Respiratory Interleukins (Cinqair®, Fasenra®, & Nucala®)

Policy Number: CS2021D0055L
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Instructions for Use

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Commercial Policy
• Respiratory Interleukins (Cinqair®, Fasenra®, & Nucala®)

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Florida	Refer to the state's Medicaid clinical policy
Indiana	Respiratory-Interleukins (Cinqair®, Fasenra®, & Nucala®) (for Indiana Only)
Kansas	Refer to the state's Medicaid clinical policy
Kentucky	Respiratory Interleukins (Cinqair®, Fasenra®, & Nucala®) (for Kentucky Only)
Louisiana	Refer to the state's Medicaid clinical policy
North Carolina	None
Pennsylvania	Refer to the state's Medicaid clinical policy
Washington	Refer to the state's Medicaid clinical policy

Coverage Rationale

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

*Fasenra and Nucala for self-administration are obtained under the pharmacy benefit.

This policy refers to the following drug products:

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

Proven

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Initial Therapy

Nucala for provider administration is proven and 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]
  - Diagnosis with EPGA; and
  - Past medical history or presence of asthma; and
  - One of the following values at diagnosis:
    - Blood eosinophil level of at least 10% of leucocytes
    - Absolute eosinophil count > 1,000 cells/µL

    and
  - Presence of at least two of the following characteristics typical of EGPA:
    - Histopathological evidence of:
      - Eosinophilic vasculitis
      - Perivascular eosinophilic infiltration
      - Eosinophil-rich granulomatous inflammation
    - Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)
    - Pulmonary infiltrates, non-fixed
    - Sino-nasal abnormality
    - Cardiomyopathy (established by echocardiography or MRI)
    - Glomerulonephritis (hematuria, red cell casts, proteinuria)
    - Alveolar hemorrhage (by bronchoalveolar lavage)
    - Palpable purpura
    - Anti-neutrophil cytoplasmic antibody (ANCA) positive

    and
  - History of relapsing or refractory disease defined as one of the following:
    - 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)
    - Refractory disease as defined as failure to attain remission within the prior 6 months following induction treatment with standard therapy regimens

  and
- Patient is currently taking standard therapy (corticosteroids with or without immunosuppressive therapy); and
- Documentation required to support one of the following:
  - Physician attestation that the patient or caregiver is not competent or is physically unable to administer the Nucala product FDA labeled for self-administration *
  - Patient has experienced severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, or hypotension) to Nucala within the past 6 months and requires administration and direct monitoring by a healthcare professional
  - Patient is new to therapy with Nucala and requires initial dose to be directly monitored by a healthcare professional before continued self-administration * (Note: Authorization will be for 1 dose)

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

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

Reauthorization/Continuation of Care Criteria

Authorization for continued use of Nucala for provider administration for the treatment of EGPA will be approved based on all of the following criteria:

- Documentation of positive clinical response as demonstrated by at least one of the following:
  - Reduction in the frequency and/or severity of relapses
  - Reduction or discontinuation of doses of corticosteroids and/or immunosuppressant
  - Disease remission
  - Reduction in severity or frequency of EGPA-related symptoms

  and
- Documentation required to support one of the following:
  - Physician attestation that the patient or caregiver is not competent or is physically unable to administer the Nucala product FDA labeled for self-administration*
  - Patient has experienced severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, or hypotension) to Nucala within the past 6 months and requires administration and direct monitoring by a healthcare professional

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

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

Severe Asthma

Cinqair®

Cinqair for intravenous use is proven and medically necessary when all of the following criteria are met:[2-6]

- Diagnosis of severe asthma; and
- Classification of asthma as uncontrolled or inadequately controlled as defined by at least one of the following:
  - Poor symptom control (e.g., ACQ score consistently greater than 1.5 or ACT score consistently less than 20); or
  - Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; or
  - Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); or
  - 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]); or
  - Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

  and
- Asthma is an eosinophilic phenotype as defined by a baseline (pre-reslizumab) peripheral blood eosinophil level of ≥ 400 cells/µL within the past 4 weeks; and
- Used in combination with one of the following:
  - One maximally-dosed (appropriately adjusted for age) combination ICS/LABA product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]; or
  - Combination therapy including both of the following:
    - One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]; and
    - One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®), leukotriene receptor antagonist – montelukast (Singulair®), theophylline]

  and
- One of the following:
  - History of failure to a 4 month trial of Fasenra or Nucala
  - Contraindication or intolerance to Fasenra or Nucala

  and

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

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

Fasenra®

Fasenra for provider administration is proven and medically necessary when all of the following criteria are met:[3,5,6,10-12]

- Diagnosis of severe asthma; and
- Classification of asthma as uncontrolled or inadequately controlled as defined by at least one of the following:
  - 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
  - Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; or
  - Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); or
  - 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]); or
  - Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

  and
- Asthma is an eosinophilic phenotype as defined by a baseline (pre-benralizumab treatment) peripheral blood eosinophil level ≥ 150 cells/µL within the past 6 weeks;[12] and
- Used in combination with one of the following:
  - One maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta$_2$-agonist (LABA) product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]; or
  - Combination therapy including both of the following:
    - One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]; and
    - One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®); leukotriene receptor antagonist – montelukast (Singulair®); theophylline]

  and
- Documentation required to support one of the following:
  - Physician attestation that the patient or caregiver is not competent or is physically unable to administer the Fasenra product FDA labeled for self-administration *
  - Patient has experienced severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, or hypotension) to Fasenra within the past 6 months and requires administration and direct monitoring by a healthcare professional
  - Patient is new to therapy with Fasenra and requires initial dose to be directly monitored by a healthcare professional before continued self-administration * (Note: Authorization will be for 1 dose)

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

  and
- Fasenra dosing for severe eosinophilic asthma is in accordance with the U.S. FDA approved labeling: 30mg subcutaneously once every 4 weeks for 3 doses, then once every 8 weeks thereafter; and
- Prescribed by or in consultation with a pulmonologist or allergist/immunologist; and
- Initial authorization will be for no more than 6 months

Nucala®

Nucala for provider administration is proven and medically necessary when all of the following criteria are met:[1,3-6]

- Diagnosis of severe asthma; and
- Classification of asthma as uncontrolled or inadequately controlled as defined by at least one of the following:
  - 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
  - Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; or
  - Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); or
  - 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]); or
  - Patient is currently dependent on maintenance therapy with oral corticosteroids for the treatment of asthma

  and
- Asthma is an eosinophilic phenotype as defined by a baseline (pre-mepolizumab treatment) peripheral blood eosinophil level ≥ 150 cells/µL within the past 6 weeks; and
- Used in combination with one of the following:
  - One maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta$_2$-agonist (LABA) product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]; or
  - Combination therapy including both of the following:
    - One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]; and
    - One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®); leukotriene receptor antagonist – montelukast (Singulair®); theophylline]

  and
- Documentation required to support one of the following:
  - Physician attestation that the patient or caregiver is not competent or is physically unable to administer the Nucala product FDA labeled for self-administration*; or
  - Patient has experienced severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, or hypotension) to Nucala within the past 6 months and requires administration and direct monitoring by a healthcare professional; or
  - Patient is new to therapy with Nucala and requires initial dose to be directly monitored by a healthcare professional before continued self-administration* (Note: Authorization will be for 1 dose); or
  - Patient is ≤ 11 years of age

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

  and
- Nucala dosing for severe eosinophilic asthma is in accordance with the U.S. FDA approved labeling: 100mg subcutaneously once every 4 weeks; and
- Prescribed by or in consultation with a pulmonologist or allergist/immunologist; and
- Initial authorization will be for no more than 6 months

Reauthorization/Continuation of Care Criteria

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

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

  and

- Used in combination with an ICS-containing controller medication; and
- Patient is not receiving the product in combination with any of the following:
  - Another anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab], respectively
  - Anti-IgE therapy [e.g., Xolair (omalizumab)]
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

  and
- One of the following:
  - 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
  - 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
  - Fasenra 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
- Prescribed by or in consultation with a pulmonologist or allergist/immunologist; and
- Reauthorization will be for no more than 12 months

  and
- For Fasenra and Nucala reauthorization/continuation only:
  - Documentation required to support one of the following:
    - Physician attestation that the patient or caregiver is not competent or is physically unable to administer the Fasenra or Nucala product FDA labeled for self-administration*
    - Patient has experienced severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, or hypotension) to Fasenra or Nucala within the past 6 months and requires administration and direct monitoring by a healthcare professional

  or
- For Cinqair reauthorization/continuation only:
  - One of the following:
    - History of failure to a 4 month trial of Fasenra or Nucala
    - Contraindication or intolerance to Fasenra or Nucala

Hypereosinophilic Syndrome (HES)

Nucala

Nucala for provider administration is proven and medically necessary when all of the following criteria are met:[1]

- Diagnosis of HES for ≥ 6 months; and
- Both of the following:
  - There is no identifiable non-hematologic secondary cause of the patient's HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy); and
  - HES is not FIP1L1-PDGRα kinase-positive

  and
- Documentation required to support one of the following:
  - Physician attestation that the patient or caregiver are not competent or are physically unable to administer the Nucala product FDA labeled for self-administration; or
  - Patient has experienced severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, or hypotension) to Nucala within the past 6 months and requires administration and direct monitoring by a healthcare professional; or
  - Patient is new to therapy with Nucala and requires initial dose to be directly monitored by a healthcare professional before continued self-administration (Note: authorization will be for 1 dose)

  and
- Submission of medical records (e.g., chart notes, laboratory values, etc.) documenting both of the following:
  - Baseline (pre-mepolizumab treatment) blood eosinophil level ≥ 1000 cells/µL within the past 4 weeks; and
  - Patient is currently receiving a stable dose of background HES therapy (e.g., oral corticosteroid, immunosuppressor, or cytotoxic therapy)

  and

- Patient is not receiving Nucala in combination with any of the following:
  - Anti-interleukin 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab)]
  - Anti-IgE therapy [e.g., Xolair (omalizumab)]
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
- Prescribed by an allergist, immunologist, hematologist, cardiologist, or pulmonologist; and
- Initial authorization will be for no more than 6 months

Reauthorization/Continuation of Care Criteria

Nucala for provider administration for the treatment of HES authorization for continued use will be approved based on all of the following criteria:

- Documentation of positive clinical response as demonstrated by at least one of the following:
  - Reduction in frequency of HES flares
  - Maintenance or reduction in background HES therapy requirements

  and
- Documentation required to support one of the following:
  - Physician attestation that the patient or caregiver are not competent or are physically unable to administer the Nucala product FDA labeled for self-administration; or
  - Patient has experienced severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, or hypotension) to Nucala within the past 6 months and requires administration and direct monitoring by a healthcare professional

  and
- Patient is not receiving Nucala in combination with any of the following:
  - Anti-interleukin 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab)]
  - Anti-IgE therapy [e.g., Xolair (omalizumab)]
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]

  and
- Prescribed by an allergist, immunologist, hematologist, cardiologist, or pulmonologist; and
- Initial authorization will be for no more than 12 months

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

*Fasenra and Nucala for self-administration are obtained under the pharmacy benefit.

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 federal, state, or contractual requirements 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 Guidelines may apply.

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

Diagnosis Code	Description
D72.11	Hypereosinophilic Syndrome
J45.50	Severe persistent asthma, uncomplicated
J45.51	Severe persistent asthma with (acute) exacerbation
J45.52	Severe persistent asthma with status asthmaticus
J82.81	Chronic eosinophilic pneumonia
J82.82	Acute eosinophilic pneumonia
J82.83	Eosinophilic asthma
J82.89	Other pulmonary eosinophilia, not elsewhere classified
M30.1	Polyarteritis with lung involvement [Churg-Strauss]

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 to 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]

