apparent external trigger. One of the studies included a 12-week double-blind treatment period, while the other was longer with 24 weeks of double-blind treatment.

Nasal Polyps Clinical Efficacy

Two pivotal studies evaluated the efficacy of Xolair in patients ≥ 18 years of age with persistent bilateral nasal polyps, despite treatment with intranasal corticosteroids.[1,14] Patients were also required to have nasal congestion, impaired health-related quality of life, and a serum IgE level between 30 IU/mL and 1,500 IU/mL. There was no requirement for prior systemic corticosteroid treatment or prior surgery. However, 60% of patients had previously undergone nasal polyp surgery and 22% of patients reported use of a systemic corticosteroid in the previous year. Patients continued treatment with intranasal corticosteroids throughout the study. Across both studies, efficacy was evaluated at Week 24.

Guidelines

Asthma Guidelines

The Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2020) proposes a step-wise approach to asthma treatment.[15] Xolair is listed as an option for add-on therapy in patients ≥ 6 years of age with moderate or severe allergic asthma that is uncontrolled by medium- to high-dose ICS/LABA therapy.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014), 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.[16] 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: FEV1 80% predicted after appropriate bronchodilator withholding.

Chronic Urticaria Guidelines

A Joint Practice Parameter from the American Academy of Allergy, Asthma, & Immunology (AAAAI); the American College of Allergy, Asthma, & Immunology (ACAAI); and the Joint Council of Allergy, Asthma, & Immunology (JCAAI) [2014] and guideline from the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA[2]LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) [2018] define chronic urticaria as urticaria that has been continuously or intermittently present for at least 6 weeks.[17,18] Continuous therapy with antihistamines (second generation H1-antagonists) is generally recommended as first-line pharmacologic treatment for urticaria following trigger avoidance. If symptoms persist following 2 to 4 weeks of initial therapy, the dose of the second generation H1-antagonist should be increased to up to 4-fold. For patients with refractory chronic urticaria, the addition of Xolair may be considered.

Nasal Polyp Guidelines

A 2014 Joint Practice Parameter on the Diagnosis and Management of Rhinosinusitis and a 2008 (evidence update in 2017) Joint Practice Parameter for the Management of Rhinitis recommend nasal corticosteroids be used in patients with chronic rhinosinusitis with nasal polyps, as they decrease nasal polyp size, prevent regrowth of nasal polyps following surgical removal, and improve nasal symptoms.[19-21] Short courses of oral corticosteroids are also recommended. Endoscopic surgical intervention may be considered as an adjunct to medical therapy in patients with chronic rhinosinusitis that is not responsive or is poorly responsive to medical therapy. The parameter lists Xolair as a therapy that may be considered for the treatment of nasal polyps based on the limited data available at the time of publication. A 2015 Clinical

Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology (AAO) makes similar recommendations, stating that clinicians should recommend saline nasal irrigation, topical nasal corticosteroids, or both for symptom relief in patients with chronic rhinosinusitis (with or without nasal polyps).[22] The AAO guidelines do not address Xolair.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xolair. All approvals are provided for the duration listed below. In cases where approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xolair, as well as the monitoring required for adverse events and long-term efficacy, approval requires Xolair to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xolair is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Asthma.** Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
       Note: "Baseline" is defined as prior to receiving any Xolair or anti-interleukin 4/13 therapy (i.e., Dupixent® [dupilumab subcutaneous injection]).
     - **iii.** 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 anti-interleukin 4/13 therapy (i.e. Dupixent). Examples of perennial aeroallergens are house dust mite, animal dander, cockroach, feathers, and mold spores. Examples of seasonal aeroallergens are grass, pollen, and weeds.
     - **iv.** Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
       - **a)** An inhaled corticosteroid; AND
       - **b)** At least one additional asthma controller/maintenance medication; AND
         Note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-IL-4/13 therapy (i.e., Dupixent® [dupilumab subcutaneous injection]) used concomitantly with an inhaled corticosteroid for at least 3 consecutive months. Examples of additional asthma controller/maintenance medications are inhaled long-acting $beta_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and theophylline. Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.

v. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):
- **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 requiring hospitalization or an Emergency Department visit in the previous year; OR
- **c)** Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
- **d)** Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
- **e)** Patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND
  Note: "Baseline" is defined as prior to receiving any Xolair or anti-interleukin 4/13 therapy (i.e. Dupixent® [dupilumab subcutaneous injection]).

vi. 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 the following criteria (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.

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

A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (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. Approve Xolair for 1 year if the patient meets the following criteria (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.

3. **Nasal Polyps.** Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
       Note: "Baseline" is defined as prior to receiving any Xolair or anti-interleukin 4/13 therapy (i.e., Dupixent® [dupilumab subcutaneous injection]).
     - **iii.** Patient is experiencing significant rhinosinusitis symptoms such as nasal obstruction, rhinorrhea, or reduction/loss of smell according to the prescriber; AND
     - **iv.** Patient is currently receiving therapy with an intranasal corticosteroid; AND
     - **v.** Patient meets ONE of the following (a or b):
       - **a)** Patient has received treatment with a systemic corticosteroid for chronic rhinosinusitis with nasal polyps within the previous 2 years or has a contraindication to systemic corticosteroid therapy; OR
       - **b)** Patient has had prior surgery for nasal polyps; AND
     - **vi.** 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 the following criteria (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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xolair is not recommended in the following situations:

