

RESPIRATORY INTERLEUKINS (CINQAIR®, FASENRA®, AND NUCALA®)

Policy Number: 2019D0055G

Effective Date: March 1, 2019

[Instructions for Use](#) ⓘ

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Related Policies

None

COVERAGE RATIONALE

 See [Benefit Considerations](#) ⓘ

This policy provides information about the use of certain specialty pharmacy medications administered by either the subcutaneous (SC) or intravenous (IV) route.

This policy refers to the following drug products:

- Cinqair® (reslizumab)
- Fasenra® (benralizumab)
- Nucala® (mepolizumab)

Proven
Eosinophilic Granulomatosis with Polyangiitis (EGPA)
I. Initial Therapy
A. Nucala for subcutaneous use is proven for the treatment of EGPA.¹
B. Nucala is medically necessary for the treatment of EGPA when ALL of the following criteria are met:

1. Diagnosis of relapsing or refractory EGPA as defined by **all** of the following:¹³
 - a. Diagnosis of EGPA; **and**
 - b. Past medical history or presence of asthma; **and**
 - c. **One** of the following values at diagnosis:
 - i. Blood eosinophil level of at least 10% of leucocytes
 - ii. Absolute eosinophil count > 1,000 cells/μL
 - d. Presence of **at least two** of the following characteristics typical of EGPA:
 - i. Histopathological evidence of:
 - 1) Eosinophilic vasculitis
 - 2) Perivascular eosinophilic infiltration
 - 3) Eosinophil-rich granulomatous inflammation
 - ii. Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)
 - iii. Pulmonary infiltrates, non-fixed
 - iv. Sino-nasal abnormality
 - v. Cardiomyopathy (established by echocardiography or MRI)
 - vi. Glomerulonephritis (hematuria, red cell casts, proteinuria)
 - vii. Alveolar hemorrhage (by bronchoalveolar lavage)
 - viii. Palpable purpura
 - ix. Anti-neutrophil cytoplasmic antibody (ANCA) positive

and

- e. History of relapsing or refractory disease defined as **one** of the following:
 - i. Relapsing disease as defined as a past history (within the past 2 years) of at least one EGPA relapse (requiring additional or dose escalation of corticosteroids or immunosuppressant, or hospitalization)
 - ii. Refractory disease as defined as failure to attain remission within the prior 6 months following induction treatment with standard therapy regimens

and

- 2. Patient is currently taking standard therapy (corticosteroids with or without immunosuppressive therapy);

and

- 3. Patient is **not** receiving Nucala in combination with **any** of the following:
 - a. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
 - b. Anti-IgE therapy [e.g., Xolair (omalizumab)]
 - c. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

and

- 4. Nucala dosing for EGPA is in accordance with the U. S. Food and Drug Administration approved labeling: 300mg subcutaneously once every 4 weeks; **and**
- 5. Prescribed by or in consultation with a pulmonologist, rheumatologist, or allergist/immunologist; **and**
- 6. Initial authorization will be for no more than 6 months.

II. Reauthorization/Continuation of Care Criteria

Nucala, for the treatment of EGPA, authorization for continued use will be approved based on ALL of the following criteria:

- A. Documentation of positive clinical response as demonstrated by at least **one** of the following:

- 1. Reduction in the frequency and/or severity of relapses
- 2. Reduction or discontinuation of doses of corticosteroids and/or immunosuppressant
- 3. Disease remission
- 4. Reduction in severity or frequency of EGPA-related symptoms

and

- B. Patient is **not** receiving Nucala in combination with **any** of the following:

- 1. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
- 2. Anti-IgE therapy [e.g., Xolair (omalizumab)]
- 3. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

and

- C. Nucala dosing for EGPA is in accordance with the U. S. Food and Drug Administration approved labeling: 300mg subcutaneously once every 4 weeks; **and**
- D. Prescribed by or in consultation with a pulmonologist, rheumatologist, or allergist/immunologist; **and**
- E. Reauthorization will be for no more than 12 months.

Severe Asthma

Cinqair

- I. **Cinqair for intravenous use is proven for add-on therapy for patients who meet BOTH of the following criteria:**²

- Have an eosinophilic phenotype; **and**
- Will be used as add-on maintenance therapy in the treatment of severe asthma.

