

**POLICY:** Immunologicals – Xolair® (omalizumab injection for subcutaneous [SC] use Genentech/Novartis)

**EFFECTIVE DATE:** 01/01/2021

**LAST REVISION DATE:** 03/22/2023

**COVERAGE CRITERIA FOR:** UCare Medicaid and Exchange Plans Only (PMAP, Connect, MSC+, MnCare, all Individual and Family Plans)

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## OVERVIEW

Xolair, an anti-immunoglobulin E (IgE) monoclonal antibody, is indicated for the following uses:<sup>1</sup>

- **Asthma**, in patients  $\geq 6$  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  $\geq 12$  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  $\geq 18$  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 IgE level measured before the start of treatment.<sup>1</sup> Dosing for these indications is only provided for patients with a pretreatment serum IgE level  $\geq 30$  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.<sup>1-11</sup> 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.<sup>12,13</sup> Across both studies evaluating Xolair in nasal polyps, efficacy was evaluated at Week 24.<sup>14</sup> Patients continued treatment with intranasal corticosteroids throughout the study.

## Guidelines

### *Asthma Guidelines*

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2022) proposes a step-wise approach to asthma treatment.<sup>15</sup> Xolair is listed as an option for add-on therapy in patients  $\geq 6$  years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with medium- to high-dose ICS/formoterol [as both maintenance and reliever therapy] or medium- to high-dose ICS/long-acting beta<sub>2</sub>-agonist [LABA] combination therapy with an as needed short-acting beta<sub>2</sub>-agonist reliever, with or without an additional controller). Higher blood eosinophil levels, elevated

fractional exhaled nitric oxide, 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.<sup>16,17</sup> 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  $\geq 1.5$  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<sub>1</sub>)  $< 80\%$  predicted after appropriate bronchodilator withholding.

### *Chronic Urticaria Guidelines*

A Practice Parameter on the Diagnosis and Management of Acute and Chronic Urticaria (2014) from the Joint Task Force on Practice Parameters (JTFPP) and guideline from the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (2018) define chronic urticaria as urticaria that has been continuously or intermittently present for at least 6 weeks.<sup>18,19</sup> 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 Practice Parameter on the Diagnosis and Management of Rhinosinusitis (2014) and a Practice Parameter for the Management of Rhinitis from the JTFPP (2020), and a 2015 Clinical Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology (AAO), make similar recommendations regarding the diagnosis and management of chronic rhinosinusitis with nasal polyposis (CRSwNP).<sup>20,22-24</sup> 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 CRS likely. However, this requires confirmation of sinonasal inflammation, which can either be done via direct visualization or computed tomography scan. Nasal corticosteroids are recommended for the management of CRSwNP, as they decrease nasal polyp size, prevent regrowth of nasal polyps following surgical removal, and improve nasal symptoms. 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 JTFPP 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. The AAO guidelines do not address Xolair.

The European Forum for Research and Education in Allergy expert board on uncontrolled severe CRSwNP and biologics (2021) recommends that these agents, including Xolair, only be used for severe uncontrolled CRSwNP when Type 2 inflammation is present.<sup>49</sup> Severe CRSwNP is defined as bilateral CRSwNP with a nasal polyp score  $\geq 4$  and persistent symptoms (e.g., loss of smell/taste, nasal obstruction, secretion or postnasal drip, facial pain or pressure) with the need for add-on treatment to supplement intranasal

corticosteroids. Severe CRSwNP is considered to be uncontrolled if the patient has received continuous treatment with an intranasal corticosteroid and has needed at least one course of systemic corticosteroids in the previous 2 years (or has a medical contraindication or intolerance) and/or has a previous sinonasal surgery.

## POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Xolair. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the durations noted below. In cases where the 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, initial 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  $\geq 6$  years of age; AND

**ii.** Patient has a baseline immunoglobulin E (IgE) level  $\geq 30$  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]).

**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 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.

**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 or asthma maintenance medication; AND

Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta<sub>2</sub>-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor 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 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):

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 a forced expiratory volume in 1 second (FEV<sub>1</sub>) < 80% predicted; OR
  - d) Patient has an FEV<sub>1</sub>/forced vital capacity (FVC) < 0.80; OR
  - e) Patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND
- 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.

**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 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<sub>1</sub> 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<sub>1</sub> 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 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.

