# Xolair® (Omalizumab)

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Instructions for Use

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## Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

| State | Policy/Guideline |
|---|---|
| Florida | Refer to the state's Medicaid clinical policy |
| Indiana | Xolair® (Omalizumab) (for Indiana Only) |
| Kansas | Refer to the state's Medicaid clinical policy |
| Louisiana | Refer to the state's Medicaid clinical policy |
| North Carolina | None |
| Pennsylvania | Refer to the state's Medicaid clinical policy |
| Texas | Refer to drug specific criteria found within the Texas Medicaid Provider Procedures Manual |
| Washington | Refer to the state's Medicaid clinical policy |

## Coverage Rationale

This policy refers to Xolair® (omalizumab) subcutaneous injection for administration by a healthcare professional. Xolair® (omalizumab) for self-administered subcutaneous injection is obtained under the pharmacy benefit.

### Moderate to Severe Persistent Asthma

Xolair for provider administration is proven and medically necessary when all of the following criteria are met:

- Diagnosis of moderate or severe asthma; and
- Classification of asthma as uncontrolled or inadequately controlled as defined by at least one of the following:
  - Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20)
  - Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months
  - Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment)

- Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second [FEV1] less than 80% predicted [in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal])
- Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

and

- One of the following:
  - Baseline (pre-omalizumab treatment) serum total IgE level greater than or equal to 30 IU/mL and less than or equal to 1,300 IU/mL; or
  - Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

and

- Positive skin test or in vitro reactivity to a perennial aeroallergen; and
- Used in combination with one of the following:
  - One maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) product [e.g., Advair/AirDuo Respiclick (fluticasone propionate/salmeterol), Symbicort (budesonide/formoterol), Breo Ellipta (fluticasone furoate/vilanterol)]; or
  - Combination therapy including both of the following:
    - One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]; and
    - One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®); leukotriene receptor antagonist – montelukast (Singulair®); theophylline]

and

- Physician attestation that self-administration of the Xolair prefilled syringe by the patient or caregiver is not appropriate, based on careful assessment of risk for anaphylaxis and mitigation strategies. Documentation required to support one of the following:
  - Patient has a history of anaphylaxis (e.g., bronchospasm, hypotension, syncope, urticaria, angioedema) to Xolair or other agents, such as foods, drugs, biologics; or
  - Patient is new to therapy with Xolair and requires initial doses to be administered under the guidance of a healthcare provider with no hypersensitivity reactions before transitioning to self-administration (Note: Authorization will be for three doses); or
  - Patient's previous Xolair therapy was interrupted for at least 6 months and will need to be re-initiated under the guidance of a healthcare provider before transitioning to self-administration (Note: Authorization will be for three doses); or
  - Patient or caregiver is unable to recognize symptoms of anaphylaxis or treat anaphylaxis appropriately; or
  - Patient or caregiver is unable to perform subcutaneous injections with Xolair prefilled syringe with proper technique or adhere to the prescribed dosing regimen; or
  - The location and circumstances for self-administration are not adequate for the potential treatment of anaphylaxis should that arise

and

- Patient is not receiving Xolair in combination with any of the following:
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]; or
  - Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (resilizumab), Fasenra (benralizumab)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

and

- Xolair dosing for moderate to severe persistent asthma is in accordance with the United States Food and Drug Administration approved labeling; and
- Prescribed by allergist/immunologist or pulmonologist; and
- Initial authorization will be for no more than 6 months.

## *Reauthorization/Continuation of Care Criteria*

Xolair, for provider administration, for the treatment of moderate to severe persistent asthma, authorization for continued use will be approved based on all of the following criteria:

- Documentation of positive clinical response as demonstrated by at least one of the following:
  - Reduction in the frequency of exacerbations
  - Decreased utilization of rescue medications
  - Increase in percent predicted FEV1 from pretreatment baseline
  - Reduction in severity or frequency of asthma-related symptoms (e.g., wheezing, shortness of breath, coughing, etc.)

and

- Used in combination with an ICS-containing controller medication; and
- Physician attestation that self-administration of the Xolair prefilled syringe by the patient or caregiver is not appropriate, based on careful assessment of risk for anaphylaxis and mitigation strategies. Documentation required to support one of the following:
  - Patient has a history of anaphylaxis (e.g., bronchospasm, hypotension, syncope, urticaria, angioedema) to Xolair or other agents, such as foods, drugs, biologics; or
  - Patient or caregiver is unable to recognize symptoms of anaphylaxis or treat anaphylaxis appropriately; or
  - Patient or caregiver is unable to perform subcutaneous injections with Xolair prefilled syringe with proper technique or adhere to the prescribed dosing regimen; or
  - The location and circumstances for self-administration are not adequate for the potential treatment of anaphylaxis should that arise

  and
- Patient is not receiving Xolair in combination with any of the following:
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
  - Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (resilizumab), Fasenra (benralizumab)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  and
- Xolair dosing for moderate to severe persistent asthma is in accordance with the United States Food and Drug Administration approved labeling; and
- Reauthorization will be for no more than 12 months.

## Chronic Urticaria

Xolair for provider administration is proven and medically necessary when all of the following criteria are met:

- Diagnosis of chronic urticaria; and
- One of the following:
  - Patient remains symptomatic despite at least a 2-week trial of, or history of contraindication or intolerance to, two H1-antihistamines [e.g., Allegra (fexofenadine), Benadryl (diphenhydramine), Claritin (loratadine)]*; or
  - Patient remains symptomatic despite at least a 2-week trial of, or history of contraindication or intolerance to both of the following taken in combination:
    - A second generation H1-antihistamine [e.g., Allegra (fexofenadine), Claritin (loratadine), Zyrtec (cetirizine)]; and
    - One of the following:
      - Different second generation H1-antihistamine [e.g., Allegra (fexofenadine), Claritin (loratadine), Zyrtec (cetirizine)]
      - First generation H1-antihistamine [e.g., Benadryl (diphenhydramine), Chlor-Trimeton (chlorpheniramine), Vistaril (hydroxyzine)]*
      - H2-antihistamine [e.g., Pepcid (famotidine), Tagamet HB (cimetidine), Zantac (ranitidine)]
      - Leukotriene modifier [e.g., Singulair (montelukast)]

