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Medication Policy Manual **Policy No:** dru538

Topic: Monoclonal antibodies for asthma and other immune conditions

- Cinqair, reslizumab
- Fasenra, benralizumab
- Nucala, mepolizumab
- Tezspire, tezepelumab-ekko
- Xolair, omalizumab

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are monoclonal antibodies that target specific proteins to treat several immune diseases such as severe asthma, chronic obstructive pulmonary disease (COPD), and chronic idiopathic urticaria. Administration is via subcutaneous (SC) or intravenous (IV) injection.

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Policy/Criteria

Most contracts require pre-authorization approval of monoclonal antibodies for asthma and other immune conditions prior to coverage.

I. Continuation of therapy (COT): Monoclonal antibodies for asthma and other immune conditions may be considered medically necessary for COT when criteria A and B below are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. For provider-administered medications: site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

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II. New starts (treatment-naïve) patients: Monoclonal antibodies for asthma and other immune conditions may be considered medically necessary when criteria A and B below are met.

A. **For provider-administered medications** (per *Table 1*): Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

AND

B. One of the following diagnostic criterion (1 through 7) below is met.

1. **Asthma:**
Fasenra (benralizumab), Nucala (mepolizumab), Cinqair (reslizumab), or Xolair (omalizumab), or Tezspire (tezepelumab-ekko) may be considered medically necessary for severe asthma when there is clinical documentation (such as chart notes) that criteria a through f below are met.

a. Patient is currently followed by an asthma specialist (allergist, immunologist, or pulmonologist).

AND

b. Adherent use of maximally tolerated inhaled corticosteroids (ICS) and long-acting inhaled beta-2 agonist (LABA) therapy (see *Appendices 1 and 2*) has been ineffective as defined by at least one of the following markers of uncontrolled asthma within the previous 12 months (as defined in criterion i, ii, or iii below):

i. Treatment with a course of oral corticosteroids (e.g., steroid bursts).

OR

ii. An emergency department (ED) visit or hospitalization.

OR

iii. There is clinical documentation of poor asthma control as demonstrated by limitation of activities of daily living (ADLs), nighttime awakening, or dyspnea.

AND

c. An evaluation has been performed to assess for underlying conditions or triggers for asthma or pulmonary disease. If identified, a documented plan is in place to address these.

AND

d. **For Fasenra (benralizumab), Nucala (mepolizumab), and Cinqair (reslizumab) only:** A blood eosinophil count of at least 150 cells/µL in the past 12 months.

AND

e. **For Xolair (omalizumab) only:** A diagnosis of **severe extrinsic (allergic) asthma** and criteria i and ii below are met:

i. Positive skin prick test or in-vitro specific IgE test (such as RAST, MAST, FAST, ELISA) to one or more allergens, (or

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is currently receiving specific immunotherapy like allergy shots) which support the patient's clinical history.

AND

ii. Total serum IgE level is one of the following (1 or 2 below):

1. For patients ≥12 years of age: 30 to 700 IU/ml

OR

2. For patients age 6 to <12 years of age, based on weight, as follows in a through g below:

a. >90 to 150 kg: 30 to 300 IU/ml.

b. >70 to 90 kg: 30 to 500 IU/ml.

c. >60 to 70 kg: 30 to 600 IU/ml.

d. >50 to 60 kg: 30 to 700 IU/ml.

e. >40 to 50 kg: 30 to 900 IU/ml.

f. >30 to 40 kg: 30 to 1,100 IU/ml.

g. 20 to 30 kg: 30 to 1,300 IU/ml.

AND

f. For Cinqair (reslizumab) only: Clinical documentation confirming that treatment with the following (i and ii) have been ineffective, not tolerated, or contraindicated:

i. provider-administered, Nucala (mepolizumab).

AND

ii. provider-administered, Fasenra (benralizumab).

OR

2. Chronic idiopathic/Spontaneous Urticaria (CIU/CSU):
Xolair (omalizumab) may be considered medically necessary for CIU/CSU when there is clinical documentation (such as chart notes) that all criteria a through e below are met.

a. Specialist evaluation: Patient has been evaluated by and is currently followed by a specialist (allergist, immunologist, pulmonologist, dermatologist).

AND

b. A diagnosis of chronic idiopathic/spontaneous urticaria and current urticarial flares as supported by i and ii below:

i. Documentation of spontaneous flares: Spontaneous urticarial flares, despite avoidance of triggers (in the absence of potential triggers).

PLEASE NOTE: Urticarial flares may also occur in the presence of a trigger ("inducible urticaria"). However, patients may have a mixed diagnosis of CSU/CIU, along with inducible urticaria. The intent of this criterion is for documentation of spontaneous flares, in the absence of a trigger.

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AND

ii. Comprehensive evaluation: An evaluation has been performed to rule out other causes of urticaria and identify potential triggers, and a trigger management plan is in place, if applicable.

AND

c. Trigger avoidance: Underlying conditions or identified triggers for urticaria are being maximally managed, including a trigger avoidance management plan for any identified triggers to reduce flares.

AND

d. Documented functional impairment due to poor urticaria control or exacerbations, which may include (but is not limited to) documentation of limitation of activities of daily living (ADLs), such as missing school or work or insomnia due to itching.

AND

e. Maximal antihistamine step therapy: The patient is compliant with H1 antihistamines (see *Appendix 3*) at the maximally tolerated doses consistent with current guidelines, unless contraindicated.

PLEASE NOTE: Clinical documentation of initial urticaria workup, as well as subsequent visits, should be submitted for review.

OR

3. Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome):

Nucala (mepolizumab) and Fasenra (benralizumab) may be considered medically necessary for EGPA when there is clinical documentation (such as chart notes) that criteria a, b, and c below are met.

a. A specialist (allergist, immunologist, pulmonologist, or rheumatologist) has established the diagnosis and is currently following the patient.

AND

b. The patient has a diagnosis of EGPA confirmed by either criterion i or ii below:

i. The patient meets **at least four** of the six criteria (1 to 6) below:

1. History of asthma (wheezing or the finding of diffusion high-pitched wheezes in expiration).

2. Blood eosinophil count of greater than 10% (% EOS) on differential white blood count (diff WBC).

3. Peripheral neuropathy.

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4. Migratory or transient pulmonary opacities detected radiographically (such as on chest X-ray; CXR).

5. Paranasal sinus abnormality.

6. Blood vessel biopsy (such as artery, arteriole, or venule) with extravascular eosinophils.

OR

ii. The patient meets ALL of the following criteria 1, 2, and 3 below:

1. Medical history of asthma.

AND

2. Peak blood eosinophil count of greater than 1500 cells/microliter.

AND

3. Systematic vasculitis involving two or more extra-pulmonary organs.

AND

c. The patient has a history of EGPA for at least 6 months with a history of relapsing or refractory disease and criteria i and ii below are met.

i. Currently on maximally tolerated oral corticosteroid within the past 90 days, unless not tolerated or contraindicated.

AND

ii. Treatment with an oral DMARD (such as azathioprine or methotrexate) in the past 90 days has been ineffective, not tolerated, or all oral DMARDs are contraindicated.

OR

4. Hypereosinophilic Syndrome (HES):

Nucala (mepolizumab) may be considered medically necessary for HES when there is clinical documentation (such as chart notes) that criteria a, b, and c below are met.

a. A specialist (allergist, dermatologist, immunologist, hematologist, neurologist, or pulmonologist) has established the diagnosis and is currently following the patient.

AND

b. The patient has a diagnosis of HES and criteria i and ii below are met.

i. FIP1L1-PDGFRA–negative.

AND

ii. Peak blood eosinophil count of greater than 1000 cells/microliter.

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AND

c. The patient has a history of flares and criteria i and ii below are met.

i. Treatment with an adequate course (at least four weeks) of oral corticosteroids within the past 6 months, unless not tolerated or contraindicated.

AND

ii. Persistent HES symptoms despite adequate treatment (at least four weeks) with a steroid-sparing therapy (as listed in Appendix 4) within the past 6 months has been ineffective, not tolerated, or all are contraindicated.

OR

5. Nasal Polyps:
Xolair (omalizumab) or Nucala (mepolizumab) may be considered medically necessary for nasal polyps when there is clinical documentation (such as chart notes) that criteria a through f below are met.

a. The diagnosis has been established by a specialist in allergy, immunology, or otolaryngology.

AND

b. Documented recurrent, persistent, and/or current symptomatic nasal polyps, defined as meeting one of the following (i or ii) below:

i. The nasal polyps are currently documented as bilateral.

OR

ii. A history of recurrent bilateral nasal polyps, requiring more than one nasal polypectomy.

AND

c. Persistent symptomatic nasal polyps despite maximal medical treatment with both of the following (i and ii), unless ineffective, contraindicated, or not tolerated:

i. A corticosteroid used intranasally (INCS) for at least 12 weeks, as documented by detailed chart notes, including, but not limited to, a non-prescription INCS, INCS eluding stent) or pharmacy claims (for prescriptions INCS).

AND

ii. At least one 5-to-14-day course of oral corticosteroids in the past two years.

AND

d. There is a treatment plan for use in combination with an intranasal corticosteroid.

AND

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e. Documented functional impairment due to CRSwNP, including, but not limited to, poor sleep quality, loss of smell, symptomatic nasal obstruction, and/or facial pain.

AND

f. **For Xolair (omalizumab) only:** Total serum IgE level is between 30 IU/ml and 1500 IU/ml.

OR

6. IgE-mediated food allergy:

Xolair (omalizumab) may be considered medically necessary for IgE-mediated food allergy when there is clinical documentation (such as chart notes) that criteria a through e below are met:

a. Multiple confirmed allergies:

i. A diagnosis of an IgE-mediated food allergy to multiple (at least two) foods.

PLEASE NOTE: use in isolated single food allergy, such as isolated peanut allergy, is considered Not Medically Necessary.

AND

ii. The food allergies are confirmed by a positive result of at least one of the following in the last 5 years (1, 2, or 3):

1. A skin prick test (SPT) to the offending food allergens.

OR

2. A food-specific IgE test to the specific offending food allergens.

OR

3. An oral food challenge to the offending food allergens.

AND

b. Age: The patient is 1-17 years old at the start of Xolair (omalizumab) therapy.
PLEASE NOTE: use in age > 17 is considered 'Not Medically Necessary'.

AND

c. Specialist: Xolair (omalizumab) is prescribed by an allergist or immunologist.

AND

d. Severity: Documentation of at least one significant allergic reaction *despite maximal allergen avoidance*, defined as meeting all the following criteria (i and ii):

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i. The reaction was a significant *systemic* allergic reaction with documented symptoms including, but not limited to, hives, swelling, wheezing, hypotension, gastrointestinal symptoms, and/or anaphylaxis, associated with exposure to the food allergen (such as ingestion or inhalation).

AND

ii. The reaction prompted a medical intervention, defined as the use of an epinephrine rescue device, an unplanned urgent medical visit (such as to the emergency department or urgent care), or hospitalization.

AND

e. Ongoing avoidance: There is a treatment plan for use in conjunction with ongoing food allergen avoidance and availability of self-administered epinephrine (such as EpiPen autoinjector) for management of anaphylaxis with accidental ingestion.

OR

7. Chronic Obstructive Pulmonary Disease (COPD):

Nucala (mepolizumab) may be considered medically necessary for *eosinophilic* COPD when there is clinical documentation (such as chart notes) that criteria a through d below are met:

a. The diagnosis has been established by a specialist in pulmonology.

AND

b. Use of combination triple inhaler therapy [inhaled corticosteroid (ICS) and a long-acting muscarinic antagonist (LAMA) and a long-acting beta agonist (LABA)] for at least three consecutive months (unless LABA or LAMA are contraindicated or not tolerated).

