Clinical Policy: Omalizumab (Xolair)

Reference Number: CP.PHAR.01
Effective Date: 10.01.08
Last Review Date: 02.19
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Omalizumab (Xolair®) is an anti-IgE antibody.

FDA Approved Indication(s)

Xolair is indicated for:

- 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 (ICS). Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Chronic idiopathic urticaria (CIU) in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.

Limitation(s) of use: Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus, treatment of other allergic conditions, or treatment of other forms of urticaria.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Xolair is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Moderate to Severe Persistent Asthma (must meet all)**:**

1. Diagnosis of moderate to severe persistent asthma;
2. Prescribed by or in consultation with an allergist, immunologist, or pulmonologist;
3. Age ≥ 6 years;
4. Member has experienced ≥ 2 exacerbations, within the last 12 months, requiring any of the following despite adherent use of controller therapy (i.e., medium- to high-dose inhaled corticosteroid (ICS) plus either a long acting beta-2 agonist (LABA) or leukotriene modifier (LTRA) if LABA contraindicated/intolerance):
   a. Oral/systemic corticosteroid treatment (or increase in dose if already on oral corticosteroid);
   b. Urgent care visit or hospital admission;
   c. Intubation;
5. Positive skin test or *in vitro* reactivity to a perennial aeroallergen (see *Appendix D*);
6. Immunoglobulin E (IgE) level ≥ 30 IU/mL;

7. Xolair is prescribed concomitantly with an ICS plus either a LABA or LTRA;
8. Dose does not exceed 375 mg administered every 2 weeks (see *Appendix E* and *F* for dosing based on pre-treatment IgE level, weight, and age).

Approval duration: 6 months

B. Chronic Idiopathic Urticaria (must meet all):

1. Diagnosis of CIU;
2. Prescribed by or in consultation with a dermatologist, immunologist, or allergist;
3. Age ≥ 12 years;
4. Failure of both of the following unless contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Two antihistamines (including one second generation antihistamine – e.g., cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine) at maximum indicated doses, each used for ≥ 2 weeks;
   b. A LTRA in combination with an antihistamine at maximum indicated doses for ≥ 2 weeks;
5. Dose does not exceed 300 mg every 4 weeks.

Approval duration: 6 months

C. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Moderate to Severe Persistent Asthma (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Demonstrated adherence to asthma controller therapy that includes an ICS plus either an LABA or LTRA;
3. Member is responding positively to therapy (examples may include but are not limited to a reduction in exacerbations or corticosteroid dose, improvement in forced expiratory volume over one second) since baseline; reduction in the use of rescue therapy);
4. If request is for a dose increase, new dose does not exceed 375 mg administered every 2 weeks (see *Appendix E* and *F* for dosing based on pre-treatment IgE level, weight, and age).

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or member's renewal period, whichever is longer

B. Chronic Idiopathic Urticaria (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;

3. If request is for a dose increase, new dose does not exceed 300 mg every 4 weeks.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or member's renewal period, whichever is longer

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents;

B. Acute bronchospasm or status asthmaticus.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AAAAI: American Academy of Allergy, Asthma, and Immunology
CIU: Chronic Idiopathic Urticaria
EAACI: European Academy of Allergy and Clinical Immunology
EDF: European Dermatology Forum
EPR3: Expert Panel Report 3
GA2LEN: Global Allergy and Asthma European Network
GINA: Global Initiative for Asthma
ICS: inhaled corticosteroids
LABA: long-acting beta-agonist
LTRA: leukotriene modifier
WAO: World Allergy Organization

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Asthma – ICS (medium – high dose)		
Qvar® (beclomethasone)	> 100 mcg/day 40 mcg, 80 mcg per actuation 1-4 actuations BID	4 actuations BID
budesonide (Pulmicort®)	> 200 mcg/day 90 mcg, 180 mcg per actuation 2-4 actuations BID	2 actuations BID
Alvesco® (ciclesonide)	> 80 mcg/day 80 mcg, 160 mcg per actuation	2 actuations BID