  and
- Physician attestation that self-administration of the Xolair prefilled syringe by the patient or caregiver is not appropriate, based on careful assessment of risk for anaphylaxis and mitigation strategies. Documentation required to support one of the following:
  - Patient has a history of anaphylaxis (e.g., bronchospasm, hypotension, syncope, urticaria, angioedema) to Xolair or other agents, such as foods, drugs, biologics; or
  - Patient is new to therapy with Xolair and requires initial doses to be administered under the guidance of a healthcare provider with no hypersensitivity reactions before transitioning to self-administration (Note: Authorization will be for three doses); or
  - Patient's previous Xolair therapy was interrupted for at least 6 months and will need to be re-initiated under the guidance of a healthcare provider before transitioning to self-administration (Note: Authorization will be for three doses); or
  - Patient or caregiver is unable to recognize symptoms of anaphylaxis or treat anaphylaxis appropriately; or
  - Patient or caregiver is unable to perform subcutaneous injections with Xolair prefilled syringe with proper technique or adhere to the prescribed dosing regimen; or
  - The location and circumstances for self-administration are not adequate for the potential treatment of anaphylaxis should that arise

and

- Patient is not receiving Xolair in combination with any of the following:
  - Anti-interleukin 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab)]
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]; and
- Xolair dosing for chronic urticaria is in accordance with the United States Food and Drug Administration approved labeling; and
- Prescribed by an allergist/immunologist or dermatologist; and
- Initial authorization will be for no more than 6 months.

### *Reauthorization/Continuation of Care Criteria*

Xolair, for provider administration, for the treatment of chronic urticaria, authorization for continued use will be approved based on all of the following criteria:

- Documentation of positive clinical response (e.g., reduction in exacerbations, itch severity, hives); and
- Physician attestation that self-administration of the Xolair prefilled syringe by the patient or caregiver is not appropriate, based on careful assessment of risk for anaphylaxis and mitigation strategies. Documentation required to support one of the following:
  - Patient has a history of anaphylaxis (e.g., bronchospasm, hypotension, syncope, urticaria, angioedema) to Xolair or other agents, such as foods, drugs, biologics; or
  - Patient or caregiver is unable to recognize symptoms of anaphylaxis or treat anaphylaxis appropriately; or
  - Patient or caregiver is unable to perform subcutaneous injections with Xolair prefilled syringe with proper technique or adhere to the prescribed dosing regimen; or
  - The location and circumstances for self-administration are not adequate for the potential treatment of anaphylaxis should that arise

  and
- Patient is not receiving Xolair in combination with any of the following:
  - Anti-interleukin 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab)]
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]; and
- Xolair dosing for chronic urticaria is in accordance with the United States Food and Drug Administration approved labeling; and
- Reauthorization will be for no more than 12 months.

*Note: Patients 65 years of age and older in whom first generation H1-antihistamines are considered high risk medications to be avoided (e.g., Beers criteria, HEDIS) should be directed to try alternatives that are not considered high risk.

## Nasal Polyps

Xolair for provider administration is proven and medically necessary when all of the following criteria are met:

- Diagnosis of nasal polyps; and
- Two or more of the following symptoms for longer than 12 weeks duration:
  - Nasal mucopurulent discharge
  - Nasal obstruction, blockage, or congestion
  - Facial pain, pressure, and/or fullness
  - Reduction or loss of sense of smell

  and
- One of the following findings using nasal endoscopy and/or sinus computed tomography (CT):
  - Purulent mucus or edema in the middle meatus or ethmoid regions; or
  - Polyps in the nasal cavity or the middle meatus; or
  - Radiographic imaging demonstrating mucosal thickening or partial or complete opacification of paranasal sinuses

  and
- One of the following:
  - Patient has required prior sinus surgery; or
  - Patient has required systemic corticosteroids (e.g., prednisone, methylprednisolone) for nasal polyps in the previous 2 years; or.

- Patient has been unable to obtain symptom relief after trial of both of the following:
  - Intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone); and
  - One other therapy used in the management of nasal polyps [i.e., nasal saline irrigations. antileukotriene agents (e.g., montelukast, zafirlukast, zileuton)]

  and
- Patient will receive Xolair as add-on maintenance therapy in combination with intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone); and
- Physician attestation that self-administration of the Xolair prefilled syringe by the patient or caregiver is not appropriate, based on careful assessment of risk for anaphylaxis and mitigation strategies. Documentation required to support one of the following:
  - Patient has a history of anaphylaxis (e.g., bronchospasm, hypotension, syncope, urticaria, angioedema) to Xolair or other agents, such as foods, drugs, biologics; or
  - Patient is new to therapy with Xolair and requires initial doses to be administered under the guidance of a healthcare provider with no hypersensitivity reactions before transitioning to self-administration (Note: Authorization will be for three doses); or
  - Patient's previous Xolair therapy was interrupted for at least 6 months and will need to be re-initiated under the guidance of a healthcare provider before transitioning to self-administration (Note: Authorization will be for three doses); or
  - Patient or caregiver is unable to recognize symptoms of anaphylaxis or treat anaphylaxis appropriately; or
  - Patient or caregiver is unable to perform subcutaneous injections with Xolair prefilled syringe with proper technique or adhere to the prescribed dosing regimen; or
  - The location and circumstances for self-administration are not adequate for the potential treatment of anaphylaxis should that arise

  and
- Patient is not receiving Xolair in combination with any of the following:
  - Anti-interleukin-5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab), Nucala (mepolizumab)]
  - Anti-interleukin-4 therapy [e.g., Dupixent (dupilumab)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]; and
- Xolair dosing for nasal polyps is in accordance with the United States Food and Drug Administration approved labeling; and
- Prescribed by an allergist/immunologist/otolaryngologist/pulmonologist; and
- Initial authorization will be for no more than 6 months.