AND

c. A blood eosinophil count of at least 300 cells/μL while on combination triple inhaler therapy (ICS and LAMA and LABA).

AND

d. COPD exacerbations within the previous year while receiving triple inhaled therapy (ICS+LAMA+LABA) when criterion i or ii is met:

i. Two or more moderate exacerbations, defined as exacerbations that resulted in treatment with a systemic glucocorticoid, antibiotic, or both.

OR

ii. One or more severe exacerbations, defined as an exacerbation that led to hospitalization or an emergency medical visit.

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III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers products in this policy covered per the administration and benefits as detailed in *Table 1*:

Table 1. Provider- versus Self-administered Products

Provider-Administered Product Pharmacy Services considers the following under the medical benefit (as provider-administered medications):	**Coverable Self-Administered Alternatives** Pharmacy Services considers the following coverable under the pharmacy benefit (as self-administered medications):
- Fasenra (benralizumab) PFS	- Fasenra (benralizumab) autoinjector
- Nucala (mepolizumab) vials - Nucala (mepolizumab) PFS [a]	- Nucala (mepolizumab) autoinjector - Nucala (mepolizumab) PFS [a]
- Xolair (omalizumab) vials - Xolair (omalizumab) PFS [a]	- Xolair (omalizumab) autoinjector - Xolair (omalizumab) PFS [a]
- Cinqair (reslizumab) vials	N/A
- Tezspire (tezepelumab-ekko) vials - Tezspire (tezepelumab-ekko) PFS	- Tezspire (tezepelumab-ekko) single-use autoinjector

[a] Pharmacy Services considers this product coverable under the pharmacy benefit (as a self-administered medication) **OR** coverable under the medical benefit (as a provider-administered medication).
PFS = pre-filled syringe

B. When pre-authorization is approved, each drug will be covered in the following quantities and for the following authorization periods outlined in *Table 2*.

TABLE 2. Authorization Limits

Product	**Authorization Limits**
Cinqair (reslizumab)	**Severe eosinophilic asthma:** - Up to 3 mg/kg every 28 days. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met, and the medication is effective, defined as sustained clinical improvement from reduced asthma symptoms (such as reduced missed days from work or school) or stable asthma control.
Fasenra (benralizumab)	**Severe eosinophilic asthma:** 12 years of age and older: - Up to 8 doses (30mg/ml PFS or 30mg/ml autoinjector; dosage form per *Table 1*) in a 52-week period, based on recommended initial dosing of 30 mg every 4 weeks for 3 doses, followed by 30 mg every 8 weeks. 6 years to 11 years of age: - *Weighing less than 35 kg*: Up to 8 doses (10mg/ml PFS) in a 52-week period, based on recommended initial dosing of 10mg every 4 weeks for 3 doses, followed by 10mg every 8 weeks.

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Product	Authorization Limits
	- *Weighing 35 kg or more*: Up to 8 doses (30mg/ml PFS or 30mg/ml autoinjector; dosage form per *Table 1*) in a 52-week period, based on recommended initial dosing of 30mg every 4 weeks for 3 doses, followed by 30mg every 8 weeks. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met, and the medication is effective, defined as sustained clinical improvement from reduced asthma symptoms (such as reduced missed days from work or school) or stable asthma control. **Eosinophilic Granulomatosis with Polyangiitis (EGPA):** - One 30mg injection (30mg PFS or 30mg autoinjector; dosage form per *Table 1)* every 28 days for up to 12 months. - Authorization **shall** be reviewed at least every 12 months to confirm that current medical necessity criteria are met, and the medication is effective, defined as disease stability, improvement, or decreased corticosteroid dose.
Nucala (mepolizumab)	**Severe eosinophilic asthma:** - Up to 100 mg (one vial, PFS, or autoinjector; dosage form per *Table 1*) every 28 days. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met, and the medication is effective, defined as sustained clinical improvement from reduced asthma symptoms (such as reduced missed days from work or school) or stable asthma control. **Eosinophilic Granulomatosis with Polyangiitis (EGPA) or Hypereosinophilic Syndrome (HES):** - Up to 300 mg (three – 100 mg vials, three – 100 mg PFS, or three – 100 mg autoinjectors; dosage form per *Table 1*) every 28 days for up to 12 months. - Authorization **shall** be reviewed at least every 12 months to confirm that current medical necessity criteria are met, and the medication is effective, defined as disease stability, improvement, or decreased corticosteroid dose. **Nasal Polyps:** - Up to 100mg (one vial, PFS, or autoinjector) every 28 days. - Authorization **may** be reviewed at least every 12 months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, that there is ongoing INCS use, and that the medication is effective, defined as sustained clinical improvement from reduced symptoms from nasal polyps (such as improved sleep quality, sense of smell, reduction in nasal obstruction symptoms, and/or facial pain) or stable chronic rhinosinusitis with nasal polyps (CRSwNP) control. **COPD:** - Up to 100mg (one vial, PFS or autoinjector) every 28 days. - Authorization **may** be reviewed at least every 12 months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is effective, defined as a sustained clinical improvement from reduced exacerbations of COPD with eosinophilic phenotype.

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Product	Authorization Limits
Tezspire (tezepelumab-ekko)	**Severe asthma:** - 210 mg (one vial, pre-filled syringe, or pen) every 28 days. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met and the medication is effective, defined as sustained clinical improvement from reduced asthma symptoms (such as reduced missed days from work or school) or stable asthma control.
Xolair (omalizumab)	**Severe extrinsic (allergic) asthma:** - Up to 375 mg every 14 days [375 mg dose supplied as up to three - single-dose 150 mg vials (total of 3 mL) OR two - 150 mg and one - 75 mg PFS or autoinjector (total of 2.5 mL) OR one - 300mg and one - 75mg PFS or autoinjector (total of 2.5 ml); dosage form per *Table 1*]. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met, and the medication is effective defined as sustained clinical improvement from reduced asthma/ symptoms (such as reduced missed days from work or school) or stable asthma control. **Chronic Idiopathic/ Spontaneous urticaria (CIU/CSU):** - Up to 300 mg every 28 days [300 mg dose supplied as up to two - 150 mg single-dose vials OR two - 150 mg PFS or autoinjectors (total of 2 ml) OR one - 300mg PFS or autoinjector (total of 2 ml); dosage form per *Table 1*]. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met and the medication is effective defined as sustained clinical improvement from reduced urticaria symptoms (such as reduced missed days from work or school) or stable urticaria control. - Dose Escalation: Doses of up to 600 mg every 28 days (such as 300 mg every 14 days) may be authorized on a case-by-case basis if documentation of objective measures supporting the need for more frequent dosing are provided, including documentation of partial response to initial dosing but incomplete urticaria control. **Nasal Polyps:** - Up to 600 mg every 14 days [600 mg dose supplied as up to four – single-dose 150 mg vials, PFS or autoinjectors (total of 4 mL) OR up to two – 300 mg PFS or autoinjectors (total of 4 ml); dosage form per *Table 1*]. - Authorization **may** be reviewed at least every 12 months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, that there is ongoing INCS use and that the medication is effective defined as sustained clinical improvement from reduced symptoms from nasal polyps (such as improved sleep quality or sense of smell, reduction in nasal obstruction symptoms and/or facial pain) or stable chronic rhinosinusitis with nasal polyps (CRSwNP) control.

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Product	Authorization Limits
	IgE-Mediated Food Allergy: - Initial authorization: (6 months): up to 600mg every 14 days [600 mg dose supplied as up to two 300 mg PFS or autoinjectors (total of 4 ml) OR up to four 150 mg single-dose vials, PFS or autoinjectors (total of 4 ml); dosage form per *Table 1*]. - Reauthorization: Authorization **shall** be reviewed at least every 12 months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and **both** of the following (1 and 2): **1.** That there is ongoing food allergen avoidance and availability of self-administered epinephrine (such as EpiPen autoinjector) for management of anaphylaxis with accidental ingestion. **2.** Documentation that the medication is effective, defined as a clear reduction in the need for a medical intervention for severe food allergen reactions, defined as the use of an epinephrine rescue device, an unplanned urgent medical visit (such as to the emergency department or urgent care), or hospitalization.

IV. Not Medically Necessary Uses

Table 3. 'Not Medically Necessary' Uses

Allergic rhinitis - Xolair (omalizumab) - Nucala (mepolizumab)	See ALLERGIC RHINITIS for additional details
Food allergy – age > 17 years old - Xolair (omalizumab)	See Adults with Severe Food Allergy for additional details
Food allergy – isolated single-food allergen, such as isolated peanut allergy - Xolair (omalizumab)	See Isolated Peanut Allergy for additional details

V. Investigational Uses

A. Combination use of any anti-IL-5, anti-IgE, anti-TSLP, or anti-IL-4 monoclonal antibodies in this and other policies (see *Cross References).*

B. Dose escalations (such as for partial or non-response) in excess of those listed in the "Quantity Limitations," *Table 2* (above) is considered investigational for any indication.

C. Unless otherwise specified in the coverage criteria above, medications included in this policy are considered investigational when used for all other conditions, due to lack of published data, lack of high-quality data, or lack of positive data. Details of select investigational uses are listed (in *Table 4*) below.

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Table 4. Investigational Uses

Combination use of any anti-IL-5, anti-IgE, anti-TSLP, or anti- IL-4 monoclonal antibodies	Data is lacking to support combination use of any anti-IL-5, anti-IgE, anti-TSLP, or anti-IL-4 monoclonal antibodies. Clinical trials did not allow combination use of these medications; therefore, safety and efficacy of combined use is unknown.
Allergic bronchopulmonary aspergillosis (ABPA)	- There is insufficient evidence to establish the efficacy of monoclonal anti-IgE or anti-IL-5 antibodies for the treatment of ABPA. - The one small crossover trial (n=13) found a reduction in exacerbations over a 4-month period in ABPA patients with use of high-dose Xolair (omalizumab) (750 mg monthly) (p=0.048); however, the long-term clinical benefit is unknown. Additional research is needed to clarify the safety, efficacy, and optimal dosing of Xolair (omalizumab) for ABPA.
Atopic dermatitis (AD)	- There is insufficient evidence to support the use of monoclonal antibodies covered by this policy for atopic dermatitis. - Nucala (mepolizumab) has been studied in atopic dermatitis, and no significant benefit was observed.
Chronic eosinophilic pneumonia (CEP)	- There is insufficient published evidence for the use of monoclonal anti-IgE or anti-IL-5 antibodies for the treatment of CEP. -
Chronic obstructive pulmonary disease (COPD)	- There is no reliable evidence to establish efficacy or safety of monoclonal anti-IgE, , or anti-TSLP antibodies for the treatment of eosinophilic COPD (except as noted in the coverage criteria above). - Additional studies are ongoing for Fasenra (benralizumab) and Tezspire (tezepelumab-ekko). [1]

