Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCRES017.1024	**RESPIRATORY AGENTS** **XOLAIR®** (omalizumab injection)
Effective Date: 11/1/2024	**Review/Revised Date**: 12/03, 12/04, 04/06, 02/07, 06/07RR, 02/08, 04/08, 08/09, 08/10, 12/11, 02/12, 06/13, 06/14, 05/15, 06/15, 05/16, 09/16, 05/17, 05/18, 11/18, 05/19, 05/20, 10/20, 04/21, 07/21, 05/22, 04/23, 08/23, 04/24, 10/24 (snm)
Original Effective Date: 12/03	**P&T Committee Meeting Date**: 12/03, 12/04, 04/06, 02/07, 06/07, 02/08, 08/09, 08/10, 12/11, 02/12, 06/13, 06/14, 05/15, 06/15, 06/16, 12/16, 06/17, 06/18, 12/18, 06/19, 06/20, 10/20 (off-cycle), 06/21, 08/21, 6/22, 06/23, 08/23, 06/24, 10/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts), must meet indication-specific criteria below:
    a. For **asthma**, must meet all of the following criteria:
        i. Diagnosis of moderate to severe persistent allergic asthma
        ii. IgE baseline levels greater than 30 IU/ml
        iii. Positive skin test to a common perennial aeroallergens
        iv. In the past three months, patient is adherent to treatment with maximally tolerated doses of both of the following, unless patient has an intolerance or contraindication to all therapies (This may be verified by pharmacy claims information):
            1) Inhaled corticosteroid
            2) One of the following:
                a) A long-acting inhaled beta 2-agonist (LABA)
                b) A leukotriene receptor antagonist (LTRA)
                c) A long-acting muscarinic antagonist (LAMA)
        v. Inadequate asthma control despite above therapy, defined as one of the following:
            1) Asthma Control Test (ACT) score less than 20 or Asthma Control Questionnaire (ACQ) score greater than or equal to 1.5

2) At least two exacerbations requiring oral systemic corticosteroids in the last 12 months
3) At least one exacerbation requiring hospitalization, emergency room or urgent care visit in the last 12 months
4) Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered
5) Baseline (prior to therapy with the requested agent) Forced Expiratory Volume (FEV1) that is less than 80% of predicted

b. For **chronic idiopathic urticaria**, must meet all the following criteria:
   i. Patient has had over six weeks of hives and itching
   ii. Condition is idiopathic and secondary causes of urticaria (such as offending allergens, physical contact, etc.) have been ruled out
   iii. Trial and failure (at least two weeks) of a second-generation non-sedating H1 antihistamine (such as levocetirizine, loratadine, cetirizine, fexofenadine)
   iv. Trial and failure (at least two weeks) of one additional medication from one of the following classes:
      1) leukotriene receptor antagonists (such as montelukast),
      2) first generation H1 antihistamine (such as diphenhydramine), or
      3) H2 antihistamine (such as famotidine, ranitidine)

c. For **nasal polyps**, must meet all of the following criteria:
   i. Evidence of bilateral nasal polyposis by direct examination, endoscopy or sinus CT scan
   ii. Patient had an inadequate response to a three-month trial of intranasal corticosteroids (such as fluticasone) or has an intolerance or contraindication to ALL intranasal corticosteroids
   iii. Patient will continue standard maintenance therapy (such as intranasal corticosteroids, nasal saline irrigation) in combination with omalizumab

d. For **IgE-mediated food allergy**, must meet all of the following criteria:
   i. The patient has a confirmed IgE-mediated food allergy confirmed by an allergy diagnostic test (such as skin prick test, serum specific IgE test, oral food challenge)
   ii. The patient will avoid known food allergens while treated with the requested agent
   iii. The requested agent will NOT be used for the emergency treatment of allergic reactions, including anaphylaxis

2. For <u>patients established</u> on the requested therapy within the previous year, response to therapy indicating improvement or stabilization of condition

EXCLUSION CRITERIA:
Concurrent use with anti-IL5 (such as mepolizumab, reslizumab, benralizumab), anti-IgE, anti-TSLP (such as tezepelumab), or anti-IL4 (such as dupilumab) monoclonal antibodies

AGE RESTRICTIONS:
For all indications, the patient's age must be within FDA labeling for the requested indication

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist, otolaryngologist, pulmonologist)

COVERAGE DURATION:
Asthma: Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

Urticaria, nasal polyps, food allergy: Initial authorization will be for one year and reauthorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Omalizumab (Xolair®) is an injectable medication for patients with moderate to severe persistent allergic asthma, chronic idiopathic urticaria (CIU) not controlled with other conventional therapies, food allergies and chronic rhinosinusitis with nasal polyps.