## *Reauthorization/Continuation of Care Criteria*

Xolair, for provider administration, for the treatment of nasal polyps, authorization for continued use will be approved based on all of the following criteria:

- Documentation of positive clinical response; and
- Patient will continue to receive Xolair as add-on maintenance therapy in combination with intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone); and
- Physician attestation that self-administration of the Xolair prefilled syringe by the patient or caregiver is not appropriate, based on careful assessment of risk for anaphylaxis and mitigation strategies. Documentation required to support one of the following:
  - Patient has a history of anaphylaxis (e.g., bronchospasm, hypotension, syncope, urticaria, angioedema) to Xolair or other agents, such as foods, drugs, biologics; or
  - Patient or caregiver is unable to recognize symptoms of anaphylaxis or treat anaphylaxis appropriately; or
  - Patient or caregiver is unable to perform subcutaneous injections with Xolair prefilled syringe with proper technique or adhere to the prescribed dosing regimen; or
  - The location and circumstances for self-administration are not adequate for the potential treatment of anaphylaxis should that arise

  and
- Patient is not receiving Xolair in combination with any of the following:
  - Anti-interleukin 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab), Nucala (mepolizumab)]
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]; and

- Xolair dosing for nasal polyps is in accordance with the United States Food and Drug Administration approved labeling; and
- Reauthorization will be for no more than 12 months.

### Unproven

Xolair for provider administration is unproven and not medically necessary in the following:

- Seasonal allergic rhinitis
- Perennial allergic rhinitis
- Atopic dermatitis
- Peanut allergy
- Acute bronchospasm or status asthmaticus

## Applicable Codes

The following list(s) of procedure codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

| HCPCS Code | Description |
|---|---|
| J2357 | Injection, omalizumab, 5 mg |

| Diagnosis Code | Description |
|---|---|
| J33.0 | Polyp of the nasal cavity |
| J33.1 | Polypoid sinus degeneration |
| J33.8 | Other polyp of sinus |
| J33.9 | Nasal polyp, unspecified |
| J44.1 | Chronic obstructive pulmonary disease with (acute) exacerbation |
| J44.9 | Chronic obstructive pulmonary disease, unspecified |
| J45.40 | Moderate persistent asthma, uncomplicated |
| J45.41 | Moderate persistent asthma with (acute) exacerbation |
| J45.50 | Severe persistent asthma, uncomplicated |
| J45.51 | Severe persistent asthma with (acute) exacerbation |
| J45.909 | Unspecified asthma, uncomplicated |
| J45.998 | Other asthma |
| L50.0 | Allergic urticaria |
| L50.1 | Idiopathic urticaria |
| L50.8 | Other urticaria |

### Maximum Dosage Requirements

#### *Maximum Allowed Quantities by HCPCS Units*

This section provides information about the maximum dosage per administration for omalizumab administered by a medical professional.

| Medication Name | | Diagnosis | Maximum Dosage per Administration | HCPCS Code | Maximum Allowed |
|---|---|---|---|---|---|
| Brand | Generic | | | | |
| Xolair | Omalizumab | Moderate to Severe Asthma | 375 mg | J2357 | 90 HCPCS units (5 mg per unit) |

| Medication Name | | Diagnosis | Maximum Dosage per Administration | HCPCS Code | Maximum Allowed |
|---|---|---|---|---|---|
| Brand | Generic | | | | |
| | | Chronic Urticaria | 300 mg | J2357 | 60 HCPCS units (5 mg per unit) |
| | | Nasal Polyps | 600 mg | J2357 | 120 HCPCS units (5 mg per unit) |

### *Maximum Allowed Quantities by National Drug Code (NDC) Units*

The allowed quantities in this section are calculated based upon both the maximum dosage information supplied within this policy as well as the process by which NDC claims are billed. This list may not be inclusive of all available NDCs for each drug product and is subject to change.

| Medication Name | | Diagnosis | How Supplied | National Drug Code | Maximum Allowed |
|---|---|---|---|---|---|
| Brand | Generic | | | | |
| Xolair | Omalizumab | Moderate to Severe Asthma | 150 mg vials | 50242-0040-62 | 3 vials |
| | | | 150 mg/1 mL PFS | 50242-0215-01<br>50242-0215-86 | 2 mL |
| | | | 75 mg/0.5 mL PFS | 50242-0214-01 | 0.5 mL |
| | | Chronic Urticaria | 150 mg vials | 50242-0040-62 | 2 vials |
| | | | 150 mg/1 mL PFS | 50242-0215-01<br>50242-0215-86 | 2 mL |
| | | Nasal Polyps | 150 mg vials | 50242-0040-62 | 4 vials |
| | | | 150 mg/1 mL PFS | 50242-0215-01<br>50242-0215-86 | 4 mL |
| | | | 75 mg/0.5 mL PFS | 50242-0214-01 | 0.5 mL |

## Background

Asthma is a common chronic inflammatory disease of the airways that affects an estimated 24 million adults and children and is associated with significant morbidity and mortality. Omalizumab is a monoclonal antibody that binds to human immunoglobulin E (IgE)'s high affinity Fc receptor, thereby preventing the binding of IgE to a variety of cells associated with the allergic response. Preventing the bridging between IgE and cells associated with allergic response prevents degranulation of such cells and, thereby, the release of inflammatory mediators. Omalizumab has been found in clinical trials to reduce free serum IgE concentrations by more than 90%, considerably suppress eosinophils in induced sputum, and blunt both early and late phase allergic reactions.[33-34]

## Clinical Evidence

### Proven

#### *Allergic Asthma*

Omalizumab is indicated for treatment of adults and adolescents 6 years of age and older, who have moderate to severe persistent asthma and a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.[3]

Deschildre et al. evaluated omalizumab efficacy and safety in a real-life setting in children aged 6 to 18 years (n = 104) with severe asthmas followed up in pediatric pulmonary tertiary care centers.[28] Asthma control levels, exacerbations, inhaled corticosteroid dose, lung function and adverse events were evaluated over 1 year. Children were characterized by allergic sensitization to three or more allergens (66%), high IgE levels (mean 1125 kU L(-1)), high rate of exacerbations (4.4 per year) and healthcare use during the previous year, and high inhaled corticosteroid dose (mean 703 µg equivalent fluticasone per day). Asthma control levels defined as good, partial, or poor, improved from 0%, 18% and 82% at entry to 53%, 30% and 17% at

week 20, and to 67%, 25% and 8% at week 52, respectively (p < 0.0001). Reported exacerbation and hospitalization rates decreased by 72% and 88.5%, respectively. At 12 months, forced expiratory volume in 1 s (FEV1) improved by 4.9% (p = 0.023), and inhaled corticosteroid dose decreased by 30% (p < 0.001). Six patients stopped omalizumab for related significant adverse events. Omalizumab improved asthma control in children with severe allergic asthma and was generally well tolerated. Authors concluded that he observed benefit was greater than that reported in clinical trials.