- II. **Cinqair is medically necessary when ALL of the following criteria are met:**²⁻⁶

- A. Diagnosis of severe asthma; **and**

- B. Classification of asthma as uncontrolled or inadequately controlled as defined by at least **one** of the following:

- 1. Poor symptom control (e.g., ACQ score consistently greater than 1.5 or ACT score consistently less than 20); **or**
- 2. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; **or**
- 3. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); **or**
- 4. Airflow limitation (e.g., after appropriate bronchodilator withhold FEV1 less than 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal));

and

- C. Asthma is an eosinophilic phenotype as defined by a baseline (pre-reslizumab) peripheral blood eosinophil level of ≥ 400 cells/ μ L within the past 4 weeks; **and**

- D. Used in combination with **one** of the following:

- 1. **One** maximally-dosed (appropriately adjusted for age) combination ICS/LABA product [e.g., fluticasone propionate/salmeterol (Advair[®]), budesonide/formoterol (Symbicort[®])]; **or**
- 2. Combination therapy including **both** of the following:
 - a. **One** high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco[®]), mometasone furoate (Asmanex[®]), beclomethasone dipropionate (QVAR[®])]; **and**

- b. **One** additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®), leukotriene receptor antagonist – montelukast (Singulair®), theophylline];

and

- E. Patient is **not** receiving Cinqair in combination with **any** of the following:
1. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
 2. Anti-IgE therapy [e.g., Xolair (omalizumab)]
 3. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

and

- F. Cinqair dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 3 mg/kg intravenously once every 4 weeks; **and**
- G. Prescribed by or in consultation with a pulmonologist or allergist/immunologist; **and**
- H. Initial authorization will be for no more than 6 months.

Fasentra

I. **Fasentra for subcutaneous use is proven for add-on therapy for patients who meet BOTH of the following criteria:**

- Has an eosinophilic phenotype; **and**
- Will be used as add-on maintenance therapy in the treatment of severe asthma.

II. **Fasentra is medically necessary when ALL of the following criteria are met:**^{3, 5, 6, 10-12}

- A. Diagnosis of severe asthma; **and**
- B. Classification of asthma as uncontrolled or inadequately controlled as defined by at least one of the following:
1. Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20); **or**
 2. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; **or**
 3. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); **or**
 4. Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second (FEV1) less than 80% predicted [in the face of reduced FEV1/forced vital capacity (FVC) defined as less than the lower limit of normal])

and

- C. Asthma is an eosinophilic phenotype as defined by a baseline (pre- benralizumab treatment) peripheral blood eosinophil level ≥ 150 cells/ μ L within the past 6 weeks¹²; **and**
- D. Used in combination with one of the following:
1. **One** maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]; **or**
 2. Combination therapy including **both** of the following:
 - a. **One** high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]; **and**
 - b. One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®); leukotriene receptor antagonist – montelukast (Singulair®); theophylline]

and

- E. Patient is not receiving Fasentra in combination with **any** of the following:
1. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
 2. Anti-IgE therapy [e.g., Xolair (omalizumab)]
 3. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

and

- F. Fasentra dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 30mg subcutaneously once every 4 weeks for 3 doses, then once every 8 weeks thereafter; **and**
- G. Prescribed by or in consultation with a pulmonologist or allergist/immunologist; **and**
- H. Initial authorization will be for no more than 6 months.

Nucala

I. **Nucala for subcutaneous use is proven for add-on therapy for patients who meet BOTH of the following criteria:**¹

- Has an eosinophilic phenotype; **and**
- Will be used as add-on maintenance therapy in the treatment of severe asthma.

II. **Nucala is medically necessary when ALL of the following criteria are met:**^{1,3-6}

- A. Diagnosis of severe asthma; **and**
- B. Classification of asthma as uncontrolled or inadequately controlled as defined by at least **one** of the following:
1. Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20); **or**

2. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; **or**
3. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); **or**
4. Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second (FEV1) less than 80% predicted [in the face of reduced FEV1/forced vital capacity (FVC) defined as less than the lower limit of normal]);

and

- C. Asthma is an eosinophilic phenotype as defined by a baseline (pre-mepolizumab treatment) peripheral blood eosinophil level \geq 150 cells/ μ L within the past 6 weeks; **and**
- D. Used in combination with **one** of the following:
 1. **One** maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta₂-agonist (LABA) product [e.g., fluticasone propionate/salmeterol (Advair[®]), budesonide/formoterol (Symbicort[®])]; **or**
 2. Combination therapy including **both** of the following:
 - a. **One** high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco[®]), mometasone furoate (Asmanex[®]), beclomethasone dipropionate (QVAR[®])]; **and**
 - b. **One** additional asthma controller medication [e.g., LABA - olodaterol (Striverdi[®]) or indacaterol (Arcapta[®]); leukotriene receptor antagonist – montelukast (Singulair[®]); theophylline];

and

- E. Patient is **not** receiving Nucala in combination with **any** of the following:
 1. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
 2. Anti-IgE therapy [e.g., Xolair (omalizumab)]
 3. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

and

- F. Nucala dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 100mg subcutaneously once every 4 weeks; **and**
- G. Prescribed by or in consultation with a pulmonologist or allergist/immunologist; **and**
- H. Initial authorization will be for no more than 6 months.

