This document addresses the use of monoclonal antibodies against interleukin-5 (IL-5) in the treatment of individuals with eosinophilic conditions, including severe uncontrolled eosinophilic asthma and eosinophilic granulomatosis with polyangiitis. The agents approved by the Food and Drug Administration (FDA) include:

- Cinqair (reslizumba), a monoclonal anti-IL-5 antibody
- Fasenra (benralizumab), a monoclonal anti-IL-5 receptor alpha antibody
- Nucala (mepolizumab), a monoclonal anti-IL-5 antibody

Eosinophilic Asthma

Researchers have discovered that eosinophils play a pivotal role in immune development and asthma. Eosinophils are a type of white blood cell whose natural role is to defend the body against disease and environmental substances and accumulate wherever allergic reactions take place, including those in allergic asthma. In individuals with eosinophilic asthma, white blood cells accumulate and release chemicals that may damage the lining of the lungs. Studies examining individuals with mild asthma have shown that airway inflammation due to eosinophils is a typical characteristic, and eosinophilic airway inflammation appears to be closely related to the risk of severe asthma exacerbations. Although the role eosinophils play in the pathophysiology of asthma is unclear, they represent a biomarker for predicting whether individuals will respond to corticosteroids, predicting which persons are at risk of exacerbations, and for guiding steroid therapy in these events.

Cinqair, Fasenra and Nucala are approved by the FDA to treat severe eosinophilic asthma. In 2013, the European Respiratory Society/American Thoracic Society (ERS/ATS) released guidance for defining, evaluating and treating severe asthma. The guidelines define severe asthma as asthma which has required treatment with high dose inhaled corticosteroids and a long-acting beta agonist, leukotriene modifier or theophylline for the previous year in order to prevent asthma symptoms from becoming uncontrolled. Alternatively, severe asthma can be defined as asthma that has required systemic corticosteroid treatment for over 50% of the previous year.

ERS/ATS guidance defines uncontrolled asthma as meeting one of the following:
- Poor symptom control: Asthma Control Questionnaire (ACQ) consistently >1.5, Asthma Control Test (ACT) <20
- Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year
- History of serious exacerbation: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year
- Airflow limitation: after appropriate bronchodilator withhold FEV₁ <80% predicted

Cinqair is approved by the FDA for add-on maintenance treatment of individuals 18 years of age and older with severe asthma with an eosinophilic phenotype. Cinqair is administered monthly by intravenous infusion. The safety and efficacy of Cinqair was evaluated in two multicenter, randomized, double-blind, placebo-controlled trials in individuals with severe eosinophilic asthma confirmed by blood eosinophils ≥ 400 cells/microliter. Participants received background treatment consisting of medium-to-high dose inhaled corticosteroids
Cinqair has a black box warning for anaphylaxis. Anaphylaxis occurred with Cinqair infusion in 0.3% of participants in placebo-controlled studies. Individuals should be observed after Cinqair administration for an appropriate period of time by a healthcare professional prepared to manage anaphylaxis that can be life-threatening. Discontinue Cinqair immediately if the patient experiences signs or symptoms of anaphylaxis.

Fasenra is approved by the FDA for add-on maintenance treatment of individuals 12 years of age and older with severe asthma with an eosinophilic phenotype. Fasenra is administered every 8 weeks by subcutaneous injection. The safety and efficacy of Fasenra was evaluated in three multicenter, randomized, double-blind placebo-controlled trials (CALIMA, SIROCCO, ZONDA) in individuals with severe eosinophilic asthma confirmed by blood eosinophils ≥ 300 cells/microliter. The steroid-sparing study (ZONDA) enrolled participants with blood eosinophils ≥ 150 cells/microliter. Participants received background treatment consisting of medium-to-high dose inhaled corticosteroids + LABA +/- oral corticosteroids. Study data confirms the efficacy of Fasenra in reducing exacerbations that require hospitalization or emergency department visits, improving asthma control and providing a steroid-sparing benefit.

Nucala is approved by the FDA as add-on maintenance treatment of individuals 12 years of age and older with severe asthma with an eosinophilic phenotype. Nucala is administered monthly by subcutaneous injection. The safety and effectiveness of Nucala was established in three multicenter, double-blind, randomized, placebo-controlled trials (DREAM, SIRIUS, MENSA) in individuals with severe eosinophilic asthma confirmed by blood eosinophils ≥ 150 cells/microliter at initiation of treatment or blood eosinophils ≥ 300 cells/microliter in the past 12 months. Participants received background treatment consisting of high dose inhaled corticosteroids + controller therapy +/- oral corticosteroids. Study data confirms the efficacy of Nucala in reducing exacerbations that require hospitalization or emergency department visits, improving asthma control and quality of life measures and providing a steroid-sparing benefit.

The 2018 Global Initiative for Asthma (GINA) guidelines include Cinqair, Fasenra and Nucala in their Step 5 treatment options. All three agents are recommend as add-on treatment for individuals with severe eosinophilic asthma not controlled with Step 4 therapy (two or more controllers plus as-needed reliever). The GINA guidance also recommends referring individuals progressing to Step 5 to a specialist for consultation.