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Eosinophilic esophagitis (EE)	- There is no reliable evidence to establish efficacy or safety of monoclonal anti-IgE or anti-IL-5 antibodies in the treatment of eosinophilic esophagitis. - One small trial found no benefit of Xolair (omalizumab) in patients with eosinophilic esophagitis. [2] - One small trial found that Nucala (mepolizumab) did not achieve the primary endpoint of improving dysphagia symptoms compared with placebo, in patients with eosinophilic esophagitis.[3] - One short trial evaluated the effect of Cinqair (reslizumab) on peak eosinophil count and the physician's global assessment score (symptoms) at week 15, compared to placebo. Despite a statistically significant reduction in esophageal eosinophil counts, the treatment effect on symptoms was not statistically significant; thus, the evidence of a true clinical benefit on symptoms is inconclusive. [4] - One trial found no benefit of Fasenra (benralizumab) on dysphagia symptoms, compared to placebo, despite a statistically significant reduction in esophageal eosinophil counts.[5]
Eosinophilic granulomatosis with polyangiitis (EGPA) / allergic granulomatosis / Churg-Strauss syndrome	- Except as noted in the coverage criteria, the use of monoclonal anti-IgE or anti-IL-5 antibodies in the treatment of EGPA is investigational. - There are no published clinical trials evaluating the safety or efficacy of Xolair (omalizumab) and Cinqair (reslizumab) for the treatment of EGPA. Additional studies are ongoing for Cinqair (reslizumab).
Hypereosinophilic syndrome (hyper E, HES)	- Except as noted in the coverage criteria, the use of monoclonal anti-IgE or anti-IL-5 antibodies in the treatment of HES is investigational. - One small phase 2 of Fasenra (benralizumab) in patients with symptomatic PDGFRA-negative HES reported a superior rate of reduction in eosinophil count at week 12 as compared to placebo. A phase 3 trial is ongoing to evaluate clinical outcomes (HES flares). [2]
IgE-mediated food allergies (other than noted in the coverage criteria above) [See Xolair (omalizumab) for IgE-Mediated Food Allergies for additional details].	- *Testing*: Use of Xolair (omalizumab) for treatment of food allergy determined by tests (other than listed in the coverage criteria) is considered investigational and not coverable. - *Other food allergies (not listed in the coverage criteria):* There is insufficient evidence to establish the efficacy of monoclonal anti-IgE and anti-IL-5 antibodies for the treatment of food allergies (other than specifically listed in the criteria above). *Note: Please see Table 3 'Not Medically Necessary' Uses above for other non-covered indications.*

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Position Statement

Summary

Monoclonal anti-IgE and anti-IL-5, and anti-TSLP antibodies may be covered for specific diagnoses where there is demonstrated safety and efficacy from randomized, controlled trials to support their use, including asthma and other specific indications.

- Anti-IgE monoclonal antibodies [e.g., Xolair (omalizumab)] reduces the levels of circulating immunoglobulin E (IgE) and inhibits binding of IgE to mast cells, to prevent the activation of the allergic cascade and decrease inflammation.
- Anti-IL-5 antibodies [e.g., Fasenra (benralizumab), Nucala (mepolizumab), and Cinqair (reslizumab)] prevent activation of interleukin 5 (IL-5) that is responsible for the growth and survival of eosinophils, to decrease inflammation.
- Anti-TSLP antibodies [e.g., Tezspire (tezepelumab-ekko)] prevent activation of the TSLP cytokine that is responsible for modulating the downstream pathway involved in the epithelial cell inflammatory response.
- Interleukin-4 receptor antagonist [IL-4; Dupixent (dupilumab)] is also used for add-on maintenance treatment for asthma (covered in a separate policy; see *Cross References*).

Asthma

- Monoclonal respiratory antibodies may be coverable for poorly controlled asthma despite use of maximal step therapy, which includes patient compliance with therapy, an assessment for triggers, and a plan to control identified triggers.
- Monoclonal respiratory antibodies may be covered when there is documentation of uncontrolled severe asthma with utilization of other appropriate medications, as detailed in the coverage criteria. Use of monoclonal respiratory antibodies for management outside of these criteria are not coverable.
- For severe asthma (STEP 5), Global Initiative for Asthma (GINA) guidelines recommend maintenance with a high-dose ICS combined with a long-acting beta-agonist (LABA); add-on therapy with a biologic agent or tiotropium may be considered after phenotypic assessment. [1]
    * In patients with severe eosinophilic phenotype asthma uncontrolled on STEP 4-5 treatment, Nucala (mepolizumab), Cinqair (reslizumab), Fasenra (benralizumab), or Dupixent (dupilumab) are recommended as add-on treatment options.
    * In patients with IgE-mediated allergic phenotype asthma uncontrolled on STEP 4-5 treatment, Xolair (omalizumab) is recommended as add-on therapy.
    * In patients with severe asthma, regardless of phenotype, on STEP 4-5 treatment, Tezspire (tezepelumab-ekko) is recommended.
- There is insufficient evidence that any one monoclonal respiratory antibody for uncontrolled asthma is superior to another. There are no comparative trials. Based on
- indirect trial comparisons, the benefits are roughly equivalent (rate of exacerbations).

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Chronic Idiopathic/Spontaneous Urticaria (CIU/CSU) (Xolair)

- Xolair (omalizumab) may be coverable for poorly controlled chronic idiopathic urticaria despite use of maximal step therapy, which includes patient compliance with antihistamines and an assessment for other causes, including triggers, as well as a plan to control identified triggers.
- Standard of care for chronic urticaria includes identification and elimination of the underlying aggravating triggers followed by use of antihistamines. [6]
- Other potential therapies include leukotriene antagonists (such as montelukast), cyclosporine, dapsone, other oral DMARDs, and corticosteroids.
- All patients in Xolair (omalizumab) urticaria clinical trials were refractory to antihistamines.
- The goal of CIU therapy is to decrease functional impairment due to itching, hives, and other related symptoms, such as missed days from work and/or school.

Eosinophilic granulomatosis with polyangiitis (EGPA) (Nucala and Fasenra)

- Nucala (mepolizumab) and Fasenra (benralizumab) may be coverable when specific diagnostic criteria for EGPA are met and persistent disease despite use of maximal step therapy, which includes steroids and immunosuppressants (oral DMARDs).
- Glucocorticoids are the mainstay of therapy for EGPA. Patients in clinical trials of Nucala (mepolizumab) and Fasenra (benralizumab) for EGPA were relapsing or refractory to corticosteroids with or without immunosuppressives.
- Immunosuppressive oral DMARD therapy [e.g., azathioprine, methotrexate] is used as add-on therapy for patients with life and/or organ manifestations for maintenance of remission.
- There are still no trials comparing the effectiveness of Nucala (mepolizumab) or Fasenra (benralizumab) to that of oral DMARD therapy in patients with EGPA;55% of patients in the MIRRA trial, and 40% of patients in the MANDARA trial, were on a non-steroid immunosuppressant.
- The 2021 American College of Rheumatology (ACR) recommend Nucala (mepolizumab) in combination with glucocorticoids as first line treatment for EGPA over oral DMARDS. However, oral DMARDS have a long-standing track record as an established treatment option for EGPA, are still recommended by the current ACR guidelines, and are a more cost-effective option. Fasenra (benralizumab) has not been added to these guidelines as they have not been updated since the approval of Fasenra (benralizumab) in EGPA.[7 8]
- Other second line therapy options for EGPA include rituximab, immunoglobulins, and interferon-alpha.

Hypereosinophilic Syndrome (HES) (Nucala)

- Nucala (mepolizumab) may be coverable for uncontrolled HES (FIP1L1-PDGFRA–negative) despite stable background therapy for HES.
- Standard treatments for HES include oral corticosteroids, hydroxyurea, other cytotoxic therapy for HES (e.g., chlorambucil, vincristine), or interferon alpha.

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Nasal Polyps

- Xolair (omalizumab) and Nucala (mepolizumab) may be coverable for nasal polyps in patient who have continued symptoms and quality of life impacts despite standard management.
- Standard treatments for nasal polyps include oral corticosteroids and intranasal corticosteroids (INCS).
- Initial coverage authorization is 24 weeks, per current guidelines to reassess effectiveness outlined in coverage criteria, as chronic rhinosinusitis with nasal polyps (CRSwNP) symptoms can resolve or medication may not provide adequate benefit.
- Monoclonal respiratory antibodies may be covered at the doses proven to be safe and effective for asthma and other associated conditions in clinical trials (as detailed in the coverage criteria above).

IgE-Mediated Food Allergy

- Xolair (omalizumab) may be coverable for confirmed severe IgE-mediated food allergy, as outlined in coverage criteria, when documentation supports the need for unplanned additional medical intervention despite maximal allergen avoidance, and when used in conjunction with ongoing food allergen avoidance.
- The goal of treatment with Xolair (omalizumab) is the reduction of severe allergic reactions, including anaphylaxis, from accidental food allergen exposure, by increasing the tolerance or sensitivity threshold to the allergen(s). However, at this time, the evidence is limited to increase in allergic reaction threshold, based on tolerance of a single dose of peanut protein without dose-limiting symptoms. It is unknown if Xolair (omalizumab) will reduce the incidence of severe reactions with real-world food allergen exposure, use of rescue epinephrine, need for an unplanned urgent medical visit (such as to the emergency department or urgent care), or improve quality of life.
- Confirmation of food allergens:
  - Given complexity of food allergen evaluation, all patients should be evaluated by a specialist.
  - Confirmatory tests used to diagnose food allergies include a skin prick test, an allergen specific IgE blood test, and an oral food challenge to the offending allergens, interpreted by a specialist, *in conjunction with* a medical history of a true food allergic reaction.
  - True food allergies are defined by moderate to severe reactions affecting the skin, respiratory tract, gastrointestinal tract, or cardiovascular system, and associated with an exposure (vs. an isolated IgE result). A positive diagnostic test, in the absence of a clinical history of a true allergic reaction, is not, by itself, indicative of a true allergy to the offending food allergen(s).
  - A severe food allergy may be outgrown. Therefore, re-assessment for persistence of food allergies is recommended.
- Ongoing food allergen avoidance: Standard management is strict food allergen avoidance and the availability of rescue epinephrine for as-needed use with accidental food allergen exposure. Ongoing food allergen avoidance is required when using Xolair (omalizumab).

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- Xolair (omalizumab) improved the percentage of subjects who were able to tolerate peanut allergy challenges in the clinical trial. However, a significant portion of subjects were unable to tolerate even very small amounts of peanut (failed the oral antigen challenge) despite Xolair (omalizumab) therapy. Patients with food allergies should continue to avoid exposure to food allergens irrespective of Xolair (omalizumab) therapy. Patients who are able to successfully avoid food allergens, and have no history of significant anaphylaxis despite avoidance, should continue successful management of their food allergy with trigger avoidance. [See Outcomes for more information]
- Xolair (omalizumab) may be considered medically necessary in patients who are too young to manage allergen exposure, who have significant cognitive or behavioral disorders, or who have severe allergies to multiple allergens such that attempts to avoid exposure are not feasible and have proven ineffective. As stated above, patients who are able to manage their severe food allergies with strict food allergen avoidance should continue such food allergen avoidance. Use of Xolair (omalizumab) in patients well-managed by food allergen avoidance is considered "not medically necessary."

COPD with an Eosinophilic Phenotype

- COPD is a heterogenous lung condition that is characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and /or exacerbations) due to abnormalities of the airways (bronchitis) and/or alveoli (emphysema) that cause progressive airflow obstruction.
- Nucala (mepolizumab) may be coverable for patients with uncontrolled moderate to severe COPD with eosinophils ≥300 cells/µL, as add-on maintenance treatment to triple inhalation therapy (ICS and LAMA and LABA) when there is a history of exacerbations, as detailed in coverage criteria.
- Clinical studies with Nucala (mepolizumab) were conducted in patients with moderate to severe COPD with eosinophils ≥300 cells/µL (over the previous year) who were not adequately controlled with triple inhaler therapy. Results from two clinical trials showed that treatment with Nucala (mepolizumab) reduced the annual rate of exacerbations compared to placebo.
- Nucala (mepolizumab) has not been added to the 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[9]
- Dupixent (dupilumab), covered in a separate policy (see *Cross References)*, is also FDA-approved for the treatment of eosinophilic COPD and is addressed in the GOLD guidelines. There are no direct, head-to-head trials comparing Dupixent (dupilumab) and Nucala (mepolizumab); their relative safety and efficacy are unknown.

Self-administration

- Several options are now available in a single-dose pre-filled syringe (PFS) or autoinjector, FDA-approved for self-administration, and coverable under the pharmacy benefit, as detailed in the coverage criteria.
- Use of self-administered options provides the best value (lower overall cost) and may offer convenience for members.