Reauthorization/Continuation of Care Criteria

For patients currently on Cinqair, Fasentra, or Nucala for the treatment of severe eosinophilic asthma, authorization for continued use will be approved based on **all** of the following criteria:

- I. Documentation of positive clinical response as demonstrated by at least one of the following:
 - A. Reduction in the frequency of exacerbations)
 - B. Decreased utilization of rescue medications
 - C. Increase in percent predicted FEV1 from pretreatment baseline
 - D. Reduction in severity or frequency of asthma-related symptoms (e.g., wheezing, shortness of breath, coughing, etc.)

and

- II. Used in combination with an ICS-containing controller medication; **and**

III. **One** of the following:

- A. Patient is **not** receiving Nucala in combination with **any** of the following:
 1. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
 2. Anti-IgE therapy [e.g., Xolair (omalizumab)]
 3. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

or

- B. Patient is **not** receiving Cinqair in combination with **any** of the following:
 1. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
 2. Anti-IgE therapy [e.g., Xolair (omalizumab)]
 3. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

or

- C. Patient is **not** receiving Fasentra in combination with **any** of the following:
 1. Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab), Fasentra (benralizumab)]
 2. Anti-IgE therapy [e.g., Xolair (omalizumab)]
 3. Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

and

IV. **One** of the following:

- A. Nucala dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 100mg subcutaneously once every 4 weeks; **or**
- B. Cinqair dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 3 mg/kg intravenously once every 4 weeks; **or**
- C. Fasentra dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 30 mg subcutaneously once every 8 weeks;

and

V. Prescribed by or in consultation with a pulmonologist or allergist/immunologist; **and**

VI. Reauthorization will be for no more than 12 months.

Unproven

Cinqair, Fasenra, and Nucala are unproven and not medically necessary in the following:^{1-2,8}

- Other eosinophilic conditions
- Acute bronchospasm
- Status asthmaticus
- Chronic obstructive pulmonary disease (COPD)
- Granulomatosis with polyangiitis (Wegener's)
- Microscopic polyangiitis
- Organ or Life-threatening EGPA

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Cinqair (reslizumab)

Cinqair is approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of patients with severe asthma aged 18 years and older, who have an eosinophilic phenotype. Cinqair is not indicated for the treatment of other eosinophilic conditions or for acute bronchospasm or status asthmaticus. Because of the risk of anaphylaxis, healthcare providers administering Cinqair should observe patients closely for an appropriate period of time and be prepared to manage anaphylaxis that can be life-threatening.²

Fasenra (benralizumab)

Fasenra is approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, who have an eosinophilic phenotype. Fasenra is not indicated for the treatment of other eosinophilic conditions or for acute bronchospasm or status asthmaticus.¹⁰

Nucala (mepolizumab)

Nucala is approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, who have an eosinophilic phenotype. Nucala is not indicated for the treatment of other eosinophilic conditions or for acute bronchospasm or status asthmaticus. Nucala is also indicated for the treatment of adult patient with eosinophilic granulomatosis with polyangiitis (EGPA).¹

BACKGROUND

Asthma is a common chronic inflammatory disease of the airways that affects an estimated 24 million adults and children. Although the disease is well controlled with inhaled therapy in most patients, approximately 1.2-2.4 million people have severe asthma (i.e., 5-10% of the asthma population) that is associated with substantial morbidity, mortality, and economic effects. Asthma has been divided into subtypes, some of which are associated with airway inflammation with eosinophils. It is estimated that about half of individuals with severe asthma exhibit the eosinophilic phenotype with elevated eosinophil levels (a marker of inflammation) in both the blood and airways. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion, which are hallmarks of asthma. Interleukin-5 (IL-5) is an important cellular signal in eosinophilic inflammation. Therapies that decrease IL-5 levels, such as Nucala (mepolizumab) and Cinqair (reslizumab), may decrease eosinophils in lung tissue. Fasenra (benralizumab) directly binds to the human IL-5 receptor on the surface of eosinophils and basophils, leading to the apoptosis of these cells through antibody-dependent cell mediated cytotoxicity.^{4,7,9,10}

Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) is characterized by asthma, sinusitis, pulmonary infiltrates, neuropathy, and eosinophilic vasculitis of one or more end organs. It is thought that eosinophils mediate the effects in patients with EGPA by infiltrating tissue and vasculature, causing inflammation. Systemic glucocorticoids are currently the standard of treatment for EGPA, however, some patients do not have sufficient response to therapy. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma and EGPA has not been definitively established.^{1,13}

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
J0517	Injection, benralizumab, 1 mg
J2182	Injection, mepolizumab, 1 mg
J2786	Injection, reslizumab, 1 mg

ICD-10 Diagnosis Code	Description
J45.50	Severe persistent asthma, uncomplicated
J45.51	Severe persistent asthma with (acute) exacerbation
J45.52	Severe persistent asthma with status asthmaticus
J82	Pulmonary eosinophilia, not elsewhere classified
M30.1	Polyarteritis with lung involvement [Churg-Strauss]

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

CLINICAL EVIDENCE

Proven

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Mepolizumab is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).¹

In a multicenter, double-blind, parallel-group, phase 3 trial, Wechsler et al, evaluated the efficacy and safety mepolizumab versus placebo for eosinophilic granulomatosis with polyangiitis (EGPA).¹³ Patients with relapsing or refractory EGPA were randomly assigned to receive 300 mg of mepolizumab (n=68) or placebo (n=68) subcutaneously every 4 weeks, plus standard care, for 52 weeks. Patients had to have received treatment for at least 4 weeks and were taking stable corticosteroid dosing for at least 4 weeks. The two primary end points were the accrued weeks of remission over the 52 week period, and the proportion of participants in remission at both week 36 and week 48. Secondary endpoints included: time to first relapse and average daily glucocorticoid use at weeks 48 through 52). Patients receiving mepolizumab had significantly more accrued weeks of remission than placebo (28% vs. 3% had ≥ 24 weeks of accrued remission; odds ratio, 5.91; 95% confidence interval [CI], 2.68 to 13.03; P<0.001) and a higher percentage of patients were in remission at both week 36 and week 48 (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; P<0.001). Remission did not occur in 47% of the patients in the mepolizumab group versus 81% of those in the placebo group. The annualized relapse rate was 1.14 in the mepolizumab group, as compared with 2.27 in the placebo group (rate ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001). A total of 44% of the patients in the mepolizumab group, as compared with 7% of those in the placebo group, had an average daily dose of prednisolone or prednisone of 4.0 mg or less per day during weeks 48 through 52 (odds ratio, 0.20; 95% CI, 0.09 to 0.41; P<0.001). The authors concluded that in patients with EGPA, mepolizumab resulted in significantly more weeks in remission and a higher proportion of patients in remission than placebo, although only half of the patients treated with mepolizumab had protocol-defined remission.

Severe Eosinophilic Asthma

Benralizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.¹⁰

Mepolizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.¹

Reslizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.²

Professional Societies

Global Initiative for Asthma

The Global Initiative for Asthma (GINA, 2018) recommends that for Step 5 treatment, adults and adolescents, may be treated with **mepolizumab** or **reslizumab** as follows (Evidence A: Randomized controlled trials and meta-analyses. Rich body of evidence):⁶

- Step 5: Higher level care and/or add-on treatment. Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in management of severe asthma (Evidence D: Panel consensus judgment).
- Add-on anti-interleukin- treatment (subcutaneous mepolizumab for patients aged ≥ 12 years; intravenous reslizumab for ages ≥ 18 years) or anti-interleukin 5 receptor treatment (subcutaneous benralizumab for ages ≥ 12 years), with severe eosinophilic asthma that is uncontrolled on Step 4 treatment. (Evidence A)

Institute for Clinical and Economic Review (ICER)

On March 14, 2016, the Institute for Clinical and Economic Review (ICER) released a clinical report entitled, "Mepolizumab (Nucala[®], GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks." ICER recommendations are as follows: ⁴

- ICER judges the current body of evidence on **mepolizumab** to be "comparable or better."
- For adult patients with severe eosinophilic asthma, ICER judges there to be moderate certainty of a comparable or better net benefit for **mepolizumab** 100mg SC every four weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and additional controller medications. There is moderate certainty because both the MENSA trial, which demonstrated a significant reduction in asthma exacerbations, and the SIRIUS trial, which demonstrated a significant reduction in oral corticosteroids dosage, were relatively small studies of short duration. There remains uncertainty about the long-term durability of the benefits of the therapy and about the potential harms from modulation of the immune system. Ongoing post-marketing trials and extension studies evaluating **mepolizumab** may demonstrate a wide variety of outcomes, from substantial net health benefit to a comparable net benefit given the potential harms associated with the monoclonal antibody (opportunistic infection, anaphylaxis).

European Respiratory Society (ERS)/American Thoracic Society (ATS)

The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines define severe asthma as that which requires treatment with high-dose ICSs plus a second controller (or systemic corticosteroids) to prevent progression to uncontrolled disease status or continuing uncontrolled disease status despite this therapy.³ The guidelines recommend that, "While the anti-IL5 antibody, mepolizumab, was not beneficial in unselected adult patients with moderate asthma, when studied in severe asthma patients with persistent sputum eosinophilia, two anti-IL-5 antibodies, mepolizumab and reslizumab, have been shown to decrease exacerbations and oral corticosteroid use, as well as improve symptoms and lung function to varying degrees."

Unproven

Nucala and Cinqair have additional uses listed in the FDA-label:¹⁻²

- Other eosinophilic conditions
- Acute bronchospasm
- Status asthmaticus
- Chronic obstructive pulmonary disease (COPD)

Statistically robust randomized controlled trials are necessary to establish the safety and efficacy of Fasenra, Nucala and Cinqair to treat these conditions.^{1-2,8,10}

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have National Coverage Determination (NCDs) specifically for respiratory interleukin-5 antagonist monoclonal antibody therapies such as CINQAIR[®] (reslizumab), NUCALA[®] (mepolizumab) and FASENRA[™] (benralizumab). Local Coverage Determinations (LCDs) do not exist at this time. (Accessed July 17, 2018)

REFERENCES

1. Nucala[®] [prescribing information]. Research Triangle Park, NC; GlaxoSmithKline, LLC; December 2017.
2. Cinqair[®] [prescribing information]. Frazer, PA; Teva Respiratory, LLC; May 2016.
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014 Feb;43(2):343-73.

4. Institute for Clinical and Economic Review (ICER). Mepolizumab (Nucala[®], GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks. March 14, 2016. Available at <http://icer-review.org/material/asthma-final-report/>. Accessed April 25, 2016.
5. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2017. Available at <http://www.ginasthma.org>. Accessed June 19, 2017.
6. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *New Eng J Med*. 2014 Sept;371(13):1189-97.
7. Parameswaran KN, Dasgupta A, et al. Mepolizumab in COPD with Eosinophilic Bronchitis: A Randomized Clinical Trial. Poster session presented at the Annual Meeting of the American Academy of Allergy, Asthma and Immunology, Los Angeles, CA. March 6, 2016.
8. Centers for Disease Control and Prevention. Asthma. Available at <http://www.cdc.gov>. Accessed May 16, 2016.
9. National Heart, Lung and Blood Institute. Explore Asthma. Available at <http://www.nhlbi.nih.gov>. Accessed May 16, 2016.
10. Fasenra[®] [prescribing information]. Wilmington, DE; AstraZeneca Pharmaceuticals LP; November 2017
11. FitzGerald JM, Bleeker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med*. 2017 Sep 8.
12. Goldman M, Hirsch I, Zangrilli JG, et al. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. *Curr Med Res Opin*. 2017 Sep;33(9):1605-1613.
13. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 2017; 376: 1921-32.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
03/01/2019	Reorganized policy template; simplified and relocated <i>Instructions for Use</i> and <i>Benefit Considerations</i> section. Archived previous policy version 2019D0055F.
01/01/2019	Off cycle review. Revised criteria regarding combination therapy. Added J0517. Approved by the National Pharmacy & Therapeutics Committee on 12/19/2018. Policy 2018D0055E archived.
09/01/2018	Annual review. No changes to coverage rationale. Updated clinical evidence and CMS statement. Approved by the National Pharmacy & Therapeutics Committee on 08/17/2018. Policy 2018D0055D archived.
03/01/2018	Off cycle review. Added coverage rationale for EGPA for Nucala. Updated clinical evidence, background, US FDA, and references. Approved by the National Pharmacy & Therapeutics Committee on 02/16/2018. Policy 2018D0055C archived.
01/01/2018	Off cycle review. Added coverage rationale for Fasenra (benralizumab). Updated clinical evidence, background, US FDA, and references. Approved by the National Pharmacy & Therapeutics Committee on 12/20/2017. Policy 2017D0055B archived.
12/01/2017	Annual review. Revised coverage rationale to include demonstration of clinical response to therapy. Updated Clinical Evidence, CMS statement and references. Approved by the National Pharmacy & Therapeutics Committee on 08/18/2017. Policy 2017D0055A archived.
01/01/2017	New policy 2016D0055A. Approved by the National Pharmacy & Therapeutics Committee on 07/27/2016.

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.