Sorkness et al conducted a post-hoc analyses which examined patient characteristics of those eligible and ineligible for omalizumab; described onset of effect after initiation of omalizumab and offset of treatment effect after stopping therapy; and determined whether the efficacy differs by age, asthma severity, dosing regimen, and pre-specified biomarkers.[27] Inner-city children and adolescents with persistent allergic asthma enrolled in the Inner-City Anti-IgE Therapy for Asthma (ICATA) trial that compared omalizumab with placebo added to guidelines-based therapy for 60 weeks were eligible for the evaluation (a significant portion of children and adolescents particularly suited for omalizumab because of asthma severity status were ineligible due to IgE > 1300 IU/mL). Two hundred ninety-three of 889 participants (33%) clinically suitable for omalizumab were ineligible for dosing according to a modified dosing table specifying IgE level and body weight criteria. Baseline symptoms were comparable among those eligible and ineligible to receive omalizumab, but other characteristics (rate of health care utilization and skin test results) differed. Patients receiving biweekly injections experienced a greater reduction in both exacerbations (OR = 2.54) and inhaled corticosteroids (ICS) usage (−204.8 μg/day) compared to patients receiving monthly injections (1.42 and −50.2 μg/day; p = 0.08 and p = 0.02, respectively). Omalizumab efficacy for symptom days per 2 weeks did not differ by dosing regimen (p = 0.62). Patients with total IgE ≥ 700 IU/mL had the greatest reduction in ICS usage (−504.6 μg/day) because of treatment with omalizumab. The time of onset of omalizumab effect was < 30 days and time of offset was between 30 and 120 days. No difference in efficacy was noted by age or asthma severity, but high exhaled nitric oxide, blood eosinophils, and body mass index predicted efficacy. Researchers concluded that results of this analysis showed that efficacy for exacerbations and ICS treatment was comparable in children 6 to 12 years of age compared with older children (> 12 years). Additionally, the data suggested that omalizumab may be efficacious in both severe disease (steps 5-6 treatments) and more moderate disease (steps 1-4). Certain subgroups of persons, for example, those with higher exhaled nitric oxide, blood eosinophils, and BMI were more likely to benefit from omalizumab according to the secondary analysis.

The Inner-City Anti-IgE Therapy for Asthma (ICATA) Study was a 60-week, randomized, double-blind, placebo-controlled, parallel-group trial (n = 419) which evaluated the effectiveness of omalizumab (75-375 mg subcutaneously every 2-4 weeks), as compared with placebo, when added to guidelines-based therapy.[21] The primary outcome was reduction in symptoms and exacerbations of asthma. Inner-city patients 6 to 20 years of age with persistent asthma (receiving long-term therapy for disease control and having symptoms of persistent asthma or evidence of uncontrolled disease as indicated by hospitalization or unscheduled urgent care in the 6 to 12 months preceding study entry), at least one positive skin test for a perennial allergen, weight between 20 and 150 kg, and having total serum levels of IgE between 30 and 1300 IU per milliliter were eligible for enrollment. Additionally, patients not receiving long-term control therapy were eligible for enrollment only if they had both persistent symptoms and uncontrolled asthma. The primary outcome defined as reduction in symptoms (number of days with symptoms during the previous two weeks) and exacerbations of asthma was evaluated every 4 weeks. Omalizumab as compared with placebo significantly reduced the number of days with asthma symptoms, from 1.96 to 1.48 days per 2-week interval, a 24.5% decrease (p < 0.001). Similarly, the percentage of participants with exacerbations (one or more) during the study was 48.8% in the placebo group as compared with 30.3% in the omalizumab group (p < 0.001), and the percentage who were hospitalized because of asthma was 6.3% as compared with 1.5%, respectively (p = 0.02). Improvements occurred with omalizumab despite reductions in the use of inhaled glucocorticoids and long-acting beta-agonists.

In a further pre-specified, subgroup [Lanier 2009] analysis, Kulus et al. evaluated efficacy and safety of omalizumab as compared to placebo in children (n = 235) with severe, persistent allergic asthma.[24] Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline inhaled corticosteroid dose and/or systemic steroids) by 34% versus placebo (0.42 vs 0.63, p = 0.047). Over 52 weeks, the exacerbation rate was reduced by 50% (p < 0.001). The overall incidence of adverse events (AEs) was similar in both omalizumab and placebo groups (93.4% vs 95.0%, p = 0.779), serious AEs were less frequent in the omalizumab group (3.6% vs 10.0%, p = 0.073), and no new safety concerns were evident. Researchers noted that the sample size was not based on providing statistical power in the severe subgroup, and no corrections were made for multiple comparisons; however, outcomes consistently favored omalizumab.

Milgrom et al. evaluated the safety of omalizumab in children (n = 926) ages 6-12 with allergic (IgE-mediated) asthma in a pooled analysis of two double-blind, placebo-controlled studies [Milgrom 2001 and Lanier 2009].[22] Children on optimized

asthma care were randomized (2:1) to omalizumab (75-375 mg every 2 or 4 weeks) or placebo. Adverse events (AEs) were more frequently reported in the placebo (91.7%) than omalizumab (89.7%) group. The most common AEs were nasopharyngitis, upper respiratory tract infection and headache. Suspected treatment-related AEs included headache, erythema and urticaria; none of which were reported by ≥ 2% of patients receiving omalizumab. Serious adverse effects were reported by 3.4% and 6.6% of patients receiving omalizumab and placebo, respectively; the most common were appendicitis, pneumonia, and bronchitis; no deaths were reported.