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	1-2 actuations BID	
Aerospan® (flunisolide)	≥ 320 mcg/day 80 mcg per actuation 2-4 actuations BID	2 actuations BID
Flovent® (fluticasone propionate)	>176 mcg/day 44-250 mcg per actuation 2-4 actuations BID	2 actuations BID
Arnuity Ellipta® (fluticasone furoate)	200 mcg/day (≥ 12 years only) 100 mcg, 200 mcg per actuation 1 actuation QD	1 actuation QD
Asmanex® (mometasone)	≥ 220 mcg/day HFA: 100 mcg, 200 mcg per actuation Twisthaler: 110 mcg, 220 mcg per actuation 1-2 actuations QD to BID	2 inhalations BID
Asthma - LABA		
Serevent® (salmeterol)	50 mcg per dose 1 inhalation BID	1 inhalation BID
Asthma - Combination products (ICS + LABA)		
Dulera® (mometasone/ formoterol)	100/5 mcg, 200/5 mcg per actuation 2 actuations BID	4 actuations per day
Breo Ellipta® (fluticasone/vilanterol	100/25 mcg, 200/25 mcg per actuation 1 actuation QD	1 actuation QD
Advair® (fluticasone/ salmeterol)	Diskus: 100/50 mcg, 250/50 mcg, 500/50 mcg per actuation HFA: 45/21 mcg, 115/21 mcg, 230/21 mcg per actuation 1 actuation BID	1 actuation BID
fluticasone/salmeterol (Airduo RespiClick®)	55/13 mcg, 113/14 mcg, 232/14 mcg per actuation 1 actuation BID	1 actuation BID
Symbicort® (budesonide/ formoterol)	80 mcg/4.5 mcg, 160 mcg/4.5 mcg per actuation 2 actuations BID	2 actuations BID
Asthma - LTRA		
montelukast (Singulair®)	4 to 10 mg PO QD	10 mg per day
zafirlukast (Accolate®)	10 to 20 mg PO BID	40 mg per day
zileuton ER (Zyflo® CR)	1200 mg PO BID	2400 mg per day
Zyflo® (zileuton)	600 mg PO QID	2400 mg per day
Asthma - Oral corticosteroids		
dexamethasone (Decadron®)	0.75 to 9 mg/day PO in 2 to 4 divided doses	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
methylprednisolone (Medrol®)	40 to 80 mg PO in 1 to 2 divided doses	Varies
prednisolone (Millipred®, Orapred ODT®)	40 to 80 mg PO in 1 to 2 divided doses	Varies
prednisone (Deltasone®)	40 to 80 mg PO in 1 to 2 divided doses	Varies
CIU		
hydroxyzine (Vistaril®)	Adult: 25 mg PO TID to QID Age ≥ 6 years: 50 mg-100 mg/day in divided doses	Adult: Will vary according to condition Age ≥ 6 years: 50 mg-100 mg/day in divided doses
diphenhydramine (Benadryl®)	Adult: 25 mg to 50 mg PO TID to QID Pediatric: 12.5 mg to 25 mg PO TID to QID or 5 mg/kg/day or 150 mg/m²/day	Adult: Will vary according to condition Children: 300 mg/day
chlorpheniramine (Aller-Chlor®)	Immediate Release: 4 mg PO every 4 to 6 hours Extended Release: 12 mg PO every 12 hours	Do not exceed 24 mg/day
cetirizine (Zyrtec®)	5 to 10 mg PO QD	10 mg/day
levocertirizine (Xyzal®)	2.5 mg to 5 mg PO QD	5 mg/day
loratadine (Claritin®)	10 mg PO QD	10 mg/day
desloratadine (Clarinex®)	5 mg PO QD	Will vary according to condition
fexofenadine (Allegra®)	60 mg PO BID or 180 mg QD	180 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): hypersensitivity
- Boxed warning(s): anaphylaxis

Appendix D: General Information

- Allergic asthma:
  - The definition of moderate to severe allergy varied among the clinical trials. The definition most often used was a patient who required oral systemic steroid bursts or unscheduled physician office visits for "uncontrolled" asthma exacerbations despite maintenance inhaled steroid use. Patients in the clinical trials most often were

