FDA APPROVED INDICATIONS AND DOSAGE

| Agent | Indications*|^ | Dose and administration |
|-------|-------------|------------------------|
| **Xolair® (omalizumab)** subcutaneous injection | Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids | 75 mg to 375 mg by subcutaneous injection every 2 or 4 weeks |
| | Chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment | 150 or 300 mg by subcutaneous injection every 4 weeks |

* Omalizumab is not indicated for treatment of other allergic conditions, other forms of urticaria, relief of acute bronchospasms, or status asthmaticus.

^ Omalizumab has not been studied for use in combination with Cinqair (reslizumab) or Nucala (mepolizumab)

CLINICAL RATIONALE

Asthma

Asthma is a chronic inflammatory disorder of the airways. It is characterized by variable and recurring clinical symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. Symptoms of asthma include wheezing, coughing, recurrent difficulty breathing, shortness of breath, and chest tightness. Generally, these symptoms will occur or worsen with exposure to allergens and irritants, infections, exercise, changes in weather, stress, or menstrual cycles. The National Asthma Education and Prevention Program (NAEPP) Expert Panel guidelines recommend the use of detailed medical history, physical examination, and spirometry to make a diagnosis of asthma. In addition, differential diagnosis of asthma should be considered.

The patient’s asthma can be considered to be well controlled when asthma symptoms are twice a week or less; the rescue bronchodilator medication is used twice a week or less; there is no nocturnal or early morning awaking due to asthma symptoms; there are no limitations of work, school, or exercise; and the Forced Expiratory Volume (FEV1) is normal or the patient’s personal best. Markers of asthma that is not adequately controlled in patients receiving therapy include limitation of normal activities, poor lung function with FEV1 of
<80% predicted, at least 2 episodes per year of asthma exacerbations requiring oral systemic corticosteroids.\textsuperscript{2} More frequent and intense exacerbations (e.g. requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control.\textsuperscript{4}

The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach for managing asthma.\textsuperscript{3} Long-term goals for asthma management are to achieve good control of symptoms, maintain normal activity level and to minimize the future risk of exacerbations, fixed airflow limitation and side-effects.\textsuperscript{3} Allergic asthma is triggered by inhalation of allergens.\textsuperscript{6} IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic asthma and the development and persistence of inflammation. GINA guidelines define moderate asthma as that which is well controlled with low dose ICS in combination with a LABA.\textsuperscript{3} Severe asthma is defined as “asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘uncontrolled’ or which remains uncontrolled despite this therapy.\textsuperscript{4} Early initiation of low dose inhaled corticosteroid (ICS) in patients with asthma has led to greater improvement in lung function than if initiation of ICS after symptoms have been present for more than 2 to 4 years.\textsuperscript{3}

GINA recommends as-needed relieve inhaler, short acting b-agonist (SABA) as Step 1. SABAs are highly effective for the quick relief of asthma symptoms. However, there is insufficient evidence for use of SABA alone for the treatment of asthma. SABA monotherapy for the treatment of asthma should be reserved for patients with occasional daytime symptoms (less than twice a month) of short duration with no night waking and with normal lung function. Step 2 is the recommendation of treatment with ICS. At low doses, ICS reduces asthma symptoms, increases lung function, improves quality of life, and reduces the risk of exacerbations and asthma-related hospitalizations or death. Leukotriene receptor antagonists (LTRA) are less effective than ICS. Step 3 involves one or two maintenance inhalers and an as-needed reliever. Combination low dose and long acting b-agonist (LABA) as maintenance treatment plus an as-needed SABA or low dose ICS with formoterol (budesonide or beclometasone) with a reliever treatment are options recommended. Step 4 involves 2 or more maintenance agents with an as-needed reliever. Combination low dose ICS with formoterol or medium dose ICS with LABA and an as-needed SABA are recommended options. Step 5 includes higher level care and/or add-on treatment. Depending on treatment options used in previous steps, long acting muscarinic antagonists (LAMA) such as tiotropium, omalizumab, or anti-interleukin-5 (mepolizumab and reslizumab) are additional pharmacologic options as add-on therapy.\textsuperscript{3}