**Dosing.** Approve 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. **Nasal Polyps.** Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):

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

- 2. Patient is  $\geq 18$  years of age; AND

- 3. Patient has chronic rhinosinusitis with nasal polyposis as evidenced by direct examination, endoscopy, or sinus computed tomography (CT) scan; AND

- 4. 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

- 5. Patient has a baseline immunoglobulin E (IgE) level  $\geq 30$  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]).

- 6. Patient meets BOTH of the following (a and b):

- 7. Patient has received at least 3 months of therapy with an intranasal corticosteroid; AND

- 8. Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Xolair; AND

- 9. Patient meets ONE of the following (a, b, or c):

- 10. Patient has received at least one course of treatment with a systemic corticosteroid for 5 days or more within the previous 2 years; OR

- 11. Patient has a contraindication to systemic corticosteroid therapy; OR

- 12. Patient has had prior surgery for nasal polyps; AND

- 13. The medication is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT] physician specialist).

- 14. Patient is currently receiving Xolair. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

- 15. 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).

- 16. Patient continues to receive therapy with an intranasal corticosteroid; AND

- 17. 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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### Conditions Not Recommended for Approval

Coverage of Xolair is not recommended in the following situations:

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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).<sup>25</sup> 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.<sup>25-27</sup> 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 (2014) note that data are limited to determine if Xolair is efficacious.<sup>28</sup> These guidelines do not make a recommendation regarding Xolair use in this patient population. European consensus guidelines for the treatment of atopic dermatitis (2018) also note the mixed data and state that they cannot recommend Xolair for the treatment of atopic dermatitis.<sup>29</sup>
2. **Concurrent use of Xolair with another Monoclonal Antibody Therapy (i.e., Cinqair, Fasenra, Dupixent, Nucala, Tezspire, or Adbry).** The efficacy and safety of Xolair used in combination with other monoclonal antibody therapies (e.g., Cinqair, Fasenra, Nucala, Dupixent, Adbry, Tezspire) 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.<sup>21,30-32</sup> Further investigation is warranted.
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.<sup>33-36</sup> 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.<sup>37</sup>
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.<sup>38</sup> 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.<sup>39</sup> Insufficient data were obtained to reach any conclusions about the efficacy of Xolair. Data are also available from a Phase II study using Xolair as pretreatment in patients receiving multi-food oral immunotherapy, as well as a small pilot study examining the use of Xolair to facilitate rapid oral desensitization in high-risk peanut-allergic patients.<sup>40,51</sup> 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.<sup>41-44</sup> 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.<sup>45,46</sup> Guidelines for the diagnosis and management of food allergy in the US from the National Institute of Allergy and Infectious Diseases (2010; 2017 addendum) 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.<sup>47</sup> The Practice Parameter on Food Allergy from the JTFPP (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.<sup>48</sup> 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. A food allergy management guideline from the Global Allergy and Asthma European Network (2022) specifically states that no recommendation can be made for or against the use of Xolair for the treatment of food allergy due to insufficient evidence.<sup>50</sup> 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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## HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/16/2022
Selected Revision	<p><b>Asthma:</b> Notes were updated to include Tezspire as an example of a monoclonal antibody therapy that may lower immunoglobulin E (IgE) levels and interfere with allergen testing. Notes were also updated to include Xolair, Cinqair, Fasenra, Nucala, and Tezspire as examples of monoclonal antibody therapies for asthma. Criteria requiring the patient to have experienced one or more asthma exacerbation(s) requiring a hospitalization or an emergency department visit in the previous year, were updated to include an urgent care visit as well.</p> <p><b>Nasal Polyps:</b> Notes were updated to include Tezspire as an example of a monoclonal antibody therapy that may lower immunoglobulin E (IgE) levels and interfere with allergen testing.</p> <p><b>Conditions Not Recommended for Approval:</b> Criteria were updated to recommend against use of Xolair with another monoclonal antibody therapy. Previously, criteria listed anti-interleukin monoclonal antibody therapies specifically.</p>	07/20/2022
Annual Revision	<p><b>Conditions Not Recommended for Approval:</b> Criteria were updated to clarify that use of Xolair with another monoclonal antibody therapy is specific to Cinqair, Fasenra, Nucala, Dupixent, Tezspire, and Adbry.</p>	03/22/2023