## Allergic Asthma with IgE Levels > 700 IU/ml

A retrospective study evaluated the response of asthmatic patients treated with omalizumab with IgE levels greater than 700 IU/mL.[29] Emergency department (ED) visits, hospitalizations, change in forced expiratory volume in 1 second (FEV1), corticosteroid bursts, and Asthma Control Test (ACT) scores were recorded for a period of 6 months before and after treatment with omalizumab in patients with elevated IgE levels or treatment length of ≥ 6 months. Twenty-six patients with an IgE level > 700 IU/mL (group 1) were matched by age, sex, and severity of asthma to patients with an IgE of 30 to 700 IU/mL (group 2). The mean numbers of ED visits before and after treatment was 0.96 vs 0.23 ($p = 0.008$) in group 1 and 0.65 vs 0.15 ($p = 0.02$) in group 2. Both groups had an improvement in asthma control based on the mean ACT score before and after treatment (15.6 vs 18.9 [$p = 0.02$] and 15.4 vs 19 [$p = 0.006$], respectively). Additionally, there was a significant reduction in the frequency of systemic corticosteroid use during the 6 months before and after treatment (2.58 vs 0.96 [$p < 0.001$] and 2.62 vs 1.23 [$p < 0.001$] systemic steroid treatments, respectively). Researchers concluded that omalizumab was just as effective in reducing ED visits, controlling asthma symptoms, and reducing the need for systemic corticosteroids in patients with IgE levels > 700 IU/mL compared with patients with levels within 30 to 700 IU/mL.

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study evaluated use of high dose omalizumab in adult patients with IgE levels > 700 IU/ml.[25] Fifty asthmatic patients (pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≥ 65% predicted; had been asthma exacerbation-free for ≥ 4 weeks; and skin reactivity to a specific allergen within 2 years before screening) with an age range of 18 to 65 years and a body weight range of 40 to 150 kg were divided into two groups according to IgE levels (group 1: 30-300 IU/ml and group 2: 700-2000 IU/ml) and randomized 2:1 to receive either omalizumab or placebo every 2 or 4 weeks. Allergen bronchoprovocation (ABP) testing was performed at baseline, week 8 and week 16. The primary efficacy endpoint measured was the early-phase allergic response (EAR; defined as the maximum percentage drop in forced expiratory volume in 1 second during the first 30 minute after ABP). Secondary outcome evaluated with the late-phase allergic response (LAR; defined as maximum percentage drop in FEV1 over 3-8 hours after ABP). Additional outcomes assessed included serum free IgE (as a pharmacodynamic endpoint) and the exhaled fractional concentration of nitric oxide (FENO; as an exploratory endpoint). At week 8, EAR was 23.1% for placebo and treatment with omalizumab reduced it to 9.3% in in group 1 ($p = 0.018$ vs placebo) and 5.6% in group 2 ($p < 0.001$ vs placebo). Additionally, at week 16, reported EAR was 20%, 11.8% ($p = 0.087$) and 5.1% ($p < 0.001$), respectively. LAR analysis was not performed due to the small number of patients studied. Serum free IgE levels decreased in groups 1 and 2 and remained < 50 ng/ml in all patients during weeks 6-16. Treatment with omalizumab suppressed FENO increases after ABP in both groups. Authors conclude that the outcomes of this study demonstrated that the protective effects of omalizumab against allergen-induced bronchoconstriction in patients with allergic asthma and baseline IgE up to 2000 IU/ml.

Researchers conducted a post-marketing observational surveillance trial to evaluate the efficacy and tolerability of omalizumab in a real-life setting in Spain, particularly in those patients with immunoglobulin E (IgE) levels out of range.[26] Patients were recruited if they had a diagnosis of uncontrolled severe, persistent, allergic asthma while on high-dose inhaled corticosteroids (ICSs) plus long-acting β2-agonist (LABA); had an age ≥ 12 years; and had received at least one dose of omalizumab between May 2006 and November 2009, Main efficacy outcomes evaluated included asthma exacerbation rate (AER), asthma control test (ACT), and global evaluation of treatment effectiveness (GETE). Of the 266 patients enrolled, 7 patients had IgE levels < 30 IU/mL and 46 patients has IgE levels > 700 IU/ml. Average AER reported for all groups showed a reduction from 3.6 in previous year to 0.67 at 4 months ($p < 0.05$) and to 1.04 at 2 years ($p < 0.05$). Average ACT increased from 14.3 at baseline to 18.4 at 4 months ($p < 0.05$) and to 20.3 $p < 0.05$) at 2 years. After 4 months, 74.6% of patients had reached a good or excellent rate on the GETE scale ($p < 0.05$) and this rate continued to increase to 81.6% at 2 years. Similarly, in the IgE > 700 IU/ml group, researchers reported an increased ACT from 13.6 at baseline to 20.9 at the 2-year visit ($p < 0.05$) and a decrease in exacerbations from 3.58 at baseline to 0.72 at the 2-year visit ($p < 0.05$). At follow-up, maintenance treatment with oral steroids was reduced from 89 patients to 19 patients ($p < 0.05$). Omalizumab was discontinued because of lack of efficacy in 28/266 (10.5%) patients and 30 patients (11.4%) reported adverse events (none were severe). Researchers conclude that this observational study confirms that omalizumab is efficacious and well tolerated in patients with uncontrolled severe asthma, including those patients with IgE levels > 700 IU/ml.

## *Chronic Urticaria*

Omalizumab is indicated for treatment of chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.[3]

Saini et al conducted a 40-week, randomized, double-blind, placebo-controlled trial (ASTERIA I) to evaluate the efficacy and safety of subcutaneous omalizumab as add-on therapy for 24 weeks in patients (n 319) with chronic idiopathic urticaria/spontaneous urticaria (CIU/CSU) who remained symptomatic despite $H_1$ antihistamine treatment.[1] Eligible patients aged 12–75 years with CIU/CSU who remained symptomatic despite treatment with approved doses of $H_1$ antihistamines were randomized (1:1:1:1) in a double-blind manner to subcutaneous omalizumab 75 mg (n = 78), 150 mg (n = 80), or 300 mg (n = 81) or placebo (n = 80) every 4 weeks for 24 weeks followed by 16 weeks of follow-up. The primary outcome measured was change from baseline in weekly itch severity score (ISS) at week 12. Secondary outcomes evaluated at week 12, included changes from baseline in UAS7 and weekly number of hives score; time to MID response (≥ 5-point decrease) in weekly ISS; the proportion of patients with UAS7 ≤ 6; the proportion of weekly ISS MID responders; changes from baseline in weekly size of largest hive score and overall DLQI score; the proportion of angioedema-free days during weeks 4 to 12; and the proportion of patients with complete response (UAS7 = 0). Compared with placebo mean weekly ISS was reduced from baseline to week 12 by an additional 2.96 points (95% confidence interval (CI): −4.71 to −1.21; p = 0.0010), 2.95 points (95% CI: −4.72 to −1.18; p = 0.0012), and 5.80 points (95% CI: −7.49 to −4.10; p < 0.0001) in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively. The omalizumab 300-mg group met all nine secondary end points, including a significant decrease in the duration of time to reach minimally important difference response (≥ 5-point decrease) in weekly ISS (p < 0.0001) and higher percentages of patients with well-controlled symptoms (urticaria activity score over 7 days (UAS7) ≤ 6: 51.9% vs. 11.3% p < 0.0001) and complete response (UAS7 = 0: 35.8% vs. 8.8% p < 0.0001) versus placebo. During the 24-week treatment period, the proportions of patients who experienced one or more treatment-emergent adverse events (AEs) ranged from 57 to 69% in the omalizumab groups versus 51% in the placebo group. Additionally, 2 (2.9%), 3 (3.4%), 0, and 4 (5.0%) patients in the omalizumab 75-mg, 150-mg, 300-mg, and placebo groups, respectively, experienced a serious adverse event. Omalizumab 300 mg administered every 4 weeks reduced weekly ISS and other symptom scores versus placebo in CIU/CSU patients who remained symptomatic despite treatment with approved doses of $H_1$ antihistamines. Additionally, the results of this study showed a sustained treatment effect of omalizumab 300 mg for up to 24 weeks on CIU/CSU symptom scores in patients with H1 antihistamine-refractory CIU/CSU. The safety profile for omalizumab over 24 weeks of treatment in patients with CIU/CSU receiving approved doses of H1 antihistamines was consistent with the established safety profile in allergic asthma and with previous observations in CIU/CSU.

## *Nasal Polyps*

Omalizumab is indicated for nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add-on maintenance treatment.

The safety and efficacy of omalizumab was evaluated in two, randomized, multicenter, double-blind, placebo-controlled clinical trials that enrolled patients with nasal polyps with inadequate response to nasal corticosteroids (Nasal Polyps Trial 1, n = 138; Nasal Polyps Trial 2, n = 127). Patients received omalizumab or placebo subcutaneously every 2 or 4 weeks, for 24 weeks followed by a 4-week follow-up period. All patients received background nasal mometasone therapy during both the treatment period and during a 5-week run-in period. Prior to randomization, patients were required to have evidence of bilateral polyps as determined by a nasal polyp score (NPS) ≥ 5 with NPS ≥ 2 in each nostril, despite use of nasal mometasone during the run-in period. NPS was measured via endoscopy and scored (range 0-4 per nostril: 0 = no polyps; 1 = small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the lower border of the middle turbinate; 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4 = large polyps causing complete obstruction of the inferior nasal cavity) for a total NPS (range 0-8). Patients were furthermore required to have a weekly average of nasal congestion score (NCS) > 1 prior to randomization, despite use of nasal mometasone. Nasal congestion was measured by a daily assessment on a 0 to 3-point severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Prior sino-nasal surgery or prior systemic corticosteroid usage were not required for inclusion in the trials and sinus CT scans were not performed to evaluate for sinus opacification.

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

Omalizumab had statistically significant improvements on sense of smell score compared to placebo. Sense of smell was measured by a daily assessment on a 0 to 3-point severity scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms). The LS mean difference for change from baseline at Week 24 in sense of smell score in omalizumab compared to placebo was -0.3 (95% CI: -0.6, -0.1) in Trial 1 and -0.5 (95% CI: -0.7, -0.2) in Trial 2. Omalizumab had statistically significant improvements on post-nasal drip compared to placebo. The LS mean difference for change from baseline at Week 24 in post-nasal drip score in omalizumab compared to placebo was -0.6 (95% CI: -0.8, -0.3) in Trial 1 and -0.5 (95% CI: - 0.8, -0.3) in Trial 2. Omalizumab had statistically significant improvements on runny nose compared to placebo. The LS mean difference for change from baseline at Week 24 in runny nose score in omalizumab compared to placebo was -0.4 (95% CI: -0.7, -0.2) in Trial 1 and -0.6 (95% CI: - 0.9, -0.4) in Trial 2. In a pre-specified pooled analysis of systemic corticosteroid use during the 24-week treatment period, there was no significant reduction in systemic corticosteroid use between the treatment arms. The proportion of patients taking systemic corticosteroid in omalizumab was 2.3% compared to 6.2% in placebo. The odds-ratio of systemic corticosteroid use with omalizumab compared to placebo was 0.4 (95% CI: 0.1, 1.5). There were no sino-nasal surgeries reported, in either placebo or omalizumab arms, in either trial.