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a multisystem disorder characterized by allergic rhinitis, asthma and prominent peripheral blood eosinophilia. EGPA is classified as a vasculitis of the small to medium-sized arteries although the vasculitis is often not apparent in the initial phases of the disease. This blood vessel inflammation affects organ systems including the lungs, gastrointestinal tract, skin, heart and nervous system. Nucala is approved by the FDA for the treatment of adults with EGPA.

The safety and efficacy of Nucala for the treatment of EGPA was evaluated in a multicenter, parallel-group, double-blind, phase III trial of 136 adults who had received at least 4 weeks of a stable prednisolone or prednisone dose for relapsing or refractory EGPA. The clinical trial inclusion criteria defined EGPA as a history or presence of asthma, a blood eosinophil level of greater than or equal to 10% of leukocytes or an absolute eosinophil count of greater than 1000 cells per mm³ and the presence of two or more features associated with EGPA. Participants were randomized to receive Nucala or placebo in addition to standard care (glucocorticoid treatment with or without immunosuppressive therapy).

The two primary endpoints in the clinical trial were the accrued weeks of disease remission over a 52-week period (defined as Birmingham Vasculitis Activity Score (BVAS) = 0 [no active vasculitis]) and the proportion of participants in remission at both week 36 and week 48 of treatment. Participants receiving Nucala achieved a significantly greater accrued time in remission compared to placebo (28% vs. 3% of participants had ≥ 24 weeks of accrued remission; odds ratio, 5.91; 95% CI, 2.68 to 13.03; p<0.001) and a significantly higher proportion of participants in remission at both week 36 and week 48 compared to placebo (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; p<0.001).

Clinical Criteria

When a drug is being reviewed for coverage under a member’s medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Cinqair (reslizumab)

Initial requests for Cinqair (reslizumab) for severe eosinophilic asthma may be approved if the following criteria are met:
I. Individual is 18 years of age or older; **AND**

II. Individual has a diagnosis of severe eosinophilic asthma; **AND**

III. Evidence of asthma is demonstrated by the following (NAEPP, 2008):
   A. A pretreatment forced expiratory volume in 1 second (FEV₁) less than 80% predicted; **AND**
   B. FEV₁ reversibility of at least 12% and 200 ml after albuterol administration; **AND**

IV. Individual has had a 3 month trial and inadequate response or intolerance to combination controller therapy (high dose inhaled corticosteroids plus long acting beta₂–agonists, leukotriene modifiers, theophylline or oral corticosteroids) (ERS/ATS, 2013); **AND**

V. Individual has experienced two or more asthma exacerbations in the prior 12 months requiring use of a systemic corticosteroid or temporary increase in the individual’s usual maintenance dosage of oral corticosteroids (ERS/ATS, 2013); **AND**

VI. Individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection) greater than or equal to 400 cells/microliter (400 cells/mm³) at initiation of therapy.

Continuation requests for Cinqair (reslizumab) for severe eosinophilic asthma may be approved if the following criteria are met:

I. Treatment with Cinqair has resulted in clinical improvement as confirmed by one or more of the following:
   A. Decreased utilization of rescue medications; **OR**
   B. Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids); **OR**
   C. Increase in percent predicted FEV₁ from pretreatment baseline; **OR**
   D. Reduction in reported asthma-related symptoms, such as asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing.

**Fasenra (benralizumab)**

Initial requests for Fasenra (benralizumab) for severe eosinophilic asthma may be approved if the following criteria are met:

I. Individual is 12 years of age or older; **AND**

II. Individual has a diagnosis of severe eosinophilic asthma; **AND**

III. Evidence of asthma is demonstrated by the following (NAEPP, 2008):
   A. A pretreatment forced expiratory volume in 1 second (FEV₁) less than 80% predicted; **AND**
   B. FEV₁ reversibility of at least 12% and 200 milliliters after albuterol administration; **AND**

IV. Individual has had a 3 month trial and inadequate response or intolerance to combination controller therapy (high dose inhaled corticosteroids plus long acting beta₂–agonists, leukotriene modifiers, theophylline or oral corticosteroids) (ERS/ATS, 2013); **AND**

V. Individual has experienced two or more asthma exacerbations in the prior 12 months requiring use of a systemic corticosteroid or temporary increase in the individual’s usual maintenance dosage of oral corticosteroids (ERS/ATS, 2013); **AND**

VI. Individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection) greater than or equal to 300 cells/microliter (300 cells/mm³) at initiation of therapy.

Continuation requests for Fasenra (benralizumab) for severe eosinophilic asthma may be approved if the following criteria are met:

I. Treatment with Fasenra has resulted in clinical improvement as confirmed by one or more of the following:
   A. Decreased utilization of rescue medications; **OR**
   B. Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids); **OR**
   C. Increase in percent predicted FEV₁ from pretreatment baseline; **OR**
   D. Reduction in reported asthma-related symptoms, such as asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing.