In patients with moderate-to-severe asthma, treatment with omalizumab (compared with placebo) can decrease the incidence of exacerbations and result in a significant reduction in the dose of inhaled or oral glucocorticoids required to control symptoms. Omalizumab has never been compared directly in a controlled clinical trial with other asthma therapies, such as inhaled glucocorticoids with long-acting beta-agonists, anti-leukotriene agents, or allergen immunotherapy. Independent of other therapies, in patients with atopic severe asthma, who have a serum IgE level of 30 to 700 IU/mL and documented sensitivity to a perennial allergen, the addition of omalizumab can be considered. The response to treatment with omalizumab is variable and difficult to predict, ranging from 30-50% in patients with moderate to severe asthma. A minimum of 12 weeks of treatment is needed to assess efficacy. There is usually little to no improvement in FEV\textsubscript{1} and airway hyperreactivity when omalizumab is added to pre-existing therapy.\textsuperscript{7,8}

**Moderate to Severe Allergic (IgE-mediated) Asthma**

Allergic asthma is triggered by inhalation of allergens.\textsuperscript{6} IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic asthma and the development and persistence of inflammation. GINA guidelines define moderate asthma as that which is well controlled with low dose ICS in combination with a LABA.\textsuperscript{3} Severe asthma is
defined as “asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy.” Guidelines recommend use of omalizumab as add on therapy for patients who have failed to respond to standard therapy and have IgE-mediated allergic asthma.

**Chronic Idiopathic Urticaria (CIU)**

Chronic urticaria is defined by the presence of urticaria (hives) that has been continuously or intermittently present for more than 6 weeks. CIU involves cutaneous mast cell granulation. The wheals usually last less than 24 hours with itching being the most common symptom. Diagnosis involves evaluation of labs including a complete blood count with differential, stool samples (assessing for parasitic activity), erythrocyte sedimentation rate, antinuclear antibody, hepatitis B and C titers, serum cryoglobulin and complement assays, thyroid function testing, and Chronic Urticaria index.

Treatment goals for CIU involves symptom control and improvement in quality of life that is acceptable to the patient. Guidelines recommend a step wise approach to treating CIU. Initial treatment with H-1 antihistamines at higher than standard doses has been shown to adequately control CIU symptoms in 60-70% of patients. A second generation H-1 antihistamine (cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine), dosed daily rather than as needed basis, is recommended as part of initial therapy. If there is insufficient response within one to two weeks, the second step is to implement one or more of the following strategies:• Addition of a different second generation H-1 antihistamine• Addition of a first-generation H-1 antihistamine at nighttime (doxepin, hydroxyzine, cyproheptadine)• Addition of H-2 antihistamine (ranitidine, famotidine, cimetidine)• Addition of leukotriene receptor antagonist (montelukast, zafirlukast), especially in patients with NSAID intolerance or cold urticaria• Increase the dose of the initial second-generation antihistamine, up to 4 times standard dose

If symptomatic control is not achieved, third step is addition and titration of high potency antihistamines as tolerated, such as hydroxyzine or doxepin. The fourth step is referral to a subspecialist for the use of an immunomodulatory agent such as omalizumab or cyclosporine. Glucocorticoids could be also help with symptom control in refractory CIU. Other agents used in CIU are dapsone, sulfasalazine, hydroxychloroquine, and immunosuppressants (tacrolimus, cyclosporine, sirolimus, and mycophenolate). Omalizumab is suggested for patients who do not respond to higher doses of H-1 antihistamine therapy. Omalizumab should be considered for refractory CIU if this is favorable from the standpoint of balancing the potential for benefit with the potential for harm/burden and cost. Patients enrolled in pivotal clinical studies were required to have a history of at least 6 months of CIU, presence of hives associated with itching for at least 8 consecutive weeks at any time before enrollment despite current use of H-1 antihistamines, and other urticaria activity assessments.