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- Provider-administered products may be needed when there is a documented reason why a patient cannot self-administer a medication (see *Appendix 5*).

The safety and efficacy of monoclonal respiratory antibodies in combination with other monoclonal respiratory antibodies or in conditions not included in coverage criteria (as listed above) have not been established. There are no trials of the use of anti-asthma monoclonal antibodies as combination or sequential therapy. Additional trials are ongoing.

Clinical Efficacy

ASTHMA BACKGROUND

- Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements (multiple cytokines and mediators, as well as potentially IgE-mediated events involving mast cells and basophils) play a role (in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells). Eosinophilic asthma is a subphenotype of severe asthma characterized by elevated sputum and blood eosinophil levels as well as increased asthma severity, atopy, late-onset disease, and steroid refractoriness.
- IgE may be in the inflammatory cascade of some events leading to asthmatic airway inflammation. Anti-IgE monoclonal antibody, Xolair (omalizumab) binds circulating IgE.
- Anti-IL-5 monoclonal antibodies (Cinqair, Nucala, and Fasenra) specifically target formation of eosinophils and depletes blood eosinophil levels.
- Various peripheral blood eosinophil levels were studied in clinical trials. The eosinophil levels in the coverage criteria for the anti-IL-5 monoclonal antibodies are based on the efficacy data from the clinical trials of these medications and where they were found to be most effective.
- Global Initiative for Asthma (GINA) guidelines recommend STEP 5 add-on therapy with long-acting muscarinic antagonists (LAMA) such as tiotropium, anti-IgE therapy (omalizumab), anti-IL-5 therapy, anti-TSLP, or anti-interleukin-4 therapy after phenotypic assessment of asthma subtype.[1]
- There is no reliable evidence to establish efficacy or safety of monoclonal anti-IL-5 antibodies for severe allergic asthma without documentation of severe eosinophilia.
- TSLP is a cytokine that is thought to stimulate the immune cascade response in epithelial cells leading to asthmatic airway inflammation. Anti-TSLP monoclonal antibody Tezspire (tezepelumab-ekko) blocks the TSLP cytokine to reduce the epithelial inflammatory response.
- Tezepelumab has demonstrated efficacy in patients regardless of eosinophils or IgE levels. [10 11]

Fasenra (benralizumab) for Eosinophilic Asthma

- Two randomized, double-blinded, placebo-controlled studies (SIROCCO and CALIMA) evaluated the safety and efficacy of Fasenra (benralizumab) 30 mg in patients with severe eosinophilic asthma, uncontrolled on moderate- to high-doses ICS. [12 13]
    * The trials enrolled patients with a history of two or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months despite

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medium to high dose ICS/LABA. Patients were stratified by baseline blood eosinophil count (<300 or ≥300 cells/microliter).

* The primary endpoint was reduction in asthma exacerbations for patients with baseline blood eosinophil count ≥300 cells/microliter in both studies. After 48-56 weeks, Fasenra (benralizumab) reduced the annual rate of exacerbations by 28-51% compared to placebo.
* However, in the SIROCCO trial, only patients with a baseline blood eosinophil count ≥300 cells/microliter responded to the standard starting dose of Fasenra (benralizumab) 30 mg every 8 weeks. For patients with baseline blood eosinophil count <300 cells/microliter, response was seen only with double the dose (30 mg every 4 weeks).

- In CALIMA, patients on medium-dose ICS/LABA were included. Therefore, the generalizability of the results to patients optimized on standard STEP 5 therapy with high-dose ICS/LABA is uncertain. One double-blind, multicenter, randomized study evaluated the efficacy of Fasenra (benralizumab) on oral corticosteroid (OCS) reduction compared to placebo. [14]
  * Patients were required to have a daily oral corticosteroid dose between 7.5 to 40 mg per day in addition to high dose ICS/LABA and a baseline eosinophil count of at least 150 cells/microliter.
  * Patients in the Fasenra (benralizumab) arms (30 mg every 4 weeks or every 8 weeks) had a statistically significant reduction in daily OCS compared to placebo (75% vs. 25%, respectively). However, the external validity of the results is uncertain, given the inclusion of patients on medium-dose ICS/LABA.
- The role of Fasenra (benralizumab) for patients with a baseline blood eosinophil count of <300 cells/microliter is unclear. The overall assessment of benefit is uncertain, with inconsistent response to standard starting dosing and confounded baseline characteristics. Patients in two of the three trials were <u>not</u> on optimized high-dose ICS/LABA, as is the standard STEP5 (NHLBI and GINA guidance), prior to addition of anti-IL5 therapy.
  * In the SIROCCO trial, patients were optimized on high dose ICS/LABA. However, there was no statistical reduction in the rate of asthma exacerbations for patients with baseline blood eosinophil count of <300 in the arm of Fasenra (benralizumab) 30 mg every 8 weeks. Benefit was seen only at higher dosing (30 mg every 4 weeks). As such, Fasenra (benralizumab) if coverable only for patients with baseline blood eosinophil count of ≥300 cells/microliter.[12]
  * In the CALIMA and ZONDA trials, there was statistically significant response to standard Fasenra (benralizumab) 30 mg every 8 weeks. However, patients were NOT optimized on high-dose ICS/LABA prior to enrollment. Both studies included patients on medium dose ICS/LABA, which is not reflective of Step 5 of NHLBI Guidelines for add-on IL-5 therapy. Therefore, the benefit in optimized Step 5 asthma patients with an eosinophil count of <300 is unknown.
    - In CALIMA, there was a statistically significant reduction in asthma exacerbation rates for patients with baseline blood eosinophil count of <300 cells/microliter in the arm of Fasenra (benralizumab) 30 mg every 8

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weeks; however, because baseline ICS/LABA was not maximized, the external validity of this finding for use in a STEP5 therapy optimized patient is unknown.[13]

- In ZONDA, there was a statistically significant reduction in the need for oral steroids for patients with baseline blood eosinophil count of >150 cells/microliter with Fasenra (benralizumab); however, because baseline ICS/LABA was not maximized, the external validity of this finding for use in a STEP 5 therapy optimized patient is unknown.[14]

Nucala (mepolizumab) for Eosinophilic Asthma

- One randomized, double-blinded, placebo- and active-controlled, 32-week study evaluated the safety and efficacy of Nucala (mepolizumab) 75 mg or 100 mg compared to placebo in patients with severe refractory eosinophilic asthma. [15]
  - The trial enrolled patients with blood eosinophil counts ≥150 cells/microliter within 6 weeks of dosing or ≥300 cells/microliter within 12 months.
  - The primary endpoint was frequency of asthma exacerbations. Nucala (mepolizumab) demonstrated a statistically significant reduction of annual exacerbation rates by 13% compared to placebo.
- One randomized, controlled trial evaluated the efficacy of Nucala (mepolizumab) in reducing daily oral corticosteroid dose compared to placebo. [16]
  - The primary end point was percent reduction of oral corticosteroid dose during weeks 20 to 24 without loss of asthma control. Overall, Nucala (mepolizumab) achieved greater reduction in oral corticosteroid use while maintaining asthma control when compared to placebo. However, the difference between the Nucala (mepolizumab) and placebo groups was not statistically significant.
- Nucala (mepolizumab) has been studied in moderate persistent asthma, and no significant benefit was observed.

Xolair (omalizumab) for Extrinsic (allergic) Asthma

- One high-quality meta-analysis evaluated the efficacy of Xolair (omalizumab) in reducing asthma exacerbations and corticosteroid use compared to placebo.
  - After 16 to 60 weeks, Xolair (omalizumab) reduced asthma exacerbations from 26% to 16% of patients suffering from an exacerbation.
  - An absolute reduction in hospitalization risk was reduced from 3% to 0.5% with Xolair (omalizumab) over 28 to 60 weeks.
- Xolair (omalizumab) increases the number of asthma patients able to reduce or withdraw their inhaled steroids and is effective in reducing asthma. [17-20]
- There is no available data demonstrating that Xolair (omalizumab) is superior to step therapy options (e.g., ICS/LABAs and oral steroids for exacerbations) recommended in treatment guidelines for moderate-to-severe persistent asthma.
- Optimal clinical response to Xolair (omalizumab) requires strict compliance with dosing, as there is a 6 to 12-week lag before beneficial effects are apparent (effects are not immediate and explain the various phases that are included in study protocols).

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- Although preliminary results are promising, there is no conclusive evidence that omalizumab is effective in patients with non-allergic (nonatopic) asthma, based on one small proof-of-concept trial. [21]

Total IgE Levels for Asthma

- Xolair (omalizumab) is only indicated in patients with elevated IgE levels and is dosed according to IgE levels between 30 to 700 IU/ml in adults with asthma. There is no established dose or benefit for IgE levels outside of this range.
- Efficacy and dosing of Xolair (omalizumab) in asthma patients (>50 kg) with IgE levels less than 30 or greater than 700 have not been established. [31] The majority of data on the use of Xolair (omalizumab) in patients with baseline IgE <30 or >700 IU/ml are limited to case reports with inconsistent results of effectiveness.
- There is evidence to support the safety and efficacy of Xolair (omalizumab) in patients aged 6 to less than 12 years old with a baseline IgE as follows:
    * >90 to 150 kg: baseline IgE of 30 to 300 IU/ml
    * >70 to 90 kg: baseline IgE of 30 to 500 IU/ml
    * >60 to 70 kg: baseline IgE of 30 to 600 IU/ml
    * >50 to 60 kg: baseline IgE of 30 to 700 IU/ml
    * >40 to 50 kg: baseline IgE of 30 to 900 IU/ml
    * >30 to 40 kg: baseline IgE of 30 to 1,100 IU/ml
    * 20 to 30 kg: baseline IgE of 30 to 1,300 IU/ml
- As with adults, there is no established dose or benefit for IgE levels outside of this range.
- Monitoring IgE levels after administration of Xolair (omalizumab) are problematic, as IgE levels post-administration measure both bound and unbound (free) IgE.

Cinqair (reslizumab) for Eosinophilic Asthma

- Cinqair (reslizumab) has been studied in people with moderate and severe refractory eosinophilic asthma that is inadequately controlled despite use of high-dose corticosteroids and a controller medication. [22-24]
- Two double-blind, controlled studies evaluated the efficacy of Cinqair (reslizumab) 3 mg/kg compared to placebo in patients with severe eosinophilic asthma.
    * Patients were required to have at least 1 asthma exacerbation requiring systematic corticosteroids.
    * The primary endpoint was frequency of asthma exacerbation. After 52 weeks, Cinqair (reslizumab) reduced the annual asthma exacerbation rate by 10-14% compared to placebo.

Tezspire (tezepelumab-ekko) for Severe Asthma [10 11 25-27]

- Tezspire (tezepelumab-ekko) has evidence for reduction in exacerbations in both non eosinophilic asthma (blood eosinophils <150cells/µL) and non-allergic asthma (IgE<30 IU/ml).
- One phase III, randomized, double-blinded, placebo controlled, 52-week study (NAVIGATOR) evaluated the safety and efficacy of Tezspire (tezepelumab-ekko) 210mg every 4 weeks compared to placebo in patients with severe asthma, uncontrolled on

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ICS/LABA therapy.

  * The trial enrolled patients who were previously diagnosed with asthma receiving a med/high dose ICS for the past 12 months (75% of patients were on high dose ICS in both arms) and secondary controller medication (LABA) for the past 3 months. Patients must have had a history of two or more asthma exacerbations (defined as requiring either oral/systemic corticosteroids or asthma-related hospital stay) in the previous 12 months. Patients were stratified by baseline blood eosinophil count (<150, 150-300,300-450, and >450 cells/µL).
  * The primary endpoints were annualized asthma exacerbations rate (AAER) overall as well as in patients with blood eosinophil counts of ≤300 cells/µL. Tezspire (tezepelumab-ekko) demonstrated a statistically significant reduction in both overall annual exacerbation rates (56%) and in patients with blood eosinophil counts of ≤300 µL (41%) when compared to placebo.
  * Sub-group analysis of patients with blood eosinophils <150 cells/µL showed a statistically significant reduction in AAER by 39% when compared to placebo.
  * The above results were supported by similar findings in a previous phase IIB randomized placebo-controlled dose optimization trial (PATHWAY). In addition, a sub-group analysis of patients with non-allergic asthma (IgE<30 IU/ml) showed a statistically significant reduction in AAER of 54% in this trial.

- One phase 3, randomized, double blind, placebo-controlled trial (SOURCE trial) evaluated the efficacy of Tezspire (tezepelumab-ekko) in reducing daily oral corticosteroid dose compared to placebo.
  * The primary end point was percent reduction of oral corticosteroid dose at week 48 without loss of asthma control. Overall, Tezspire (tezepelumab-ekko) achieved a greater reduction in oral corticosteroid use while maintaining asthma control when compared to placebo.
- Tezspire (tezepelumab-ekko) has evidence for reductions in exacerbations in both non eosinophilic asthma (blood eosinophils <150cells/µL) and non-allergic asthma (IgE<30 IU/ml).

CHRONIC IDIOPATHIC URTICARIA (CIU/CSU) BACKGROUND

- Standard of care includes identification and elimination of the underlying aggravating triggers followed by use of antihistamines, which are FDA-approved for treatment of urticaria and may be used at doses exceeding the manufacturer's recommended dosages. [6]
- Second-line treatment options for antihistamine-refractory urticaria include H2-antihistamines (e.g., ranitidine, famotidine), leukotriene antagonists, cyclosporine, dapsone, other oral DMARDs/anti-inflammatories (methotrexate, sulfasalazine), and corticosteroids. The guidelines acknowledge the evidence supporting the use of these second-line therapies is of lower quality; however, their costs and safety profiles should be considered when choosing therapies. [6]

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- The terms “chronic urticaria” (CU), “chronic spontaneous urticaria” (CSU), and “chronic idiopathic urticaria” (CIU) are used interchangeably but are generally defined as a frequent cause of severe chronic urticaria, lasting greater than 6 weeks. [6] However, in clinical trials, all patients had CIU/CSU symptoms for at least 6 months. [28-30]
- The diagnosis of “CIU/CSU” requires exclusion of triggers as a main cause of the urticaria symptoms, such as:
    * Physical causes [dermatographism (firm stroking), delayed pressure urticaria (pressure), cold urticaria (cold), solar urticaria (exposure to sun), or vibratory urticaria (vibration)].
    * Other causes [aquagenic urticaria (water exposure), cholinergic urticaria (heat, stress, exercise), exercise-induced anaphylaxis/urticaria, contact with urticariogenic substances].
    * Urticaria despite avoidance of any triggers is a hallmark feature of CIU/CSU. [6]
- In addition, spontaneous flares in the absence of a trigger must be documented to establish the diagnosis of spontaneous urticaria (CSU/CIU).
- A subset of patients with a diagnosis of CSU/CIU may have autoimmune urticaria, which can be associated with some type of trigger which can aggravate symptoms but is not the main cause of CU symptoms. Aggravating triggers may include but are not limited to extreme hot or cold, and irritation from clothing. Primary treatment for CU should include aggravating trigger control and histamine blockade. Refractory patients may be responsive to Xolair (omalizumab). [6 28 29]

Xolair (omalizumab) for CIU/CSU

- Two randomized, double-blinded, placebo-controlled 12- to 24-week studies evaluated the safety and efficacy of Xolair (omalizumab) in patients with refractory chronic idiopathic/spontaneous urticaria. [28 31]
    * The trial enrolled patients with a urticaria activity score (UAS) >4 despite use of H1-antihistamines and a weekly itch severity score (ISS) >8.
    * Xolair (omalizumab) doses of up to 300 mg every 4 weeks were used.
    * The primary endpoint of the study was changed from baseline in weekly ISS at week 12. Additional endpoints included the change in UAS over 7 days and proportion of complete responders.
    * Mean change in weekly ISS with Xolair (omalizumab) decreased by -3.0 from placebo. Although, this is a subjective endpoint with a lack of defined minimal clinically important difference, it is clinically relevant to patients. The FDA recognizes reduction of itching as the most important outcome.
- Xolair (omalizumab) may reduce urticaria severity, as measured by itch-severity score, in patients with chronic idiopathic urticaria who remained symptomatic despite use of H1-antihistamine therapy. However, Xolair (omalizumab) has not been proven to eliminate itching or improve functional impairment due to urticaria symptoms. [6 28-30]
- Xolair (omalizumab) has only been studied as add-on therapy in patients who are refractory to antihistamines.

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    * Guidelines recommend use of maximally tolerated doses of non-sedating (2nd generation) antihistamines, up to four-times the recommended FDA-approved doses. [6]
    * All patients in clinical trials of Xolair (omalizumab) for chronic urticaria were refractory to antihistamines. However, Xolair (omalizumab) has not been compared to the many other available therapies for antihistamine-refractory urticaria. Therefore, it is unknown if Xolair (omalizumab) is superior to these less-costly alternatives.

- IgE levels are not measured nor used as a marker for Xolair (omalizumab) therapy with urticaria.
- Urticarial flares may also occur in the presence of a trigger ("inducible urticaria"). However, patients may have a mixed diagnosis of CSU/CIU, along with inducible urticaria. Spontaneous flares, in the absence of a trigger, must be documented to establish the diagnosis of spontaneous urticaria (CSU/CIU).
- The efficacy or safety of Xolair (omalizumab) in other types of urticaria with a clearly defined cause, such as physical (inducible) urticaria (e.g., "cold" urticaria, dermographism, delayed-pressure urticaria, cholinergic urticaria, aquagenic urticaria, solar urticaria, or vibratory urticaria), urticarial vasculitis, or contact urticaria, has not been established. [6 30 32]
    * Patients with a clearly defined cause for urticaria, such as physical cause, were excluded from CIU/CSU phase 3 clinical trials. [6 28-30]
    * Avoidance of the stimulus is the primary treatment for physical (inducible) urticaria. Other treatments vary, dependent on the trigger, but may include antihistamines, steroids, desensitization protocols, and immunomodulators (such as cyclosporine). [33]
    * Two small phase 2 trials investigated Xolair (omalizumab) in patients with cold and solar urticaria refractory to antihistamines.
        - CUTEX (n=30): [32] Patients with refractory cold urticaria were randomized to 150 mg, 300 mg, or placebo every 4 weeks. The primary endpoint was the individual temperature required to induce symptoms [critical temperature threshold (CTT)]. Although the CTT reduced in the treatment period, the benefit on health outcomes (such as systemic reactions and anaphylaxis) is unknown.
        - XOLUS (n=10): [34] Patients with refractory solar urticaria [to photoprotection (SPF 50 sunscreen) and antihistamines] were treated with Xolair (omalizumab) 300 mg every 4 weeks. The primary endpoint was response to therapy, measured by the percent of patients without urticaria triggering with exposure to UV light (10-times baseline level). Two of 10 met the primary endpoint. However, the benefit on health outcomes (such as systemic reactions and anaphylaxis) is unknown.
        - Additional trials are needed to clarify the benefit of Xolair (omalizumab) in refractory cold and/or solar urticaria. Of note: both of these trials were published as a 'letter to the editor' and were not peer-reviewed.

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    * The published evidence for the use of Xolair (omalizumab) in other types of physical (inducible) urticaria is limited to case reports. [33]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) WITH EOSINOPHILIC PHENOTYPE

Background – COPD [35 36]

- Eosinophilic COPD is a specific subtype or phenotype of COPD characterized by elevated levels of eosinophils, typically greater than 300 cells/µL.
- Clinical features of eosinophilic COPD include more frequent and severe exacerbations, and an often-better response to inhaled corticosteroids (in addition to LAMA and LABA treatment).
- There are currently two FDA-approved options for eosinophilic COPD: Nucala (mepolizumab) and Dupixent (dupilumab), see *Cross References*,
- There are no direct comparison trials between Dupixent (dupilumab) and Nucala (mepolizumab) in patients with eosinophilic COPD; their relative safety and efficacy are unknown.

Nucala (mepolizumab) for eosinophilic COPD [35 37 38]

- The safety and efficacy of Nucala (mepolizumab) as add-on maintenance therapy for the management of eosinophilic COPD was evaluated in three (MATINEE, METREX, and METREO) randomized, double-blind, placebo-controlled trials of 52-week duration in patients with uncontrolled COPD while on background combinations of triple inhaler therapies (ICS and LABA and LAMA).
    * All patients had moderate to severe COPD, eosinophil counts of at least 300 cells/µL within the past 12 months, and a history of 2 or more moderate (requiring systemic glucocorticoids or an antibiotic, or both) or one or more severe (leading to hospitalization) exacerbations over the previous year.
    * Patients received treatment with mepolizumab or placebo in addition to background triple inhaler maintenance therapy.
- In the clinical trials, the primary endpoint was a reduction in annualized exacerbation rates. After 52 weeks, in two clinical trials (MATINEE and METREX), Nucala (mepolizumab) reduced the annual rate of exacerbations by 18-21%, compared with standard of care alone. In the third clinical trial (METREO), there was no statistically significant difference in annualized exacerbation rates demonstrated between mepolizumab-treated or placebo-treated patients.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA) BACKGROUND

- Eosinophilic granulomatosis with polyangiitis (EGPA), also known as allergic granulomatosis or Churg-Strauss syndrome, is a multisystem autoimmune syndrome characterized by eosinophil-rich granulomatosis inflammation of microscopic vessels. The respiratory tract is typically affected, and EGPA commonly includes asthma among its manifestations; however, widespread manifestations are found, including neurological, cardiac, and renal involvement.

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- Classification of EGPA is most often according to 1990 classification criteria from the American College of Rheumatology. Patients with vasculitis may be classified as having EGPA if they have at least 4 of 6 typical findings: [7]
    - Asthma (a history of wheezing or finding or diffuse high-pitched wheezes on expiration).
    - Greater than 10 percent eosinophils on the differential leukocyte count.
    - Mononeuropathy (including multiplex) or polyneuropathy.
    - Migratory or transient opacities detected radiographically.
    - Paranasal sinus abnormality.
    - Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas.
- The primary therapy for EGPA is systemic corticosteroids. An additional immunosuppressive agent (e.g., cyclophosphamide) is typically added for patients with more active or severe disease and in those whose disease flares with tapering of systemic glucocorticoids. Once remission is induced, patients can be switched to less toxic immunosuppressives, such as azathioprine or methotrexate, for maintenance therapy. Second or third-line drugs include rituximab, immunoglobulins, and interferon-alpha. [39 40]

Nucala (mepolizumab) for EGPA

- The MIRRA trial (multicenter, randomized, double-blind, controlled) evaluated the efficacy of Nucala (mepolizumab) 300 mg in patients with relapsing or refractory EGPA not optimally controlled with an oral corticosteroid with or without oral DMARDs compared to placebo. [41]
- The primary endpoint was total accrued weeks of remission. Nucala (mepolizumab) was found to result in significantly more weeks in remission than placebo (28% vs. 3% of patients had ≥24 weeks of accrued remission).
- After 48 weeks, 32% of Nucala (mepolizumab) patients remained in remission allowing for reduced corticosteroid use compared to 3% of placebo patients.
- Nucala (mepolizumab) has only been studied as add-on therapy for EGPA. It has not been compared to oral DMARDs for corticosteroid-refractory EGPA. Therefore, it is unknown if Nucala (mepolizumab) is superior to these less costly alternatives.
- The 2021 American College of Rheumatology (ACR) guidelines for EGPA recommend systemic steroids in combination with Nucala (mepolizumab) as first line treatment for patients with active non-severe disease over methotrexate (MTX), azathioprine (AZA) or mycophenolate (MMF), however this is based solely on Nucala (mepolizumab) having a randomized trial showing benefit in EPGA compared to only clinical experience and observational studies with MTX, AZA, and MMF. [8]
- There are no trials comparing efficacy of Nucala (mepolizumab) to that of MTX, AZA, or MMF in patients with EGPA, and 55% of patients in the pivotal MIRRA trial were on a non-steroid immunosuppressant such as MTX, AZA, or MMF. [8]
- These non-steroid immunosuppressants have demonstrated effectiveness in observational trials and well as in clinical experience, are still recommended and recognized as treatment options by the ACR guidelines and are significantly less costly.

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Adverse effects may limit use in some patients, but monitoring can alleviate most adverse events. [8]

Fasenra (benralizumab) for EGPA

- The efficacy of Fasenra (benralizumab) was evaluated in a randomized, double-blind, active-controlled noninferiority trial (MANDARA) of 52 weeks duration, comparing its efficacy to Nucala (mepolizumab).[42]
- All subjects had asthma, eosinophilia (1,000 cells per microliter or >10% leukocytes), a history of relapsing or refractory disease of at least 6 months in duration with at least two additional features of EGPA and treated with background prednisone/prednisolone with or without immunosuppressive therapy.
- The primary endpoint was the proportion of subjects in remission at weeks 36 and 48, defined as a Birmingham Vasculitis Activity Score (BVAS) = 0 (no active vasculitis) plus a prednisone/prednisolone dose of less than 4mg/day.
- Fasenra (benralizumab) demonstrated noninferiority to Nucala (mepolizumab) for the primary endpoint of remission (59% compared to 56%, respectively, achieved remission at weeks 36 and 48).
- Fasenra (benralizumab) has only been studied as add-on therapy for EGPA. It has not been directly compared to corticosteroids or DMARDs (methotrexate, azathioprine) for corticosteroid-refractory EGPA. Therefore, it is unknown if Fasenra (benralizumab) is superior to these less costly alternatives.

HYPEREOSINOPHILIC SYNDROME (HES) BACKGROUND [43 44]

- HES is a rare blood disorder. It occurs when an individual's blood has very high numbers of eosinophils. Eosinophils make their way into various tissues, causing inflammation and eventually organ dysfunction. The most commonly involved organs in HES include the skin, lungs, heart, and nervous system.
- In approximately 75% of cases, the underlying cause is unknown. However, recent advances have led researchers to believe that eosinophilia may be due to a variety of causes including myeloproliferative disorders or other disorders that affect bone marrow (myeloproliferative HES), increased production of interleukin-5 (lymphocytic HES), or a mutation in an unknown gene passed genetically (familial HES).
- The goal of HES treatment is to reduce eosinophil levels in the blood and tissues, thereby reversing and preventing end organ tissue damage, especially in the heart.
- For imatinib-sensitive HES variants (including those associated with the FIP1-like-1-platelet-derived growth factor receptor a fusion gene [FIP1L1-PDGFRA]), tyrosine kinase inhibitors such as imatinib (generic, Gleevec) are used for controlling malignant cell growth. [43 44]
- For all other types of HES (including FIP1L1-PDGFRA-negative HES), standard HES treatment includes: [43 44]
    * First line: corticosteroids such as prednisone
    * Steroid-sparing and second line options: immunosuppressives and chemotherapeutic agents such as cyclophosphamide, rituximab, imatinib (in

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select patients), vincristine, hydroxyurea, chlorambucil, interferon-alpha, and other kinase inhibitors (such as tofacitinib, ruxolitinib). Choice of treatment is dependent on presence/absence of myeloid features and suspected myeloid malignancy. In clinical trials, other steroid sparing therapies also included cyclosporine, imatinib, methotrexate, tacrolimus, and azathioprine. [45]

- At this time, Nucala (mepolizumab) is the only respiratory mAb with evidence for efficacy in HES as a steroid-sparing disease modifier. Trials of Fasenra (benralizumab) are ongoing. [46]

Nucala (mepolizumab) for HES

- The efficacy of Nucala (mepolizumab) in HES was evaluated in a phase 3, randomized, double-blind, placebo-controlled trial in patients with a diagnosis of FIP1L1-PDGFRA–negative HES ≥6 months (Study 200622). [45]
    * All enrolled patients had FIP1L1-PDGFRA–negative HES.
    * HES was required to be uncontrolled (defined as a history of ≥2 flares within the past 12 months and a blood eosinophil count ≥1000 cells/µL) despite stable background with HES therapy.
    * Background HES therapy included at least four weeks on a stable dose of oral corticosteroids and/or various immunosuppressants/cytotoxic agents, including, but not limited to, hydroxyurea, cyclosporine, imatinib, methotrexate, tacrolimus, and azathioprine.
    * Patients received treatment with mepolizumab or placebo, in addition to their existing HES therapy.
    * The primary endpoint was the proportion of patients with 1 or more flares at the end of the 32-week study.
    * At the end of the treatment period, less patients treated with Nucala (mepolizumab) experienced a flare compared to patients treated placebo (28% vs. 56%, respectively).
- Nucala (mepolizumab) has only been studied as add-on therapy for HES and has not been compared to other alternatives. Therefore, it is unknown if Nucala (mepolizumab) is superior to less costly alternatives.

CHRONIC RHINOSINUTISIS WITH NASAL POLYPS (CRSwNP) BACKGROUND[47-49]

- Chronic rhinosinusitis (CRS) is a common condition. It is defined as inflammation of at least one paranasal sinus.
- It is characterized as chronic when symptoms persist for at least 12 weeks. CRS is divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP).
- Endoscopy or on a sinus computed tomographic (CT) is needed to confirm the diagnosis of nasal polyps.
- Symptoms of nasal polyps include chronic congestion, facial pressure, purulent postnasal drip, throat clearing, coughing, and reduced ability to smell.
- Oral corticosteroids and intranasal corticosteroids (INCS) are the mainstay of therapy. Oral corticosteroids decrease nasal polyp size but are not used long-term.

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- INCS decrease polyp size and prevent recurrence in patients who have had polyps removed through surgery. INCS include those products for intranasal use specifically (such as sprays), as well as other steroid solutions (such as budesonide nebs, used intranasally) or surgically implanted steroid-eluding stents.

Xolair (omalizumab) for Nasal Polyps

- The safety and efficacy of Xolair (omalizumab) for nasal polyps was established based on two phase 3 studies: POLYP-1 and POLYP-2. [50]
    * Both studies compared Xolair (omalizumab) in combination with mometasone fumarate nasal spray (MFNS) vs. MFNS alone.
    * The studies included patients with bilateral polyposis that persisted despite treatment with oral corticosteroids.
    * The primary endpoints were change in Nasal Polyp Score (NPS) and nasal congestion score (NCS). Secondary endpoints other measures such as polyp size, disease severity, and symptoms.
    * Treatment with Xolair (omalizumab) with MFNS improved nasal polyp scores and improved symptoms compared to MFNS alone. Secondary endpoints also favored the Xolair (omalizumab) group.
- Xolair (omalizumab) is only indicated in patients with elevated IgE levels and is dosed according to IgE levels between 30 and 1600 IU/mL in patients with nasal polyps. There is no established dose or benefit for IgE levels outside of this range.

Nucala (mepolizumab) for Nasal Polyps

- The safety and efficacy of Nucala (mepolizumab) for nasal polyps was established in one 52-week phase 3 study. [51]
    * The study compared Nucala (mepolizumab) in combination with MFNS versus MFNS alone.
    * Patients were required to have had at least one surgery for nasal polyps in the past 10 years and must have received background nasal corticosteroids for at least 8 weeks prior to the study.
    * The co-primary endpoints were change in total endoscopic Nasal Polyp Score (NPS) from baseline and change in mean nasal obstruction VAS score during weeks 49-52. Secondary endpoints included other measures such as polyp size, disease severity, and symptoms.
    * Treatment with Nucala (mepolizumab) decreased the size of nasal polyps and improved nasal obstruction through 52 weeks. Treatment with Nucala (mepolizumab) also resulted in a longer time to nasal surgery (nasal polypectomy) compared to standard of care.

IgE-MEDIATED FOOD ALLERGY

Background – IgE-Mediated Food Allergy [52 53]

- IgE-mediated food allergies typically develop within seconds or minutes after ingestion of the culprit food with widespread activation of immune cells, which are responsible for the accompanying allergic symptoms--the most life-threatening being anaphylaxis.

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- IgE-mediated allergic symptoms usually involve more than one organ system, and may include severe airway problems (bronchospasm, angioedema), hypotension, severe gastrointestinal symptoms (nausea, vomiting), and skin reactions (urticarial rash, erythema, flushing).
- Given the complexity of assessment of allergic reactions, a full evaluation by a clinical specialist (such as an allergist/immunologist) is recommended.
- The diagnosis of an IgE-mediated food allergy is confirmed by a positive result of at least one of the following allergy-diagnostic tests, in combination with a history of a food-related allergic reaction to the suspected foods:
    * Skin prick test (SPT)
    * Allergen-specific IgE test
    * Double-blind oral-food challenge to the offending food(s) [gold standard].

  The many *other non-standardized testing methods are considered non-confirmatory.* *[53]*
- The diagnosis must be confirmed with a reaction associated with a suspected allergen. A positive skin or IgE test without a confirmed objective systemic reaction is considered non-confirmatory of a food allergy.
- In addition, as noted by the AAAAI guidance (2014), many children outgrow food allergies to cow's milk, egg, soy and wheat.[54] Therefore, a history of a severe food allergy may (or may not) persist in adulthood. As such, coverage criteria reflect the need for reassessment of food allergies.
- Avoidance of culprit food allergens to decrease the risk of allergic reactions is the preferred strategy outlined in guidelines, in addition to as-needed antihistamines (diphenhydramine) and epinephrine use for the treatment of an acute allergic reaction.
- Desensitization:
    * Oral immunotherapy (OIT) is commercially available for peanuts (Palforzia, for those less than 17 years of age) and along with compounded desensitization preparations (allergen immunotherapy extracts) for various other common food allergens.
    * Current guidelines do not recommend the use of oral immunotherapy (OIT) as a treatment approach for severe food allergy. However, the guidelines have not been recently updated (2011) and many allergists/immunologists use OIT as part of comprehensive management of allergies, when appropriate.[55]
    * More recently, the AAAAI does not recommend use of OIT in combination with Xolair (omalizumab), but acknowledges that trials in combination with Xolair (omalizumab) are ongoing.[56]

Xolair (omalizumab) for IgE-Mediated Food Allergies

- The safety and efficacy of Xolair (omalizumab) for reduction of food allergy reactions was evaluated in one 16-week, phase 3 randomized, double blind, placebo-controlled trial in 168 patients with moderate-to-severe food allergies (of which 165 were pediatric). [57]
    * All subjects had an allergy to peanut plus at least two other foods, including milk, egg, wheat, cashew, hazelnut, and/or walnut.