Hypereosinophilic Syndrome (HES) is a disorder marked by the sustianed overproduction of eosinophils associated with damage to one or more organs due to eosinophilic infiltration and mediator release. HES is rare and the true prevalence is unknown. One study that used clinician coding of eosinophilia to identify patients with HES in the Surveillance, Epidemiology, and End Results (SEER) database, concluded the estimated prevalence was between 0.36 to 6.3 per 100,000. Most patients are between 20 and 50 years of age at the time of diagnosis, although HES can develop in children. One study suggested that the frequencies of clinical HES variants (including myeloproliferative variants) were similar in children and adults. Certain variants of HES (i.e., those associated with aberrations in the gene for tyrosine kinase receptor platelet-derived growth factor receptor alpha [PDGFRA] and platelet-derived growth factor beta [PDGFRB]) occur almost exclusively in males, whereas others (lympcytic variant HES [L-HES] and HES of unknown etiology) appear to be equally distributed between the sexes. Patients with HES usually have more than 1500 eosinophils/µL in their blood for 6 months or more, and the cause cannot be identified. The eosinophils disperse to various tissues, causing inflammation and eventually organ dysfunction. Mepolizumab binds to IL-5 inhibiting the production of eosinophils, thereby reducing inflammation.[16, 17, 18]

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]

Hypereosinophilic Syndrome

Mepolizumab is indicated for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥ 6 months without an identifiable non-hematologic secondary cause.

In a multicenter, randomized, placebo-controlled, 32-week treatment trial. Patients with non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy) or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of Nucala (n=54) or placebo (n=54) subcutaneously once every 4 weeks. Patients were required to have been on a stable dose of background HES therapy (oral corticosteroids, immunosuppressive, or cytotoxic therapy) for 4 weeks prior to randomization and continue their therapy throughout the trial. Patients entering the trial had experienced at least 2 HES flares within the past 12 months and blood eosinophil count of 1,000 cells/mcL or higher during screening. The primary endpoint was percentage of patients who experienced ≥1 HES flare during the 32-week treatment period or who withdrew from the study. A HES flare was defined as a HES related clinical manifestation based on a physician-documented change in clinical signs or symptoms which resulted in need for an increase in the maintenance oral corticosteroid dose by at least 10 mg per day for 5 days or an increase in or addition of any cytotoxic or immunosuppressive HES therapy. HES flare was also defined as receipt of two or more courses of blinded active oral corticosteroid during the treatment period. The secondary endpoints included time to first flare, proportion of patients who experienced flares during Week 20 to Week 32, and number of HES flares per participant per year. Over the 32-week treatment period, the incidence of HES flare was 56% for the placebo group and 28% for the Nucala group (odds ratio, 0.28; 95% CI 0.12 to 0.64; P=0.002). The risk of first HES flare over the treatment period was 66% lower for patients treated with Nucala compared to placebo (hazard ratio: 0.34; 95% CI 0.18 to 0.72; P=0.002). From Week 20 through Week 32, significantly fewer patients experienced a HES flare or withdrew from the trial when treated with Nucala compared with placebo (17% versus 35%, respectively; P=0.02; odds ratio, 0.33; 95% CI: 0.13 to 0.85). Patients who received Nucala experienced significantly fewer HES flares during a 32-week treatment period compared with the placebo group (rate ratio, 0.35; 95% CI 0.19 to 0.63; Wilcoxon P value (unadjusted/adjusted) 0.002/0.02).[1]

Professional Societies

Severe Eosinophilic Asthma

Global Initiative for Asthma

The Global Initiative for Asthma (GINA, 2020) recommends that for Step 5 treatment, adults and adolescents, may be treated with benralizumab, mepolizumab or reslizumab as follows:[6]

- Consider add-on anti-interleukin-5/5R treatment or anti-interleukin 5 receptor treatment for those with severe eosinophilic asthma that is uncontrolled on Step 4-5 treatment.
- Step 5: Refer for phenotypic investigation and/or add-on treatment. Patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be referred to a specialist with expertise in investigation and management of severe asthma.
- Add-on treatments for severe eosinophilic asthma include: anti-interleukin 5 treatment (subcutaneous mepolizumab for patients aged ≥ 12 years; intravenous reslizumab for ages ≥ 18 years), anti-interleukin 5 receptor treatment (subcutaneous benralizumab for ages ≥ 12 years) with severe asthma that is uncontrolled on Step 4-5 treatment, or anti-interleukin-4R α treatment (subcutaneous dupilumab for ages ≥ 12 years) with severe Type 2 asthma, or requiring treatment with maintenance OCS.