**Safety**

The most common adverse events reported in patients 12 years and above with asthma were arthralgia, general pain, fatigue, dizziness, pruritus, dermatitis, and earache. Most common adverse events among pediatric patients treated with omalizumab for asthma included nasopharyngitis, headache, pyrexia, abdominal pain, otitis media, and epistaxis. Omalizumab has a boxed warning due to risk of anaphylaxis. It is also contraindicated in patients with history of hypersensitivity to omalizumab or any ingredients of omalizumab.
REFERENCES

Xolair (omalizumab) Prior Authorization

OBJECTIVE
The intent of the Xolair (omalizumab) Prior Authorization (PA) Criteria is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies while adhering to the dosing guidelines for age, weight, and pretreatment IgE levels (for allergic asthma) as recommended in FDA labeling. For renewal of therapy, all dosing parameters must continue to be met with omalizumab contributing to the improvement or maintenance of asthma or improvement of urticaria symptoms.

TARGET AGENT
Xolair® (omalizumab)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
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<tbody>
<tr>
<td>Xolair (omalizumab)</td>
<td>44603060002120</td>
<td>M, N, O, or Y</td>
</tr>
</tbody>
</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Xolair (omalizumab) will be approved when ALL of the following are met:

1. ONE of the following
   A. The patient has a diagnosis of moderate to severe persistent asthma AND ALL of the following:
      i. If the patient is 6 to less than 12 years of age, the patient meets BOTH of the following:
         a. The pretreatment IgE level is 30 IU/mL to 1300 IU/mL AND
         b. The patient’s weight is 20 kg to 150 kg
      AND
      ii. If the patient is 12 years of age and over, the patient meets ALL of the following:
         a. The pretreatment IgE level is 30 IU/mL to 700 IU/mL AND
         b. The patient’s weight is 30 kg to 150 kg AND
         c. The patient has a baseline FEV1 <80% predicted
      AND
   iii. Allergic asthma has been confirmed by a positive skin test or in vitro reactivity test (RAST) to a perennial aeroallergen
      AND
   iv. The patient has ONE of the following:
      a. Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months OR
      b. Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months OR
      c. Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered
      AND
   v. ONE of the following:
      a. The patient is NOT currently being treated with the requested agent AND is currently treated with a maximally tolerated inhaled corticosteroid in the past 90 days OR
b. The patient is currently being treated with the requested agent AND is currently treated with an inhaled corticosteroid that is dosed as needed to control symptoms

OR

c. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to inhaled corticosteroids

AND

vi. ONE of the following:

a. The patient is currently treated with ONE of the following in the past 90 days:
   1. A long-acting beta-2 agonist (LABA) OR
   2. A Leukotriene receptor antagonist (LRTA) OR
   3. Long-acting muscarinic antagonist (LAMA) OR
   4. Theophylline

OR

b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a long-acting beta-2 agonist (LABA), leukotriene receptor antagonist (LRTA), Long-acting muscarinic antagonist (LAMA), AND theophylline

AND

vii. The requested dose is within dosing based on pre-treatment serum IgE level and the patient’s body weight as defined in FDA approved labeling AND does NOT exceed 375 mg every 2 weeks

OR

B. The patient has a diagnosis of chronic idiopathic urticaria with at least 6 weeks of hives and itching AND ALL of the following:

i. The patient is 12 years of age and over

AND

ii. ONE of the following:

a. The patient has tried and had an inadequate response to TWO different classes of CIU therapies for at least 2 weeks duration of each course (first generation H-1 antihistamine [e.g. doxepin, hydroxyzine, cyproheptadine], second generation H-1 antihistamine [e.g. cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine], H-2 antihistamine [e.g. ranitidine, famotidine, cimetidine], leukotriene receptor antagonist [e.g. montelukast, zafirlukast])

OR

b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL prerequisite agents

AND

iii. The requested dose is within the FDA labeled dose AND does NOT exceed 300 mg every 4 weeks

OR

C. The patient has another FDA approved indication for the requested agent AND the requested dose is within the FDA labeled dose for the requested indication

AND

2. The prescriber is a specialist (e.g. allergist, immunologist, pulmonologist) in the area of the patient’s diagnosis or the prescriber has consulted with a specialist in the area of the patient’s diagnosis

AND

3. The requested agent will NOT be used in combination with another biologic agent for the requested indication [e.g. injectable IL-5 inhibitor (Cinqair, Fasenra, Nucala), injectable IL-4 inhibitor (Dupixent)]

AND
4. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

**Length of approval:** 24 weeks for asthma and chronic idiopathic urticaria
12 months for all other FDA approved indications