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* DIAGNOSIS: All food allergies were confirmed by all of the following positive diagnostic tests:
    - Skin prick test (SPT) defined as ≥ 4mm wheal greater than saline control to allergen.
    - Allergen specific immunoglobulin, IgE, ≥ 6kUA/L determined by ImmunoCAP.
    - Double blinded placebo-controlled food challenge (DBPCFC) defined as experiencing dose-limiting symptoms at a single dose of ≤ 100mg of peanut protein or ≤ 300mg of other above-listed allergen protein [100mg of peanut protein is the equivalent of 1/2 of a peanut].
    - Use of Xolair (omalizumab) for treatment of food allergy determined by tests (other than listed in the coverage criteria) is considered investigational and not coverable.
* All subjects had a moderate-to-severe peanut allergy, defined as: Dose-limiting food allergy symptoms to a single dose of 100mg or less of peanut protein (equivalent to one-half of a peanut) and 300mg or less of protein for each of the other six foods at baseline.
* SEVERITY: Moderate to severe symptoms including skin, respiratory, and/or gastrointestinal (GI) symptoms.
* The primary efficacy endpoint was the percentage of patients who were able to consume a single dose of 600mg or more of peanut protein at week 16 without dose-limiting symptoms.
    - At week 16, a higher percentage of subjects in the Xolair (omalizumab) arm were able to consume at least 600mg of peanut protein as compared to placebo (68% vs. 5%, p<0.001).
    - The clinical meaningfulness of the primary endpoint is unknown, as the 600 mg dose is a small amount of peanut protein relative to what may be consumed during an accidental exposure [600 mg is the equivalent to three whole peanuts or one-half teaspoon of peanut butter]. It is unknown if this endpoint predicts any clinically meaningful outcomes, such as reduced healthcare utilization, reduction in fatal anaphylaxis, need for rescue epinephrine use, an unplanned urgent medical visit (such as to the emergency department or urgent care), or hospitalization
    - Of note, 17% of subjects treated with Xolair (omalizumab) had no significant change in the amount of peanut protein tolerated. Therefore, the use of Xolair (omalizumab) for ongoing treatment of IgE-mediated food allergies is coverable only when there is a clear reduction in the severe food allergic reactions requiring the need for additional medical care, as compared to baseline reactions.
* Secondary endpoints included tolerance of a food challenge with a variety of other allergen food challenges (cashews, milk, egg), all of which met statistical significance in favor of omalizumab [≥ 1000mg cashew protein (~3.5 cashews), milk protein (~2 tablespoons of milk) or egg (1/4 of an egg)]. Responses were inconsistent across food allergies; 41% of study subjects were unable to tolerate >

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300mg cashew protein. Despite numerical trends of improvement, more adequately powered studies are needed to confirm any clinical utility of the use of Xolair (omalizumab) for other food allergies.

- OUTCOMES:
  - Based on the available evidence:
    - Xolair increases the allergic reaction threshold (tolerance of very small amounts of a food allergen). However, Xolair has not been shown to prevent severe anaphylaxis, need for additional medical intervention (such as antihistamines, epinephrine autoinjectors (such as EpiPen), hospitalization, ED use, etc.), or improved quality of life, all clinically relevant outcomes.
    - In addition, many subjects in the trial did not respond to Xolair, roughly 1 in 5 patients.[56 57] Therefore, it is unclear why some benefit and others do not, and it is not possible to identify responders *a priori*. Specifically, from the Xolair labeling:[47]
      - Seventeen percent of omalizumab-treated subjects were *not* able to consume > 100mg of peanut protein without moderate to severe dose limiting symptoms.
      - 18%, 22%, and 41% of omalizumab-treated subjects were *not* able to consume > 300mg of milk, egg, or cashew protein, respectively, without moderate to severe dose-limiting symptoms.
  - Use of Xolair (omalizumab) for food allergy has not been shown to reduce the need for additional unplanned medical care [such as emergency department (ED) use, epinephrine (EpiPen) use, or hospitalization], induce permanent tolerance to allergens, or improve ability to eat an unrestricted diet. Because Xolair (omalizumab) is not curative, treatment will require chronic administration, continuation of allergen avoidance, and availability of "as needed" epinephrine (EpiPen) rescue use for allergic reactions from accidental exposure.
- RATIONALE FOR COVERAGE:
  - For patients less than 17 years of age, coverage of Xolair (omalizumab) is based on the evidence, along with consideration of other treatment options.
    - Based on the available evidence: (see *Outcomes* for additional details)
      - Xolair (omalizumab) increases allergic reaction threshold but has not been shown to prevent severe anaphylaxis or need for additional medical intervention.
      - A majority of trial subjects were able to tolerate a higher oral allergen challenge. However, the response rate was inconsistent across food allergens and clinical benefit has not been demonstrated. It is unclear why some patients respond and others do not. [See *Outcomes* for more information]
    - Therefore, the use of Xolair for food allergy is considered medically necessary only when the patient's diagnosis is confirmed, reactions are severe, and other usual therapies are maximized. Specifically:
      - Have confirmed IgE mediated allergy to multiple foods, by a specialist.

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- Allergic reactions are severe, systemic, and time-related to food allergen exposure, and require medical intervention, defined as the use of an epinephrine rescue device, an unplanned urgent medical visit (such as to the emergency department or urgent care), or hospitalization.
- Have other usual therapy maximized. Namely:
  - Ongoing strict allergen avoidance, or are unable to strictly avoid allergens, namely children (age <17), which also coincides with the vast majority of patients enrolled in the clinical trial.
  - Have used oral immunotherapy (OIT) for food allergen desensitization, if appropriate, such as commercially available Palforzia [peanut (Arachis hypogaea) allergen oral powder-dnfp] for peanut allergy in those < 17 years of age. Similar to Xolair (omalizumab), there is limited evidence for Palforzia for management of peanut allergy. However, Palforzia has years of clinical experience and may be a treatment option for some patients.

* For patients over the age of 17: see Adults with Severe Food Allergy

Not Medically Necessary Uses

IGE-MEDIATED FOOD ALLERGY: Adults and Isolated Peanut Allergy

- Isolated Peanut Allergy:
  * The use of Xolair (omalizumab) in isolated peanut allergy is considered 'not medically necessary.' The rationale is as follows:
    - The available trial evidence required peanut plus "at least two" other allergens. Therefore, the use of Xolair (omalizumab) in patients with isolated peanut allergy is not supported by the available published clinical trial evidence.
    - If a patient has an isolated peanut allergy, commercially available OIT therapy with Palforzia [peanut (Arachis hypogaea) allergen oral powder-dnfp] is a coverable treatment option for those < 17 years of age.
    - Given the lack of evidence for isolated peanut allergy and the availability of other treatment options, the use of Xolair (omalizumab) in isolated peanut allergy is considered 'not medically necessary.'
- Adults with Severe Food Allergy:
  * The use of Xolair (omalizumab) in adults (>17 years of age) with severe food allergy is considered 'not medically necessary.' The rationale is as follows:
    - The FDA approved the use of Xolair (omalizumab) for IgE-mediated food allergy, without an upper restriction to age (for those > 1 year old). However, FDA approval does not, in and of itself, establish medical necessity.

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- The FDA approval was based on a single clinical trial in 168 patients, of which only three were adults (> 17 years old). Given the very small number of adults in the trial, the researchers excluded the adult subject data from the efficacy analysis. Therefore, there is limited evidence to clearly establish the safety and efficacy of Xolair (omalizumab) in adult patients with severe IgE-mediated food allergies.
- Despite the lack of evidence in adults, the mechanism of action of Xolair (omalizumab) is unlikely to change for IgE-mediated food allergies between childhood and adulthood. However, adults are able to maximize other therapies, namely food allergen avoidance, and the use in adults is considered 'Not medically necessary.'
    - Medical necessity is guided by member contracts with the health plan, with consideration for safety and efficacy of other treatment options.
    - The mainstay of therapy remains food allergen avoidance.
    - As noted in the pivotal trial publication, [57] some patients will outgrow their food allergies. In addition, the AAAAI guidance (2014) more specifically notes that many children outgrow food allergies to cow's milk, egg, soy and wheat.[54] Therefore, a history of a severe food allergy may (or may not) persist in adulthood. Re-assessment for food allergies is recommended.

* Because adults are better able to manage exposure to allergens by the nature of age and maturity, along with the fact that many patients outgrow food allergies as they age, the use of Xolair in those over the age of 17 is considered "not medically necessary."

ALLERGIC RHINITIS

- Xolair (omalizumab) reduces seasonal and perennial allergic rhinitis symptoms but has not been shown to have better efficacy than first-line alternatives, such as nasal corticosteroids, antihistamines, or allergen desensitization therapy. [58-60]
- There is interest in the use of other monoclonal antibodies for allergic rhinitis, such as mepolizumab (Nucala). However, there is insufficient evidence to establish benefit versus the many available lower cost treatment options. [61]

Safety

- All monoclonal antibodies for asthma have a theoretical risk of opportunistic infections (including parasitic infections) and malignancy. Immunogenicity and development of antidrug antibodies was observed in clinical trials of Nucala (mepolizumab) and Cinqair (reslizumab). [62 63]
- Anaphylaxis is a concern with administration of anti-asthma monoclonal antibodies. Xolair (omalizumab) FDA labeling details assessment of risk for anaphylaxis (see *Appendix 5*).
- The safety and effectiveness of dose escalation for patients not responding to standard doses have not been established.

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Appendix 1: Low, Medium, and High Daily Doses of Inhaled Corticosteroids (Adapted from GINA 2019 Guidelines) [64]

Adults and Adolescents (Age 12 years and Older)				
Drug	**Products**	**Daily Dose**		
		Low	**Medium**	**High**
Beclomethasone dipropionate (CFC)	None	200-500	>500-1000	>1000
Beclomethasone dipropionate (HFA)	QVAR Redihaler	100-200	>200-400	>400
Budesonide (DPI)	- Pulmicort - Pulmicort Flexhaler	200-400	>400-800	>800
Ciclesonide (HFA)	Alvesco	80-160	>160-320	>320
Fluticasone furoate (DPI)	- Breo Ellipta - Arnuity Ellipta - Trelegy Ellipta	100	N/A	200
Fluticasone propionate (DPI)	- Advair Diskus - Flovent Diskus - Wixela Inhub - AirDuo RespiClick - ArmonAir RespiClick	100-250	>250-500	>500
Fluticasone propionate (HFA)	- Advair HFA - Flovent HFA	100-250	>250-500	>500
Mometasone furoate	- Dulera - Asmanex	110-220	>220-440	>440
Triamcinolone acetonide	Azmacort	400-1000	>1000-2000	>2000

Key: DPI: dry power inhaler; HFA: hydrofluoroalkane.

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Children age 6-11 years				
Drug	**Products**	**Daily Dose**		
		Low	**Medium**	**High**
Beclomethasone dipropionate (CFC)	None	100-200	>200-400	>400
Beclomethasone dipropionate (HFA)	QVAR Redihaler	50-100	>100-200	>200
Budesonide (DPI)	Symbicort - Pulmicort Flexhaler	100-200	>200-400	>400
Ciclesonide (HFA)	Alvesco	80	>80-160	>160
Fluticasone furoate (DPI)	- Breo Ellipta - Arnuity Ellipta - Trelegy Ellipta	N/A	N/A	N/A
Fluticasone propionate (DPI):	- Advair Diskus - Flovent Diskus - Wixela Inhub - AirDuo RespiClick - ArmonAir RespiClick	100-200	>200-400	>400
Fluticasone propionate (HFA)	- Advair HFA - Flovent HFA	100-200	>200-500	>500
Mometasone furoate	- Dulera - Asmanex	110	≥220-<440	≥440
Triamcinolone acetonide	Azmacort	400-800	>800-1200	>1200

Key: DPI: dry power inhaler; HFA: hydrofluoroalkane.