Omalizumab is a monoclonal antibody that binds to and blocks immunoglobulin E (IgE) which is responsible for causing the release of histamine and other inflammatory mediators from mast cells and basophils.

Omalizumab is given via a subcutaneous injection. The doses and dosing frequency in treating allergic asthma and nasal polyps is determined by total serum IgE level at baseline, and body weight. The dose in CIU is between 150 to 300 mg every four weeks and is independent of serum IgE level or body weight. . The dose for IgE-mediated food allergy is 75 mg to 600 mg every 2 or 4 weeks based on serum total IgE level (IU/mL), measured before the start of treatment, and by body weight.

FDA APPROVED INDICATIONS:

- Moderate to severe persistent asthma in patients six 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
- Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment
- Add-on maintenance treatment of chronic rhinosinusitis with nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add-on maintenance treatment
- Reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with IgE-mediated food allergy

POSITION STATEMENT:

Concomitant Asthma and Allergic Rhinitis

- According to the asthma management guidelines of the National Heart, Lung and Blood Institute (NHLBI), for individuals with moderate to severe persistent asthma already taking low- or medium dose ICS, the preferred treatment is a single inhaler with ICS-formoterol (referred to as single maintenance and reliever therapy, or “SMART”) used both daily and as needed.[16]
- The Global Initiative for Asthma (GINA) 2023 update utilizes a five-step treatment approach separated in two tracks (a preferred controller and reliever track and an alternative controller and reliever track) . If asthma remains uncontrolled despite good adherence and inhaler technique a step up in treatment is recommended. Add on therapy with omalizumab is an option for adults and children six years of age or older with moderate to severe allergic asthma if asthma is persistently uncontrolled despite step 4 or 5 treatments. Medium to high dose ICS-LABA is the recommended treatment in step 4.[14]
- Vignola and colleagues evaluated the efficacy of omalizumab in a randomized, double-blind, placebo-controlled trial involving 405 adults and adolescents with

concomitant allergic asthma and PAR. Enrollment criteria included an IgE concentration of 30–1300 IU/mL, a positive skin-prick test to an indoor allergen, a history of moderate-to-severe PAR for at least two years, asthma requiring ICS therapy, and a history of 2–3 unscheduled medical visits for asthma over the prior 1–2 years. Patients were also required to have quality of life testing scores that indicate greater than mild symptoms. Patients were randomized to subcutaneous omalizumab (at least 0.016 mg/kg per IU of IgE/mL per four weeks) or placebo for 28 weeks. End-of-trial comparisons to placebo revealed that fewer omalizumab recipients had experienced an asthma exacerbation (30.1% vs 20.6%, *P* = .02), and the mean rate of exacerbations was lower. Additionally, more omalizumab recipients reported clinically relevant changes and large improvements in quality of life.[6]

Numerical asthma control tools for assessment of asthma symptom control:[14]

- Asthma Control Test (ACT): Scores range from 5 to 24 (higher is better controlled symptoms). Scores of 20 to 25 is classified as well-controlled asthma; 16 to 19 as not well-controlled, and 5 to 15 as very poorly controlled asthma. The ACT includes a patient self-assessed level of asthma control, frequency of shortness of breath, use of rescue medications, and the effect on daily function due to asthma. The minimum clinically important difference is 3 points
- Asthma Control Questionnaire (ACQ): Scores range from 0 to 6 (higher score is worse control). A score of 0.0 to 0.75 is classified as well-controlled asthma; 0.75 to 1.5 is a "gray zone," and 1.5 or greater as poorly controlled asthma. ACQ score is calculated as the average of 5 to 7 items that includes five symptom questions. ACQ-7 includes a score for pre-bronchodilator FEV1, in addition to questions on symptoms and use of rescue medications. The minimum clinically important difference is 0.5 points.

Chronic Idiopathic Urticaria

- For the treatment of CIU, omalizumab has been approved based on two similarly designed Phase III randomized, double-blind, placebo-controlled studies (ASTERIA I and ASTERIA II). Patients (n=319 and n=322 respectively) with CIU were randomized to either Xolair 75, 150, or 300 mg or placebo by SC injection every four weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks. In both studies, patients receiving 150 mg and 300 mg had greater decreases in UAS7 (Weekly Urticarial Activity Score) from baseline compared to placebo. These results were not consistently demonstrated in the patients receiving the 75 mg dose.[1]
- Guidelines created by the American Academy of Allergy , Asthma & Immunology (AAAAI); American College of Allergy , Asthma &Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI) recommended a step

wise approach for the management of chronic urticaria. Step 1 includes the use of monotherapy with second-generation antihistamines and the avoidance of triggers as first-line therapy. Step 2 may include one or more of the following measures, higher doses of second-generation antihistamines used in step 1 with or without the addition of another second-generation antihistamine, a H2-antagonist, a leukotriene receptor antagonist, or a first-generation antihistamine (at bedtime). Step 3 involves the dose advancement of potent antihistamines (e.g., hydroxyzine or doxepin) as tolerated. Step 4 recommends the addition of alternative agents such as omalizumab, cyclosporine, other anti-inflammatory agents, or immunosuppressants.[8]

- Efficacy and dosing of omalizumab in patients with IgE levels greater than 30 IU/ml has been established for individuals with concomitant allergic asthma and allergic rhinitis.[1]
- Beneficial effects may not be seen with omalizumab for 6-12 weeks.[1]

Nasal Polyps

- Chronic rhinosinusitis with nasal polyposis (CRSwNP) is an inflammatory disease of the nasal mucosa and sinuses that lasts at least 12 weeks.[16]
- Omalizumab was assessed as add-on maintenance therapy for patients with nasal polyps, with an inadequate response to nasal corticosteroids, in two double-blind, placebo-controlled trials. Patients received either omalizumab or placebo every two to four weeks for 24 weeks. Dosing was based on pretreatment serum IgE and bodyweight. All patients received background nasal mometasone. Primary endpoints were changes in baseline bilateral Nasal Polyp Score (NPS) and Nasal Congestion Score (NCS). NPS was scored (range 0-4 per nostril: 0= no polyps; 1=small polyps in the middle meatus; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps; 4=large polyps causing complete obstruction of the inferior nasal cavity) for a total NPS (range 0-8). Nasal congestion was measured by a daily assessment on a 0 to 3 point severity scale (0=none, 1=mild, 2=moderate, 3=severe). The co-primary endpoint showed statistically significant improvement with omalizumab.[1]
- The 2023 Joint Task Force, consisting of members from the American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma, and Immunology, recommend the following: (1) In people with CRSwNP, the guideline panel suggests INCS rather than no INCS (conditional recommendation, low certainty of evidence). (2) In people with CRSwNP, the guideline panel suggests biologics rather than no biologics (conditional recommendation, moderate certainty of evidence). [16]

IgE – Mediated Food Allergy

- Omalizumab is the first FDA-approved medication to reduce allergic reactions to more than one type of food after accidental exposure.
- Omalizumab does not treat acute allergic food reactions and does not replace the use of epinephrine. Omalizumab is intended to be used in conjunction with food allergen avoidance.[1]
- Diagnosis of IgE-mediated food allergy includes a combination of clinical history and physical examination, skin testing, and food challenges.[19]
- Efficacy was established in a randomized, double-blind, placebo-controlled Food Allergy (FA) trial [NCT03881696] in 168 adult patients and pediatric patients 1 year of age to less than 56 years who were allergic to peanut and at least two other foods, including milk, egg, wheat, cashew, hazelnut, or walnut (i.e., studied foods).[18]
    - The primary efficacy endpoint was the percentage of patients who were able to consume a single dose of ≥600 mg of peanut protein without dose-limiting symptoms (e.g., moderate to severe skin, respiratory or gastrointestinal symptoms) during the double-blind placebo-controlled food challenge
    - Omalizumab treatment led to a statistically higher response rate, defined as the consumption of a single dose of the specified amount of food without dose-limiting symptoms vs. placebo (68% [75/110] vs. 5% [3/55]; treatment difference, 63% [95% CI, 50% to 73%]).
    - 17% of Omalizumab-treated patients had no significant change in the amount of peanut protein tolerated.