**Nucala (mepolizumab)**

Initial requests for Nucala (mepolizumab) for severe eosinophilic asthma may be approved if the following criteria are met:

I. Individual is 12 years of age or older; **AND**

II. Individual has a diagnosis of severe eosinophilic asthma; **AND**

III. Evidence of asthma is demonstrated by the following (NAEPP, 2008):
   A. A pretreatment forced expiratory volume in 1 second (FEV₁) less than 80% predicted; **AND**
   B. FEV₁ reversibility of at least 12% and 200 milliliters after albuterol administration; **AND**
IV. Individual has had a 3 month trial and inadequate response or intolerance to combination controller therapy (high dose inhaled corticosteroids plus long acting beta_2_–agonists, leukotriene modifiers, theophylline or oral corticosteroids) (ERS/ATS, 2013); AND

V. Individual has experienced two or more asthma exacerbations in the prior 12 months requiring use of a systemic corticosteroid or temporary increase in the individual's usual maintenance dosage of oral corticosteroids (ERS/ATS, 2013); AND

VI. Individual has one of the following blood eosinophil counts (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease and known or suspected parasitic infection):
   A. Greater than or equal to 150 cells/microliter (150 cells/mm³) at initiation of therapy; OR
   B. Greater than or equal to 300 cells/microliter (300 cells/mm³) in the prior 12 months.

Continuation requests for Nucala (mepolizumab) for severe eosinophilic asthma may be approved if the following criteria are met:

I. Treatment with Nucala has resulted in clinical improvement as confirmed by one or more of the following:
   A. Decreased utilization of rescue medications; OR
   B. Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids); OR
   C. Increase in percent predicted FEV₁ from pretreatment baseline; OR
   D. Reduction in reported asthma-related symptoms, such as asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing.

Initial requests for Nucala (mepolizumab) for eosinophilic granulomatosis with polyangiitis may be approved if the following criteria are met:

I. Individual is 18 years of age or older; AND
II. Individual has been diagnosed with relapsing or refractory eosinophilic granulomatosis with polyangiitis for at least 6 months defined as (Wechsler, 2017):
   A. A history or presence of asthma; AND
   B. A blood eosinophil level of greater than or equal to 10% of leukocytes or an absolute eosinophil count of greater than 1000 cells per mm³ (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease and known or suspected parasitic infection); AND
   C. The presence of two or more features of eosinophilic granulomatosis with polyangiitis (such as, a biopsy showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatosis inflammation; neuropathy, mono or poly [motor deficit or nerve conduction abnormality]; pulmonary infiltrates, non-fixed; sinonasal abnormality; cardiomyopathy; glomerulonephritis; alveolar hemorrhage; palpable purpura; antineutrophil cytoplasmic antibody [ANCA] positive status).

Continuation requests for Nucala (mepolizumab) for eosinophilic granulomatosis with polyangiitis may be approved if the following criteria are met:

I. Treatment with Nucala has resulted in clinical improvement as confirmed by the achievement of remission at some point during treatment defined as (Wechsler, 2017):
   A. Birmingham Vasculitis Activity Score (BVAS), version 3, of 0 (on a scale from 0 to 63); AND
   B. Receipt of prednisolone or prednisone at a dose of 4 mg or less per day.

**Coding**

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**HCPCS**

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<th>Code</th>
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<tr>
<td>J0517</td>
<td>Injection, benralizumab, 1 mg [Fasenra]</td>
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<td>J2182</td>
<td>Injection, mepolizumab, 1 mg [Nucala]</td>
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<td>J2786</td>
<td>Injection, reslizumab, 1 mg [Cinqair]</td>
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**ICD-10 Diagnosis**

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<th>Code</th>
<th>Description</th>
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<td>J82</td>
<td>Pulmonary eosinophilia, not elsewhere classified</td>
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<td>Polyarteritis with lung involvement (Churg-Strauss) [mepolizumab (Nucala) only]</td>
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### Document History

Reviewed: 2/22/2019

Document History:

- 2/22/2019 – Annual Review: No changes.
- 11/16/2018 – Select Review: Initial P&T review of Monoclonal Antibodies to Interleukin-5. Standardize severe asthma criteria across all three agents based on ERS/ATS guidance. Standardize exacerbation criteria across all three agents based on ERS/ATS guidance. Remove ACQ-6/7 criteria as inconsistent between agents and there are other criteria elements that confirm asthma severity and control. Update Cinqair eosinophil criteria to reflect the level at the initiation of treatment to mirror clinical trial inclusion parameters. Add references for non-label-based criteria elements. HCPCS and ICD-10 coding review: Delete J3490, J3590, and C9166 for Fasenra. Added J0517 for Fasenra effective 1/1/2019. No changes to ICD-10.

### References

8. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2018; Updated periodically.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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