1. **Atopic Dermatitis.** There have been several case series/reports and two small randomized, double-blind, placebo-controlled pilot studies evaluating the efficacy and safety of Xolair for the treatment of patients with atopic dermatitis.[23,24] Efficacy data have been mixed. One systematic review and meta-analysis reported that of the studies reviewed (n = 103 patients total), 43% of patients achieved an excellent clinical response with Xolair, while 27.2% of patients had satisfying results and another 30.1% had no clinical change or worsening of their disease. However, these data are difficult to interpret due to the very small sample sizes in each case series/report and the non-controlled, non-randomized design of the majority of the available studies. 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 (AAD) [2014] note that data are limited to determine if Xolair is efficacious.[25] These guidelines do not make a recommendation regarding Xolair use in this patient population. European consensus guidelines for the treatment of atopic dermatitis (2018) from multiple European dermatology associations, including the European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), and the European Academy of Allergy and Clinical Immunology (EAACI) also note the mixed data and state that they cannot recommend Xolair for the treatment of atopic dermatitis.[26] There is currently one randomized, double-

blind, placebo controlled study evaluating Xolair for the treatment of pediatric AD (Atopic Dermatitis Anti-IgE Paediatric Trial [ADAPT]).[27] This trial is ongoing and results are not yet available.

2. **Concurrent use of Xolair with an Anti-Interleukin (IL) Monoclonal Antibody.** The efficacy and safety of Xolair used in combination with IL antagonist monoclonal antibodies (e.g., Cinqair® [reslizumab injection for intravenous use], Fasenra™ [benralizumab injection for subcutaneous use], Nucala® [mepolizumab injection for subcutaneous use], Dupixent® [dupilumab subcutaneous injection]) 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.[28-30] Further investigation is warranted.

3. **Eosinophilic Gastroenteritis, Eosinophilic Esophagitis, or Eosinophilic Colitis.** There are limited and conflicting data on the use of Xolair for the treatment of eosinophilic gastrointestinal conditions. In a case series evaluating patients with eosinophil-associated gastrointestinal disorders, Xolair was effective in decreasing absolute eosinophil count, allergen skin test wheal and erythema responses, and symptom scores.[31] Subsequently, a small (n = 15), open-label, single-arm, unblinded study (published) evaluated Xolair for the treatment of patients 12 to 75 years of age with eosinophilic esophagitis.[32] Following 12 weeks of Xolair therapy, tissue IgE levels were significantly reduced in 13 of the 15 patients, with full remission (defined as histologic and clinical improvement) present in 33% of patients. Conversely, a prospective, randomized, double-blind, placebo-controlled trial (n = 30) also examined the effects of Xolair in patients 12 to 60 years of age with eosinophilic esophagitis who were either refractory to or relapsed after a trial of topical corticosteroids.[33] Patients received either Xolair or placebo every 2 to 4 weeks for 16 weeks. Xolair therapy was not found to improve symptoms (dysphagia scores) or eosinophil counts in biopsy samples when compared with placebo. An additional case series including two patients with multiple food allergies and eosinophilic esophagitis reported an improvement in patient symptoms with Xolair therapy, but did not find an improvement in esophageal endoscopy and histology in short-term follow-up.[34] The 2013 American College of Gastroenterology guidelines for the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis do not recommend Xolair therapy for these conditions; the guidelines note that Xolair was ineffective in a case series involving two patients (referenced above).[35,36] It is recognized that corticosteroids (systemic or topical administered by swallowing a formulation for inhalation) are the standard treatment for management of both eosinophilic gastroenteritis and eosinophilic esophagitis. Adequate controlled clinical studies have not been conducted in patients less than 12 years of age with eosinophilic gastroenteritis, eosinophilic esophagitis, or eosinophilic colitis. A 2014 updated food allergy practice parameter from the AAAAI, ACAAI, and JCAAI Joint Task Force also addresses these conditions, but does not address Xolair as a treatment for these conditions.[37]

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.[38] 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.

5. **Peanut and Other Food Allergies.** Limited data are available regarding the use of Xolair to facilitate desensitization to food allergens. A Phase II multicenter clinical trial was initiated using Xolair in patients with peanut allergy; however, it was discontinued prematurely due to concerns regarding the safety of the oral peanut challenges in some patients.[39] Insufficient data were obtained to reach any conclusions about the efficacy of Xolair. Data are also available from a small pilot study examining

the use of Xolair to facilitate rapid oral desensitization in high-risk peanut-allergic patients.[40] There are also minimal data (a Phase I study and a case series) on the use of Xolair to facilitate desensitization in patients with severe cow's milk allergy.[41-44] Additionally, a Phase I study and a Phase II study have evaluated the use of Xolair to facilitate desensitization in patients with multiple food allergies.[45,46] Guidelines for the diagnosis and management of food allergy in the US from the National Institute of Allergy and Infectious Diseases (NIAID) [2010] indicate there are currently no medications recommended to prevent IgE-mediated or non-IgE-mediated food-induced allergic reactions from occurring in an individual with existing food allergies.[47] Allergen avoidance and use of antihistamines are recommended for treatment of food-induced allergic reactions. The updated food allergy practice parameter from the AAAAI, ACAAI, and JCAAI Joint Task Force (2014) also states that immunotherapies (such as the oral immunotherapy desensitization described above) show promise for the treatment of food allergy; however, there is currently inadequate evidence that the therapeutic benefit outweighs the risk.[37] Trials of these have been uncontrolled, small studies, which are subject to selection bias and uncertain safety profiles. However, treatment with anti-IgE monoclonal antibodies might increase the threshold for doses needed to stimulate an allergic reaction and potentially may enhance the safety profile for patients. Additional well-controlled trials are needed.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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