**Renewal Evaluation**

**Xolair** (omalizumab) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through Prime Therapeutics PA process AND
2. ONE of the following:
   A. The patient has a diagnosis of moderate to severe persistent asthma AND ALL of the following
      i. The patient’s weight is within the FDA indicated range for their age (i.e. 20 kg to 150 kg for patients age 6 to less than 12 years and 30 kg to 150 kg for patients 12 years of age and above)
      AND
      ii. The patient has had clinical response or disease stabilization as defined by ONE of the following:
          a. Increase in percent predicted FEV1 from baseline OR
          b. Decrease in the dose of inhaled corticosteroid required to control the patient’s asthma OR
          c. Decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma OR
          d. Decrease in the number of hospitalizations, need for mechanical ventilation, or visits to the emergency room or urgent care due to exacerbations of asthma
      AND
      iii. ONE of the following:
          a. The patient is currently treated and is compliant with standard therapy (e.g. inhaled corticosteroids, long acting beta-2 agonists (LABA), leukotriene receptor antagonists (LTRA), Long-acting muscarinic antagonist (LAMA), theophylline) in the past 90 days OR
          b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL standard therapies
      AND
      iv. The requested dose is based on pre-treatment serum IgE level and the patient’s body weight as defined in FDA approved labeling AND does not exceed 375 mg every 2 weeks
   OR
   B. The patient has a diagnosis of chronic idiopathic urticaria AND BOTH of the following:
      i. The patient has had improvement in symptoms (e.g. number of hives, size of hives, reduction in itching)
      AND
      ii. The requested dose is within the FDA labeled dose AND does NOT exceed 300 mg every 4 weeks
   OR
   C. The patient has another FDA approved indication for the requested agent AND the requested dose is within the FDA labeled dose for the requested indication
3. The prescriber is a specialist (e.g. allergist, immunologist, pulmonologist) in the area of the patient’s diagnosis or the prescriber has consulted with a specialist in the area of the patient’s diagnosis

AND

4. The requested agent will NOT be used in combination with another biologic agent for the requested indication [e.g., injectable IL-5 inhibitor (Cinqair, Fasenra, Nucala), injectable IL-4 inhibitor (Dupixent)]

AND

5. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

**FDA-Approved Dosing for Patients Age 6 to less than 12 Years**

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<th>Dosing Freq.</th>
<th>Body Weight</th>
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<tr>
<td></td>
<td>20-25 kg</td>
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<tr>
<td>30-100</td>
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<td>&gt;100-200</td>
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<td>&gt;200-300</td>
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<td>&gt;300-400</td>
<td>225</td>
<td>300</td>
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<tr>
<td>&gt;400-500</td>
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<td>&gt;500-600</td>
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</tr>
<tr>
<td>&gt;600-700</td>
<td>375</td>
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</table>

**DO NOT DOSE**

**FDA-Approved Dosing for Patients 12 years of Age and Above**

<table>
<thead>
<tr>
<th>Pre-treatment serum IgE (IU/mL)</th>
<th>30-60</th>
<th>&gt; 60-70</th>
<th>&gt; 70-90</th>
<th>&gt; 90-150</th>
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<tbody>
<tr>
<td>≥ 30-100</td>
<td>150 mg q 4 wks</td>
<td>150 mg q 4 wks</td>
<td>150 mg q 4 wks</td>
<td>300 mg q 4 wks</td>
</tr>
<tr>
<td>&gt; 100-200</td>
<td>300 mg q 4 wks</td>
<td>300 mg q 4 wks</td>
<td>300 mg q 4 wks</td>
<td>225 mg q 2 wks</td>
</tr>
<tr>
<td>&gt; 200-300</td>
<td>300 mg q 4 wks</td>
<td>225 mg q 2 wks</td>
<td>225 mg q 2 wks</td>
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</tr>
<tr>
<td>&gt; 300-400</td>
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<tr>
<td>&gt; 400-500</td>
<td>300 mg q 2 wks</td>
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<tr>
<td>&gt; 500-600</td>
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<td>375 mg q 2 wks</td>
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<tr>
<td>&gt; 600-700</td>
<td>375 mg q 2 wks</td>
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Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE

The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL

The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

2. The patient's medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria