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

DATE REVIEWED: 02/12/2020; selected revision 03/25/2020

OVERVIEW

Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody which selectively binds to human immunoglobulin E (IgE), thus inhibiting IgE from binding to the surface of mast cells and basophils (at the high-affinity IgE receptor [FcεRI]), and resulting in a decrease of mediators released in the allergic response.[1] Xolair treatment also reduces the number of FcεRI receptors on basophils in atopic patients. Xolair is indicated for use in patients ≥ 6 years of age with moderate to severe persistent asthma and 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 decreases the incidence of asthma exacerbations in these patients. Safety and efficacy of Xolair in pediatric patients with asthma aged < 6 years have not been established. Xolair is also indicated for the treatment of adults and adolescents (aged ≥ 12 years) with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment. In chronic idiopathic urticaria, Xolair binds to IgE and lowers free IgE levels; subsequently, FcεRI on cells down-regulate. How these effects of Xolair result in an improvement in chronic idiopathic urticaria is not known. Xolair is not indicated for the treatment of other allergic conditions, other forms of urticaria, for relief of acute bronchospasm, or status asthmaticus.

Guidelines

Asthma Guidelines

Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a step-wise approach to asthma treatment.[2] Patients with persistent symptoms or exacerbations despite a medium-dose ICS/long-acting $beta_2$-agonist (LABA) combination with or without an additional controller, GINA recommends referral of the patient to a specialist with expertise in the management of severe asthma for phenotypic assessment and add-on treatment. Xolair is listed as an option for add-on therapy in patients ≥ 6 years of age with moderate or severe allergic asthma. Blood eosinophil levels ≥ 260 cells per microliter, fractional exhaled nitric oxide (FeNO) ≥20 ppb, allergen-driven symptoms, and childhood-onset asthma may predict a good asthma response to Xolair.

The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014) for the definition, evaluation, and treatment of severe asthma suggest a trial of Xolair in both adults and children with severe allergic asthma.[3] If a trial of Xolair is considered, patients (adults and children ≥ 6 years of age) should have confirmed IgE-dependent allergic asthma that is uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance and their total serum IgE level should be ≥ 30 IU/mL and < 700 IU/mL. It is also noted that further administration of Xolair is unlikely to be beneficial if a patient does not respond to therapy within the first 4 months of treatment. The ERS/ATS guidelines also provide a definition of severe asthma. 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. Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control; frequent severe exacerbations; serious exacerbations; or airflow limitation. Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids.

Urticaria Guidelines

Urticaria guidelines 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] also stress the importance of identification and elimination of underlying causes and trigger avoidance followed by pharmacologic treatment to reduce release of mast cell mediators (e.g. histamine) and/or decrease the effect of these mast cell mediators at target organs.[4] Continuous therapy with antihistamines (second generation H_1-antagonists) is recommended as first-line treatment. If symptoms persist following 2 to 4 weeks of initial therapy, the dose of the second generation H_1-antagonist should be increased to up to 4-fold. If symptoms persist an additional 2 to 4 weeks despite the higher dosing, the addition of Xolair may be considered. Cyclosporine is referenced as an add-on therapy to Xolair if there is inadequate control or symptoms are intolerable within 6 months. Short courses of oral corticosteroids may also be considered if needed to control exacerbations. However, long-term use of systemic corticosteroids is not recommended.

In 2014, 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) published a Joint Task Force Practice Parameter on the diagnosis and management of acute and chronic urticaria.[5] This parameter recommends a four-step approach to treatment of chronic urticaria. Initially, trigger avoidance is indicated along with a second generation antihistamine (Step 1). Step 2 includes increasing the dose of the antihistamine; a 2- to 4-fold increase in the FDA-approved dose of the second-generation antihistamine may be effective to achieve symptom control in some patients. Additionally, adding a second non-sedating antihistamine, an H_2 antagonist, a leukotriene receptor antagonist (LTRA), or a first generation antihistamine to be taken at bedtime may also be beneficial. If the patient's urticarial remains poorly controlled, hydroxyzine or doxepin may be considered as part of Step 3 therapy. Patients with refractory chronic urticaria (Step 4) may consider other alternative therapies, such as Xolair and cyclosporine.

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 indication(s). 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). 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. 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.

RECOMMENDED AUTHORIZATION 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 Xolair 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.** Xolair is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND
     - **iii.** Patient has a baseline (prior to treatment with Xolair or anti-interleukin-4/13 therapy [Dupixent]) immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
     - **iv.** The patient has a baseline (prior to treatment with Xolair) 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: 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 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 (Dupixent) 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 a long-acting $beta_2$-agonist would fulfil the requirement for both criteria a and b.
     - **vi.** Patient's asthma is uncontrolled or was uncontrolled prior to receiving any Xolair or anti-IL-4/13 therapy (Dupixent) therapy as defined by ONE of the following (a, b, c, d, or e):
       - **a)** The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
       - **b)** The patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) 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)** The patient's asthma worsens upon tapering of oral corticosteroid therapy; OR
   - **B)** Patients Continuing Xolair Therapy. Approve Xolair for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** The patient has already received at least 4 months of therapy with Xolair; AND
       Note: Patients who have received < 4 months of therapy or those who are 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.** The 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 (ED)/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 (SC) 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 Xolair for 4 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** Xolair is prescribed by, or in consultation with, an allergist, immunologist, or dermatologist; AND
     - **iii.** 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; OR
       Note: Examples of non-sedating H_1 antihistamine therapy are cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine.
   - **B)** Patients Continuing Xolair Therapy. Approve Xolair for 1 year if the patient meets the following criteria (i and ii):
     - **i.** The patient has already received at least 4 months of therapy with Xolair; AND
       Note: Patients who have received < 4 months of therapy or those who are restarting therapy with Xolair should be considered under criterion 2A (Chronic Idiopathic Urticaria, Initial Therapy).
     - **ii.** The 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 (SC) once every 4 weeks; OR
- **B)** 300 mg administered subcutaneously (SC) once every 4 weeks.

Conditions Not Recommended for Approval

Xolair has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Atopic Dermatitis (AD).** 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 AD.[6,7] 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 AD. AD guidelines from the American Academy Dermatology (AAD) [2014] note that data are limited to determine if Xolair is efficacious in the treatment of AD.[8] These guidelines do not make a recommendation regarding Xolair use in this patient population. European consensus guidelines for the treatment of AD (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 AD[91] 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]).[10] This trial is ongoing and results are not yet available.

2. **Chronic Rhinosinusitis.** A small study assessed the effects of Xolair in patients (n = 14) with chronic rhinosinusitis.[11] The majority of patients had severe and refractory disease and presented with nasal polyposis; all had undergone endoscopic sinus surgery. After 6 months Xolair-treated patients showed reduced sinus inflammation (as determined by computed tomography [CT] imaging) while placebo-treated patients showed no change in inflammation; however, the net difference between groups was not statistically significant. A small, single arm study (n = 13) also demonstrated efficacy of Xolair in improving symptoms in patients with chronic rhinosinusitis with nasal polyps.[12] Further study is warranted. The 2015 Clinical Practice Guideline: Adult Sinusitis from the American Academy of Otolaryngology (AAO) does not mention Xolair or anti-IgE therapy in its recommendations.[13]

3. **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 very limited case reports describing the combination use of Nucala and Xolair for severe asthma as well as off-label indications.[14-16] Further investigation is warranted.

4. **Eosinophilic Gastroenteritis (EG), Eosinophilic Esophagitis (EE), 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.[17] 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 EE.[18] Following 12 weeks of Xolair therapy (dose calculated in mg/kg per IU IgE units/mL), 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 EE who were either refractory to or relapsed after a trial of topical corticosteroids.[18,19] Patients received either Xolair or placebo every 2 to 4 weeks for 16 weeks (dose of Xolair based on weight and serum IgE level). Xolair therapy was not found to improve the symptoms of EE (dysphagia scores) or eosinophil counts in biopsy samples when compared with placebo. An additional case series including two patients with multiple food allergies and EE 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.[20] The 2013 American College of Gastroenterology guidelines for the diagnosis and management of esophageal eosinophilia and EE do not recommend Xolair therapy for these conditions; the guidelines note that Xolair was ineffective in a case series involving two patients (referenced above). It is recognized that corticosteroids (systemic or topical administered by swallowing a formulation for inhalation) are the standard treatment for management of both EG and EE.[21,22] Adequate controlled clinical studies have not been conducted in patients less than 12 years of age with EG, EE, or eosinophilic colitis. A 2014 updated food allergy practice parameter from the AAAAI, ACAAI, and JCAAI Joint Task Force also addresses EE and EG, but does not address Xolair as a treatment for these conditions.[23]

5. **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.[24] 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.

6. **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.[37] 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.[25] There are also minimal data (a Phase I study and a case series) on the use of Xolair in patients with severe cow's milk allergy.[26-30] 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.[31,32] Guidelines for the diagnosis and management of food allergy in the US (published in 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.[33] 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.[22] 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.

7. 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	Date Reviewed
New policy	--	09/26/2018
Early annual revision	• Updated initial therapy criteria for "Asthma in Patients with Moderate to Severe Persistent Disease" to state that the baseline IgE level ≥ 30 IU/mL should be prior to treatment with Xolair or anti-IL-4/13 therapy (Dupixent). Previously criteria only noted the level should be prior to Xolair therapy. • Updated initial therapy criteria for "Asthma in Patients with Moderate to Severe Persistent Disease" to more concisely state the previous therapies required. Added the following: 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 (Dupixent) used concomitantly with an ICS for at least 3 consecutive months. • Updated initial therapy criteria for "Asthma in Patients with Moderate to Severe Persistent Disease" to state that the patient's asthma is uncontrolled or was uncontrolled prior to receiving any Xolair or anti-IL-4/13 therapy (Dupixent). Previously criteria only stated it should be uncontrolled prior to Xolair therapy. • Updated dosing for "Asthma in Patients with Moderate to Severe Persistent Disease" to remove information about dose being based on serum IgE and patient body weight. Updated to approve up to a maximum dose of 375 mg administered subcutaneously (SC) not more frequently than once every 2 weeks. • Updated dosing for "Chronic Idiopathic Urticaria" to specify to approve either 150 mg administered SC once every 4 weeks or 300 mg administered SC once every 4 weeks. • Updated dosing for "Allergic Rhinitis, Seasonal or Perennial" to approve up to a maximum dose of 300 mg administered SC not more frequently than once every 3 weeks. Removed previous requirements for weight-based and IgE-based dosing.	02/20/2019
Annual Revision	• Asthma: Approval indication was changed from "Asthma in Patients with Moderate to Severe Persistent Disease" to "Asthma". Removed examples of in vitro allergen-specific IgE tests: enzyme-linked immunoabsorbant assay (ImmunoCAP™, ELISA] or the radioallergosorbent test [RAST]). Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". Removed lists of examples of inhaled asthma controller/maintenance medications. • Chronic Idiopathic Urticaria: Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". • Allergic Rhinitis: Approval indication was changed from "Allergic Rhinitis, Seasonal or Perennial" to "Allergic Rhinitis". Updated requirement that patient have a positive skin test or in vitro test for allergen-specific IgE for "one or more relevant allergens" to "one or more perennial aeroallergens AND/OR for one or more seasonal aeroallergens" (previously criteria listed both perennial and aeroallergen examples as relevant allergens, updated wording to be consistent with Asthma approval criteria). Wording in reference to "second-generation/less-sedating antihistamines" was changed to "non-sedating H1 antihistamines". Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". Removed lists of examples of intranasal antihistamines and intranasal corticosteroids.	02/12/2020
Selected Revision	• Removed Allergic Rhinitis as an "Other Use with Supported Evidence"	03/25/2020

IgE – Immunoglobulin E; IL – Interleukin; SC – Subcutaneous.