Black Box Warning[1]: Anaphylaxis
Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair®. Anaphylaxis has occurred as early as after the first dose of Xolair®, but also has occurred beyond one year after beginning regularly administered treatment. Omalizumab should be initiated under the guidance of a healthcare provider with possible patient self-administration after assessment of anaphylaxis risk and mitigation strategies. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after Xolair® administration, and health care providers administering Xolair® should be prepared to manage anaphylaxis that can be life-threatening. Patients should be informed of the signs and symptoms of anaphylaxis and now how to treat anaphylaxis appropriately.

REFERENCES:

1. Xolair® (omalizumab) for injection prescribing information. South San Francisco, CA: Genentech Inc. February 2023.

2. FDA Advisory Pulmonary-Allergy Subcommittee May 15, 2003.
3. Busse W, Corren J, Lanier Q. et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108:184-190.
4. Soler M. Matz J. Townley R. et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;18:254-261.
5. Holgate S et al. Omalizumab, reduces inhaled corticosteroid use in patients with severe allergic asthma receiving high dose inhaled corticosteroid therapy compared with placebo. Abstract 2001.
6. Vingola AM, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy, 2004 Jul;59(7):709-17.
7. Bernstein JA, Saini SS, Maurer M, et al. Efficacy Of Omalizumab In Patients With Chronic Idiopathic/Spontaneous Urticaria With Different Background Therapy: Post Hoc Analysis Of Asteria I, Asteria II, and Glacial Studies. Presented at: American Academy of Allergy, Asthma & Immunology Annual Meeting; March 2, 2014; San Diego, CA.
8. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-1277.
9. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018 Jul;73(7):1393-1414. doi: 10.1111/all.13397. PMID: 29336054.
10. DeConde AS, Soler ZM. Chronic rhinosinusitis: Epidemiology and burden of disease. *Am J Rhinol Allergy*. 2016; 30:134-139
11. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical Practice Guideline (Update): Adult Sinusitis. 2015; 152(2 suppl): S1-S39
12. Bachert C, Gevaert P, Hellings P. Biotherapeutics in Chronic Rhinosinusitis with and without Nasal Polyps. *J Allergy Clin Immunol Pract*. 2017 Nov-Dec;5(6):1512-1516.
13. Kartush AG, Schumacher JK, Shah R, Patadia MO. Biologic Agents for the Treatment of Chronic Rhinosinusitis With Nasal Polyps. *Am J Rhinol Allergy*. 2019 Mar;33(2):203-211.
14. Global Initiative for Asthma. Global initiative for asthma management and prevention (2023 update). Available at: http://www.ginasthma.org. Accessed on May 10, 2024.
15. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, Baptist AP, et al. 2020 Focused Updates to the Asthma Management

Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol 2020; 146:1217.

16. Rank MA, Chu DK, Bognanni A, et al. The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis. J Allergy Clin Immunol. 2023;151(2):386-398. doi:10.1016/j.jaci.2022.10.026
17. Orlandi, RR, Kingdom, TT, Smith, TL, et al. International consensus statement on rhinology and allergy: rhinosinusitis. Int Forum Allergy Rhinol. 2021; 11: 213– 739. https://doi.org/10.1002/alr.22741
18. Wood RA, et al. Omalizumab for the treatment of multiple food allergies. N Engl J Med. Published online February 25, 2024. doi:10.1056/NEJMoa2312382
19. Santos AF, et al. EAACI guidelines on the diagnosis of IgE-mediated food allergy. Allergy. 2023;78(12):3057-3076. doi:10.1111/all.15902