## Unproven

### *Seasonal Allergic Rhinitis*

Researchers conducted a systemic review and meta-analysis of the efficacy and safety of omalizumab in poorly controlled allergic rhinitis in randomized controlled trials dating through 2013.[16] Eleven studies that assessed 2870 randomized patients were included. A statistically significant reduction in the daily nasal symptom severity score (standardized mean difference -0.67 [95% CI, -1.3 to -0.31]; p < .0001; I(2), 92%) and a statistically significant reduction in daily nasal rescue medication score (-0.22 [95% CI, -0.39 to -0.05; p = 0.01; I(2), 58%) were observed. There was not a statistically significant difference in the occurrence of any adverse event (relative risk 1.06 [95% CI, 0.94-1.19; I(2), 55%). The meta-analysis showed that, in seasonal and perennial allergic rhinoconjunctivitis, treatment with omalizumab provided an improvement of the daily nasal symptom severity score (DNSSS) and a reduction of antiallergic medication use compared with placebo. The rhinosinusitis-related quality of life (rQoL) appeared to be improved in the limited randomized evidence available. The observed safety profile indicated an adequate tolerability and a comparable overall AEs pattern. The potential benefits of omalizumab need to be considered in the context of costs of therapy and rare AEs. Larger clinical trials and economic studies are needed to address issues of rare events occurrence and cost-effectiveness, respectively.

Several studies have evaluated the use of omalizumab therapy in children, adolescents, and adults with seasonal allergic rhinitis. Though results appear to be promising, additional trials are warranted to establish long-term efficacy and safety, as well as appropriate dosage and timing.[6-11]

### *Perennial Allergic Rhinitis*

Corren et al. assessed 19 patients (ages 18-65 years) with perennial allergic rhinitis in a 26-week open-label study of intravenous (IV) omalizumab 0.015-0.03mg/kg/IgE [IU/mL] every 2 weeks.[12] Serum free IgE concentrations decreased by up to 99%. Nasal allergen challenge symptom scores (e.g., sneezing, rhinorrhea) decreased significantly.

In another study, 40 patients with perennial allergic rhinitis receiving open-label omalizumab 0.015-0.030 mg/kg/IgE [IU/mL] IV every 2 weeks for 28 weeks showed up to 99% decrease in serum free IgE and decreased reaction to wheal-and-flare skin tests at day 98.[13] However, upon decreased dosage to 0.0015-0.005mg/kg/IgE [IU/mL] for another 18 weeks, serum free IgE and skin test reactivity increased significantly and returned to baseline upon discontinuation.

Chervinsky et al. studied the efficacy, safety, and tolerability of omalizumab in the short-term treatment of patients 12 to 70 years of age with perennial allergic rhinitis with moderate to severe symptoms in a randomized, double-blind trial.[14] The patients completed 16 weeks of either placebo (n = 145) or at least 0.016 mg/kg/IgE [IU/mL] subcutaneous omalizumab every four weeks (n = 144). Patients maintained a diary of their daily symptoms including nasal severity scores throughout the study period, which was based on a 4-point scale (0 = no symptoms to 3 = severe symptoms). Patients in the omalizumab group had a 69% reduction in the average daily nasal severity score from baseline compared to 49% of the placebo treated patients (p = 0.001). Symptoms were controlled, which was defined as a score of less than 0.75 on a 4-point scale, in 28% (40/143) of patients in the omalizumab group compared to 10% (14/145) of patients in the placebo group. In both study groups, antihistamine use was low, however omalizumab significantly decreased antihistamine use per month more than placebo (omalizumab; 4.5 to 1.5 days per month, placebo: 3.6 to 2.7 days per month, p = 0.005). Three patients in each group dropped out due to intolerance of study medication or placebo, but no severe safety concerns were noted throughout the study. In this

study, there was a large placebo effect making the true effect of omalizumab difficult to determine. Additional and larger studies are needed in this population.

### *Atopic Dermatitis*

Heil et al. investigated the effects of omalizumab or placebo on the expression of IgE and its receptors on cells and on serum components of patients with atopic dermatitis (AD).[25] Additional evaluation included whether omalizumab would revert preexisting lesions in patients with long lasting and ongoing AD. Twenty patients were randomized 2:1 in a placebo-controlled, double blind study for 16 weeks. Male and female patients (ages 12-60 years) with a clinical diagnosis of AD and a serum IgE between 30 and 1300 IU/ml were included. Patients in the omalizumab treatment had reduced serum levels of free IgE and decreased surface-bound IgE. However, omalizumab treatment did not significantly alter several measures of clinical disease activity (i.e., atopy patch test results in single patients). Researchers conclude that a therapeutic benefit of omalizumab treatment, if present at all, would be seen in patients with acute rather than chronic forms of AD.

### *Peanut Allergy*

In a phase II, double-blind, randomized clinical trial, omalizumab was evaluated in patients with a hypersensitivity reaction to peanut and compared with placebo.[17-19] During screening, patients underwent a double-blind oral food challenge with either peanut flour or wheat flour. Patients who reacted to less than or equal to 250 mg of peanut flour and not wheat flour were randomized to omalizumab (minimum 0.016 mg/kg/IgE [IU/mL] every 4 weeks or 0.008 mg/kg/IgE [IU/mL] every 2 weeks) or placebo for 20 to 22 weeks. At 24 weeks, patients were to receive a second double-blind oral challenge to either peanut or wheat flour. However, due to safety concerns of the oral food challenge, an external data and safety monitoring committee terminated the trial early.

### *Acute Bronchospasm or Status Asthmaticus*

The U.S. Food and Drug Administration (FDA) has required the manufacturer of omalizumab to state in its labeling that Xolair cannot be used to treat acute bronchospasm or status asthmaticus.[3]

## Professional Societies

### *Allergic Asthma*

The Global Initiative for Asthma (GINA, 2020) recommends that for Step 5 treatment, patients 6 years and older may be treated with omalizumab as follows:[2]

- Consider add-on for those with moderate or severe allergic asthma that is uncontrolled on Step 4-5 treatment including high dose ICS/LABA, add on long-acting muscarinic antagonist, or LTRA.
- Step 5: Refer for phenotypic investigation and/or add-on treatment. Patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be referred to a specialist with expertise in investigation and management of severe asthma.
- Add-on treatments for moderate or severe allergic asthma, anti-IgE treatment (subcutaneous omalizumab for patients aged ≥ 6 years) that is uncontrolled on Step 4-5 treatment.

In April 2013, The National Institute for Health and Care Excellence (NICE) published a technology appraisal guidance addressing use of omalizumab in children aged 6 to 11 years with severe, persistent asthma.[4] In the assessment, NICE noted the 'life-changing' effect of omalizumab reported by patients and concluded that omalizumab as an add-on to optimized standard therapy is more clinically effective in treating severe persistent allergic asthma than optimized standard therapy alone, leading to a reduction in total emergency visits (including hospital admissions, A&E visits and unscheduled general physician visits) in adults, reduced hospital admissions in children, improved lung function in adults and a reduction in the frequency and use of rescue medication and oral corticosteroids. The committee recommended that omalizumab be used as follows:

- Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimized standard therapy [defined - as a full trial of (and, if tolerated, documented compliance with) inhaled high-dose corticosteroids, long-acting ß2-agonists, leukotriene receptor antagonists, theophylline, oral corticosteroids, and smoking cessation if clinically appropriate].
- In people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as four or more courses in the previous year)

- Optimized standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

In June 2015, NICE published an additional technology appraisal guidance addressing use of omalizumab in children and adults aged 12 years and over for the treatment of spontaneous urticaria.[32] The committee recommended that omalizumab be used as follows:

- Omalizumab is recommended as an option as add-on therapy for treating severe chronic spontaneous urticaria in adults and young people aged 12 years and over only if:
  - The severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more
  - The person's condition has not responded to standard treatment with $H_1$-antihistamines and leukotriene receptor antagonists
  - Omalizumab is stopped at or before the fourth dose if the condition has not responded
  - Omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded, to establish whether the condition has gone into spontaneous remission, and is restarted only if the condition relapses
  - Omalizumab is administered under the management of a secondary care specialist in dermatology, immunology, or allergy

### European Respiratory Society (ERS)/American Thoracic Society (ATS)

The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines define severe asthma as that which requires treatment with high-dose ICSs plus a second controller (or systemic corticosteroids) to prevent progression to uncontrolled disease status or continuing uncontrolled disease status despite this therapy.[3] The guidelines recommend omalizumab in adults and children with severe allergic asthma (Recommendation: Conditional, Low for adults, Very Low in children). This recommendation places higher value on the clinical benefits from omalizumab in some patients with severe allergic asthma and lower value on increased resource use.

The guidelines remark:

- Those adults and children aged ≥ 6 years with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance if their total serum IgE level is 30–700 IU/mL (in three studies the range was wider: 30–1300 IU/mL).
- Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare utilization, and improvement in quality of life.
- If a patient does not respond within 4 months of initiating treatment, it is unlikely that further administration of omalizumab will be beneficial.

## *Chronic Urticaria*

In 2014, the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology updated the practice parameter for the diagnosis and management of acute and chronic urticaria (CU). The practice parameter established a step-care approach to the treatment of chronic urticaria and angioedema. The task force recommended the following step-care treatment approach:[20]

- Monotherapy with second-generation antihistamines: H1-antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients.
- Dose advancement of H1-antihistamine therapy, combining first- and second-generation agents and adding an H2-antihistamine and/or an antileukotriene agent: Higher doses of second-generation antihistamines can provide greater efficacy when control is not achieved with conventional doses of these agents.
- Therapeutic trial of potent antihistamine (e.g., hydroxyzine or doxepin): First-generation antihistamines should be prescribed cautiously in the elderly or patients with occupations (e.g., machine operators, airline pilots, or alpine skiers) for which alertness is essential.
- Add an immunosuppressant or biologic agent: Omalizumab and cyclosporine have the greatest published experience documenting efficacy in patients with CU compared with all other alternative agents.

# U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage

Xolair is approved by the U.S. Food and Drug Administration (FDA) for use in adults and adolescents 6 years of age and older, who have moderate to severe persistent asthma and a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair is not indicated for acute bronchospasm or status asthmaticus. Xolair is also approved for chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite $H_1$ antihistamine treatment. Xolair is also indicated for nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add-on maintenance treatment. It is not indicated for other allergic conditions or other forms of urticaria. Because of the risk of anaphylaxis, healthcare providers administering Xolair should observe patients closely for an appropriate period of time and be prepared to manage anaphylaxis that can be life-threatening.[3]

On September 26, 2014, the U.S. FDA released a drug safety alert entitled: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events.[16] An FDA review of safety studies suggests a slightly increased risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the asthma drug Xolair (omalizumab) than in those who were not treated with Xolair. As a result, FDA has added information about these potential risks to the drug label. Additionally, reviewers found no difference in the rates of cancer between those patients being treated with Xolair and those who were not being treated with Xolair. However, due to limitations in the 5-year study, FDA cannot rule out a potential risk of cancer with Xolair, so this information was added to the Warnings and Precautions section of the drug label.

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# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 11/01/2022 | **Coverage Rationale**<br>*Nasal Polyps*<br>• Revised coverage criteria for initial therapy:<br>  ○ Removed criterion requiring the presence of bilateral nasal polyposis or the patient has previously required surgical removal of bilateral nasal polyps<br>  ○ Replaced criterion requiring:<br>  ▪ "Diagnosis of *chronic rhinosinusitis with* nasal polyps *(CRSwNP) defined by all of the [listed criteria]*" with "diagnosis of nasal polyps"<br>  ▪ "Patient has required systemic corticosteroids (e.g., prednisone, methylprednisolone) for *CRSwNP* in the previous 2 years" with "patient has required systemic corticosteroids (e.g., prednisone, methylprednisolone) for *nasal polyps* in the previous 2 years"<br>  ▪ "Patient has been unable to obtain symptom relief after trial of *two* of the following *classes of agents*: nasal saline irrigations, intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone), antileukotriene agents (e.g., montelukast, zafirlukast, zileuton)" with "patient has been unable to obtain symptom relief after trial of *both* of the following: intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone) *and one other therapy used in the management of nasal polyps [i.e.,* nasal saline irrigations, antileukotriene agents (e.g., montelukast, zafirlukast, zileuton)]"<br>• Updated list of examples of anti-interleukin-5 therapy drug products the patient cannot receive in combination with Xolair; added Nucala (mepolizumab)<br>**Supporting Information**<br>• Updated *References* section to reflect the most current information<br>• Archived previous policy version CS2022D0033Z |

# Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.