Institute for Clinical and Economic Review (ICER)

On March 14, 2016, the 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 (opportunist infection, anaphylaxis).

On November 13, 2018, ICER released a clinical report entitled, "Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks." ICER recommendations are as follows:[5]

- ICER judges the current body of evidence on omalizumab and mepolizumab to be "incremental" compared to standard of care.
- ICER judges the current body of evidence on reslizumab, benralizumab, and dupilumab to be "comparable or better" compared with standard of care.
- Comparisons between biologic therapies for asthma resulted in low certainty in the comparative clinical effectiveness of agents, and was given an I rating, or insufficient.

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 Nucala and Cinqair to treat these conditions.[1-2,8]

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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 6 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) and the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause.[1]

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Policy History/Revision Information

Date	Summary of Changes
08/01/2021	**Application** • Added language to indicate this policy does not apply to the state of North Carolina
05/01/2021	**Template Update** • Removed *CMS* section • Replaced reference to "MCG™ Care Guidelines" with "InterQual® criteria" in *Instructions for Use* **Application** • Added language to indicate this policy does not apply to the state of Indiana; refer to the state-specific policy version **Coverage Rationale** • Added coverage criteria for treatment of Hypereosinophilic Syndrome (HES) using Nucala to indicate: ○ Nucala for provider administration is proven and medically necessary when all of the following criteria are met: ▪ Diagnosis of HES for ≥ 6 months; and ▪ Both of the following: – There is no identifiable non-hematologic secondary cause of the patient's HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy); and – HES is not FIP1L1-PDGRα kinase-positive and ▪ Documentation required to support one of the following: – Physician attestation that the patient or caregiver are not competent or are physically unable to administer the Nucala product FDA labeled for self-administration; or – Patient has experienced severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, or hypotension) to Nucala within the past 6 months and requires administration and direct monitoring by a healthcare professional; or

Date	Summary of Changes
	– Patient is new to therapy with Nucala and requires initial dose to be directly monitored by a healthcare professional before continued self-administration (Note: authorization will be for 1 dose) and ▪ Submission of medical records (e.g., chart notes, laboratory values, etc.) documenting both of the following: – Baseline (pre-mepolizumab treatment) blood eosinophil level ≥ 1000 cells/µL within the past 4 weeks; and – Patient is currently receiving a stable dose of background HES therapy (e.g., oral corticosteroid, immunosuppressor, or cytotoxic therapy) and ▪ Patient is not receiving Nucala in combination with any of the following: – Anti-interleukin 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab)] – Anti-IgE therapy [e.g., Xolair (omalizumab)] – Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)] ▪ Prescribed by an allergist, immunologist, hematologist, cardiologist, or pulmonologist; and ▪ Initial authorization will be for no more than 6 months ○ Nucala for provider administration for the treatment of HES authorization for continued use will be approved based on all of the following criteria: ▪ Documentation of positive clinical response as demonstrated by at least one of the following: – Reduction in frequency of HES flares – Maintenance or reduction in background HES therapy requirements and ▪ Documentation required to support one of the following: – Physician attestation that the patient or caregiver are not competent or are physically unable to administer the Nucala product FDA labeled for self-administration; or – Patient has experienced severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, or hypotension) to Nucala within the past 6 months and requires administration and direct monitoring by a healthcare professional and ▪ Patient is not receiving Nucala in combination with any of the following: – Anti-interleukin 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab)] – Anti-IgE therapy [e.g., Xolair (omalizumab)] – Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)] and ▪ Prescribed by an allergist, immunologist, hematologist, cardiologist, or pulmonologist; and ▪ Authorization will be for no more than 12 months **Applicable Codes** • Added ICD-10 diagnosis code D72.11 **Supporting Information** • Updated *Background*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version CS2020D0055K

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. 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.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit 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.