Children age 0-5 years		
Drug	**Products**	**Daily Dose**
		Low
Beclomethasone dipropionate (HFA)	QVAR Redihaler	100 (ages ≥5 years)
Budesonide nebulized	Generic	500 (ages ≥1 years)
Budesonide pressurized MDI	Pulmicort Flexhaler	Not sufficiently studied in this age group
Ciclesonide (HFA)	Alvesco	Not sufficiently studied in this age group
Fluticasone propionate (HFA)	Flovent HFA	50 (ages ≥4 years)
Mometasone furoate	Asmanex	110 (ages ≥4 years)
Triamcinolone acetonide	Azmacort	Not sufficiently studied in this age group

Key: DPI: dry power inhaler; HFA: hydrofluoroalkane.

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Appendix 2: Inhaled Corticosteroid/Long-acting Beta-agonist (ICS/LABA) Combinations

Product	Dosing	Max Puff/Day	High Dose?	Available Strength [a]
Fluticasone propionate/salmeterol DPI (Advair Diskus)	Twice daily	2 (1,000 mcg)	Yes (>500)	100/50 250/50 500/50
Fluticasone propionate/ salmeterol MDI (Advair HFA)	Twice daily	4 (920 mcg)	Yes (>440)	45/21 115/21 230/21
Budesonide + formoterol MDI (Symbicort)	Twice daily	4 (640 mcg)	No[a]	80/4.5 160/4.5
Fluticasone propionate / salmeterol DPI (AirDuo RespiClick)	Twice daily	2 (464 mcg)	No[b]	55/14 113/14 232/14
Mometasone/ formoterol MDI (Dulera)	Twice daily	4 (800 mcg)	Yes (>400)	100/5 200/5
Fluticasone furoate/vilanterol DPI (Breo Ellipta)	Once daily	1 (200 mcg)	Yes (>200)	100/25 200/25

[a] High dose budesonide is >1,200 mcg/day. Maximum daily dose of budesonide from Symbicort (budesonide/formoterol) is 640 mcg/day, a medium dose of ICS.

[b] High dose fluticasone propionate DPI is >500 mcg/day. Maximum daily dose of fluticasone propionate from AirDuo RespiClick (fluticasone propionate/salmeterol DPI) is 464 mcg/day, a medium dose of ICS.

Appendix 3: Antihistamines

H_1-Antihistamines

First Generation (non-selective, "sedating")

- brompheniramine
- chlorpheniramine (generic Chlor-Trimeton)
- clemastine (generic Tavist)
- cyproheptadine (generic Periactin)
- dexbrompheniramine
- dexchlorpheniramine
- diphenhydramine (generic Benadryl)
- hydroxyzine (generic Vistaril)

Second Generation (peripherally-selective, "non-sedating")

- cetirizine (generic Zyrtec)
- desloratadine (Clarinex)
- fexofenadine (generic Allegra)
- levocetirizine (Xyzal)
- loratadine (generic Claritin)

H_2-Antihistamines

- cimetidine (generic Tagamet)
- famotidine (generic Pepcid)
- nizatidine (generic Axid)
- ranitidine (generic Zantac)

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Appendix 4:

Steroid-sparing therapies for Hypereosinophilic syndrome (HES) [43-45]
Immunosuppressives and chemotherapeutic agents: - cyclophosphamide - rituximab - imatinib (in select patients) [a] - vincristine - hydroxyurea [a] - chlorambucil - interferon-alpha - other kinase inhibitors (such as tofacitinib, ruxolitinib) - cyclosporine [a] - methotrexate [a] - tacrolimus [a] - azathioprine [a] - alemtuzumab - Other: cladribine, etoposide, mycophenolate mofetil (MMF)

[a] One of the baseline HES therapies reported in the mepolizumab pivotal HES trial (Study 200622)

Appendix 5. Monoclonal antibodies for asthma and other immune conditions approved for self-administration – Examples of Medical Rationale for Contraindications to Self-Injection

For all self-administered options	
The healthcare provider determines self-injection is not appropriate, as documented by a medically justifiable rationale, such as: - Patient or patient's caregiver is not able to self-administer the prescribed monoclonal antibody as a PFS or autoinjector (Fasenra, Nucala, Tezspire, or Xolair) due to significant behavioral issues and/or cognitive impairment including, but not limited to, those associated with developmental delay, down syndrome, dementia, or excessive anxiety such as severe needle phobia, documented in the clinical records. - Prior severe infusion reactions. - Medically unstable asthma, such as concurrent treatment with medications that require a higher level of monitoring (such as oxygen) or acute treatment of asthma despite maximal medical management.	
Product-specific contraindications	
Fasenra (benralizumab)[65]	History of hypersensitivity reactions to Fasenra (benralizumab).
Nucala (mepolizumab)[35]	Hypersensitivity to mepolizumab or excipients in the formulation.
Xolair (omalizumab)[47]	Patient is higher risk of anaphylaxis (has known risk factors) - Prior history of anaphylaxis, including to Xolair (omalizumab) or other agents, such as foods, drugs, biologics, etc. - History of hypersensitivity reactions to Xolair (omalizumab). - Patient or caregiver is NOT able to recognize symptoms of anaphylaxis and treat anaphylaxis appropriately.

PFS = pre-filled syringe

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Appendix 6. Monoclonal Antibodies and Targeted Immunomodulators for Asthma and other Autoimmune (Inflammatory) conditions

Fasenra (benralizumab)
Dupixent (dupilumab) [refer to Monoclonal antibodies for skin and other inflammatory conditions, Medication Policy Manual, Policy No. dru493]
Nucala (mepolizumab)
Cinqair (reslizumab)
Xolair (omalizumab)
Tezspire (tezepelumab-ekko)
Targeted immunomodulators Antibodies for CID [refer to Drugs for chronic inflammatory diseases, Medication Policy Manual, Policy No. dru444 and Provider-administered drugs for chronic inflammatory diseases (for UMP plans), Medication Policy Manual, Policy No. dru900]

Cross References

Cross References
Allergy Testing lab01, TRG Medical Policy Manual, Laboratory
Implantable Sinus Devices for Postoperative Use Following Endoscopic Sinus Surgery and for Recurrent Sinonasal Polyposis SUR198, TRG Medical Policy Manual, Surgery
Monoclonal Antibodies for Skin and Other Inflammatory Conditions, Medication Policy Manual, Policy No. dru493
Drugs for Chronic Inflammatory Diseases, Medication Policy Manual, Policy No. dru444
Provider-Administered Drugs for Chronic Inflammatory Diseases (for UMP plans), Medication Policy Manual, Policy No. dru900
Site of Care Review, Medication Policy Manual, Policy No. dru408
Palforzia, peanut (Arachis hypogaea) allergen oral powder-dnfp, Medication Policy Manual, Policy No. dru634

Codes	Number	Description
HCPCS	J2182	Injection, mepolizumab (Nucala), 1 mg
HCPCS	J2357	Injection, omalizumab (Xolair), 5 mg
HCPCS	J2786	Injection, reslizumab (Cinqair), 1 mg
HCPCS	J0517	Injection, benralizumab (Fasenra), 1 mg
HCPCS	J2356	Injection, tezepelumab (Tezspire), 1 mg

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Revision History

Revision Date	Revision Summary
10/2/2025	Effective 11/15/2025 • Added coverage criteria for a new indication for Nucala (mepolizumab) for COPD with an eosinophilic phenotype. • Clarified Xolair (omalizumab) for severe food allergy criteria. - Intent remains the same (multiple confirmed food allergens, severity, maximal avoidance, age <17). - Changed "Use in age >17" and "Use in isolated peanut allergy" to 'Not Medically Necessary.'
4/3/2025	• Clarified intent of severity criterion for Xolair (omalizumab): at least one significant allergic reaction to peanut **and** *at least* one other food allergen. No change to intent. • Clarified investigational stance on combination use of monoclonal antibodies.
12/12/2024	• Added coverage criteria for Fasenra (benralizumab) in EGPA, a newly approved FDA indication. • Added step therapy for Cinqair (reslizumab) with provider-administered Fasenra AND Nucala.
6/20/2024	• Added coverage criteria for a new indication for Xolair (omalizumab) for treatment of IgE-mediated food allergy. Limits coverage to patients with one or more food allergies, confirmed with allergy diagnostic testing and use in combination with ongoing food allergen avoidance (effective 9/1/2024). • Added Tezspire (tezepelumab) to site of care program (effective 10/1/2024).
12/7/2023	• Removed monoclonal antibody step for Tezspire (tezepelumab) in severe asthma. • Updated reauthorization criteria for operational consistency.
6/15/2023	• Clarification of steroid-sparing therapy step criteria for Nucala (mepolizumab) in hypereosinophilic syndrome (HES), for operational consistency (no change to intent). • Added Tezspire single-use autoinjector as a self-administered treatment option.

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Revision Date	Revision Summary
12/9/2022	• Reworded criteria for chronic idiopathic urticaria, (CIU) criteria for operational consistency (no change to intent). • Updated CIU/CSU reauthorization and quantity limit for patients with a partial response to Xolair (omalizumab), but persistent symptoms. • Added chronic eosinophilic pneumonia (CEP) and Hyper E Syndrome (HES) (except as listed in the coverage criteria) to the list of "Investigational Uses." • Clarified that allergic rhinitis is "Not Medically Necessary Uses" to include allergic rhinitis for all monoclonal antibody therapies in this policy.
6/17/2022	• Added coverage criteria for the newly FDA-approved drug Tezspire (tezepelumab-ekko). Limits coverage to patients with severe asthma when prescribed by a specialist, adherent use of ICS/ LABA has been ineffective, and blood eosinophils are less than 150 cells/ L. Additionally the asthma must be non-allergic, and the patient is not oral corticosteroid dependent. Step therapy with at least one monoclonal antibody for severe asthma is required. • Updated nasal polyp criteria for initial authorization to be at 24 weeks per guidelines, and continued reauthorization may be annually thereafter.
3/18/2022	• Updated nasal polyp criteria to show that both Xolair (omalizumab) and Nucala (mepolizumab) require combination use of intranasal corticosteroids. IgE levels are only required for use of Xolair (omalizumab) in nasal polyps.
10/15/2021	• Added Site of Care (SOC) requirements for provider-administered doses. • Added coverage criteria for Nucala (mepolizumab) for nasal polyps and clarified severity criteria. • Updated benefit and administration language section.

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Revision Date	Revision Summary
4/21/2021	• Added coverage criteria for use of Nucala (mepolizumab) in hypereosinophilic syndrome (HES), a newly FDA approved indication. • Added coverage criteria for use of Xolair (omalizumab) in nasal polyps, a newly FDA approved indication. • Revised asthma criteria: - Changed requirement for previous courses of oral corticosteroids in past 12 months from two to one. - Simplified eosinophil count criteria for Fasenra (benralizumab), Nucala (mepolizumab), and Cinqair (reslizumab). - Removed requirement that smoking must have been discontinued. • Added Continuation of Therapy (COT) criteria • Updated "Investigational Uses" • Added Xolair pre-filled syringe as a self-administered treatment option.
10/23/2019	• Added Fasenra (benralizumab) and Nucala (mepolizumab) single-dose pre-filled autoinjector for self-administration to the policy. All other anti-asthma antibodies in the policy remain provider-administered only. Effective November 15, 2019: • Updated coverage criteria for asthma: - Clarified that maximally tolerated inhaled corticosteroid and long-acting inhaled beta-2 agonist therapy must have been tried. - Removed requirement for use of oral corticosteroids if exacerbations are present. - Revised definition of poor asthma control to include clarify requirement for two additional oral corticosteroid bursts or emergency department visits or hospitalizations.
4/25/2019	Updated and fixed incorrect references. No changes to policy criteria with this update.
1/31/2019	Clarified intent of trigger criteria.
11/16/2018	Clarified intent of trigger, step therapy, quantity limit and reauthorization criteria.
3/16/2018	New policy: • The Xolair, Nucala, and Cinqair policies were combined. • Coverage criteria added for asthma for newly-approved Fasenra. • Coverage criteria added for EGPA for Nucala.

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