required to have an FEV_1 between 40% and 80% of predicted. No patients were enrolled with an FEV_1 greater than 80% of predicted.
  - Xolair has been shown to be marginally effective in decreasing the incidence of asthma exacerbations in patients who have met all the criteria described above.
  - Xolair provides little therapeutic benefit over existing therapies. Use in patients on inhaled corticosteroids or chronic oral steroids plus or minus a second controller agent decreased asthma exacerbation by 0.5 to 1 per year. Use of rescue beta-agonists declined by 1 inhalation per day. Small changes in pulmonary function tests were also seen. An analysis of unpublished data indicated that hospital admissions declined by 3 per hundred patient years, emergency department (ED) visits by 2 per hundred patient years, and unscheduled physician office visits by 14 per one hundred patient years.
  - The National Heart, Lung and Blood Institute's Expert Panel Report 3 (EPR3) Guidelines for the Diagnosis and Management of Asthma recommend Xolair may be considered as adjunct therapy for patients 12 years and older with allergies and Step 5 or 6 (severe) asthma whose symptoms have not been controlled by ICS and LABA.
  - The four perennial aeroallergens most commonly tested for in the clinical trials were dog dander, cat dander, cockroach, and house dust mite.
  - Serious and life-threatening allergic reactions (anaphylaxis) in patients after treatment with Xolair have been reported. Usually these reactions occur within two hours of receiving a Xolair subcutaneous injection. However, these new reports include patients who had delayed anaphylaxis—with onset two to 24 hours or even longer-after receiving Xolair treatment. Anaphylaxis may occur after any dose of Xolair (including the first dose), even if the patient had no allergic reaction to the first dose.
  - Positive response to therapy for asthma may include reduction in exacerbations or corticosteroid dose, improvement in forced expiratory volume over one second since baseline, or reduction in the use of rescue therapy.
- CIU:
  - CIU is classified as spontaneous onset of wheals, angioedema, or both, for more than 6 weeks due to an unknown cause.
  - Clinical studies have shown that Xolair 150 mg and 300 mg significantly improved the signs and symptoms of chronic idiopathic urticaria compared to placebo in patients who had remained symptomatic despite the use of approved dose of H_1-antihistamine.
  - The Joint Task Force on Practice Parameters representing various American allergy organizations include Xolair in combination with H1-antihistamines as a fourth line treatment option following a stepwise approach starting with a second generation antihistamine. This is followed by one or more of the following: a dose increase of the second generation antihistamine, or the addition of another second generation antihistamine, H2-antagonist, LTRA, or first generation antihistamine. Treatment with hydroxyzine or doxepin can be considered in patients whose symptoms remain poorly controlled.
  - The EAACI/GA2LEN/EDF/AAAAI/WAO Guideline for the Management of Urticaria include Xolair in combination with H_1-antihistamines as a third line treatment option in patients who have failed to respond to higher doses of H_1-Antihistamines.

- Xolair is the first medicine in its class approved for CIU since non-sedating antihistamines.
- The use of over-the-counter H_1 antihistamines may not be a benefit to the treatment of chronic idiopathic urticaria. Credit will be given for its use, but will not be covered under plan.
- Anaphylaxis has occurred as early as after the first dose of Xolair, but also occurred beyond 1 year after beginning regularly administered treatment.

Appendix E: Age ≥ 12 years: Asthma dosing based on pre-treatment IgE and body weight†

Pre-treatment serum IgE IU/mL	Dosing Frequency	Body Weight			
		30-60 kg	>60-70 kg	>70-90 kg	>90-15 kg
≥ 30-100	Q 4 weeks	150 mg	150 mg	150 mg	300 mg
> 100-200		300 mg	300 mg	300 mg	225 mg
> 200-300		300 mg	225 mg	225 mg	300 mg
> 300-400	Q 2 weeks	225 mg	225 mg	300 mg	
> 400-500		300 mg	300 mg	375 mg	
> 500-600		300 mg	375 mg	Insufficient Data to Recommend a Dose	
> 600-700		375 mg			

†The manufacturer recommends dose adjustments for significant body weight changes during treatment.

Appendix F: Age 6 to < 12 years: Asthma dosing based on pre-treatment IgE and body weight†

Pre-treatment serum IgE IU/mL	Dosing Frequency	Body Weight									
		20-25 kg	>25-30 kg	>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	>125-150 kg
≥ 30-100	Q 4 weeks	75	75	75	150	150	150	150	150	300	300
>100-200		150	150	150	300	300	300	300	300	225	300
>200-300		150	150	225	300	300	225	225	225	300	375
>300-400		225	225	300	225	225	225	300	300		
>400-500		225	300	225	225	300	300	375	375		
>500-600		300	300	225	300	300	375				
>600-700		300	225	225	300	375					
>700-800	Q 2 weeks	225	225	300	375						
>800-900		225	225	300	375						
>900-1000		225	300	375							
>1000-1100		225	300	375	Insufficient Data to Recommend a Dose						
>1100-1200		300	300								
>1200-1300		300	375								

†The manufacturer recommends dose adjustments for significant body weight changes during treatment.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Allergic asthma	75 to 375 mg SC every 2 or 4 weeks based on serum total IgE level (IU/mL) measured before the start of treatment, and body weight (kg)	375 mg/4 weeks

Indication	Dosing Regimen	Maximum Dose
	Xolair is not approved for use in patients weighing more than 150 kg. (*See Appendix E and F*). Do not administer more than 150 mg (contents of one vial) per injection site. Divide doses of more than 150 mg amongst two or more injection sites.	
CIU	150 mg or 300 mg SC every 4 weeks	300 mg/4 weeks

VI. Product Availability

- Single-dose vial: 150 mg
- Single-dose prefilled syringe: 75 mg/0.5 mL, 150 mg/mL

VII. References

1. Xolair Prescribing Information. Irvine, CA: Spectrum Pharmaceuticals, Inc.; September 2018. Available at: https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed October 11, 2018.
2. National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). Available at http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines. Accessed November 2017.
3. 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.
4. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014;69:868-87.
5. Fine LM, Bernstein JA. Guideline of Chronic Urticaria Beyond. Allergy Asthma Immunol Res. 2016 September; 8(5): 396-403.
6. MICROMEDEX® Healthcare Series [Internet database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed October 11, 2018.
7. Global Initiative for Asthma: Global strategy for asthma management and prevention (2018 update). Available at: https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed November 13, 2018.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J2357	Injection, omalizumab, 5 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Removed peak flow meter reading improvement from reauthorization algorithm	02.14	03.14
Added indication for urticaria	06.14	06.14
Reworded FDA-approved indication to mirror package insert. Added safety section to discuss black box warning. Appendix B: Modified appendix to require use of high-dose corticosteroids along with leukotriene modifiers, rather than leukotriene modifiers by themselves. Figure 1: Modified wording to read "Does patient practice adequate ICS dose titration or use of oral steroid therapy for asthma exacerbations?" Figure 3: Modified algorithm to require failure or intolerance to at least two (rather than one) H1 antihistamines at maximum tolerated doses.	04.15	05.15
Policy converted to new format. Age included per PI; all documentation requests removed; modified requirement for 3 months of adherent use to requirement for at least 2 exacerbations in the last 12 months despite adherent use of controller medication; changed "RAST" to "immunoassay." Changed requirement for nonsmoker and nonsmoking home to engaged in smoking cessation efforts if smoker. Added requirement for concomitant use of maintenance therapy in asthma, failure or contraindication to step therapy for CIU, maximum allowed dose to asthma and CIU criteria; "positive response" to CIU continuation criteria; definition of positive response to asthma continuation criteria; safety information to background regarding anaphylaxis and provider administration of Xolair. Removed criteria regarding response to therapy and rescuer inhaler use from asthma renewal criteria; questions about adverse reaction to Xolair for continuation of therapy requirement for both asthma and CIU.	03.16	05.16
Minimum age changed to 6 for asthma, per PI. Added pediatric dosing to Appendix B.	09.16	09.16
Asthma step therapy edited to require LABAs before LTRAs unless contraindicated or intolerant. Added positive response to therapy under continued approval. CIU: Examples of second-generation antihistamines added.	02.17	02.17
Initial criteria: IgE level between 30-700 IU/mL is edited to read "between 30-1300 IU/mL" per PI.	03.17	
Requirement for FEV1 < 80% is removed from the asthma criteria. Approval durations increased from 3/6 to 6/12 months.	07.17	07.17
1Q18 annual review:	11.07.17	02.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
- Converted to the new template - Combined Medicaid and commercial policies. - New policy for HIM line of business. - Removed smoking cessation program requirements from existing Medicaid policy as this cannot be enforced. - Added "Acute bronchospasm or status asthmaticus" to section III as indications for which coverage is not authorized per PI. For CIU, modified length of trials from 4 to 2 weeks each - References reviewed and updated		
Updated Appendix E to align with PI dosing table.	03.29.18	
1Q 2019 annual review: modified ICS requirement to include medium dose ICS per GINA 2018 recommendations; added option for immunologist prescribing; 6 month initial approval duration applied to all lines of business for all indications; references reviewed and updated.	10.11.18	02.19

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan

retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.