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

**Policy Number**: CS2025D0055V
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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 |
|---|---|
| Arizona | Refer to the drug-specific criteria found within the state's Medicaid clinical policy, if available for the specific product, otherwise this Medical Benefit Drug Policy applies |
| Florida | Refer to the state's Medicaid clinical policy |
| Indiana | Refer to the state's Medicaid clinical policy |
| Kansas | Refer to the state's Medicaid clinical policy |
| Louisiana | Refer to the state's Medicaid clinical policy |
| North Carolina | None |
| Ohio | Respiratory Interleukins (Cinqair®, Fasenra®, & Nucala®) (for Ohio Only) |
| Pennsylvania | Refer to the state's Medicaid clinical policy |
| Texas | Refer to the drug-specific criteria found within the *Texas Medicaid Provider Procedures Manual* |
| Washington | Refer to the state's Medicaid clinical policy |

## Coverage Rationale

This policy refers to the following drug products for administration by a healthcare professional:

- Cinqair® (reslizumab) for intravenous (IV) route
- Fasenra® (benralizumab) for subcutaneous (SC) route
- Nucala® (mepolizumab) for subcutaneous (SC) route

*Fasenra® (benralizumab) and Nucala® (mepolizumab) for self-administered subcutaneous injection are obtained under the pharmacy benefit.

## Eosinophilic Granulomatosis With Polyangiitis (EGPA)

### *Initial Therapy*

### Fasenra

**Fasenra, for provider administration, is proven and medically necessary for the treatment of EGPA when all of the following criteria are met:**

- Diagnosis of relapsing or refractory EGPA as defined by **all** of the following:[25]
  - Diagnosis of EGPA; **and**
  - Past medical history or presence of asthma; **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
    - 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); **or**
    - 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 [i.e., systemic glucocorticoids (e.g., prednisone, methylprednisolone) with or without immunosuppressive therapy (e.g., cyclophosphamide, rituximab)]; **and**
- **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*; **or**
  - Patient has documented history of 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; **or**
  - 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 5 therapy [e.g., Nucala (mepolizumab), Cinqair (reslizumab)]
  - Anti-IgE therapy [e.g., Xolair (omalizumab)]
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the United States Food and Drug Administration-approved labeling; **and**
- Prescribed by a pulmonologist, rheumatologist, or allergist/immunologist; **and**
- Initial authorization will be for no more than 12 months

### Nucala

**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 of EPGA; **and**
  - Past medical history or presence of asthma; **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
      - 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); **or**
    - 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 [i.e., systemic glucocorticoids (e.g., prednisone, methylprednisolone) with or without immunosuppressive therapy (e.g., cyclophosphamide, rituximab)]; **and**
- **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 documented history of 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**
- 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)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the U. S. Food and Drug Administration-approved labeling; **and**
- Prescribed by 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 Fasenra or 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; **or**
  - Reduction or discontinuation of doses of corticosteroids and/or immunosuppressant; **or**
  - Disease remission; **or**
  - Reduction in severity or frequency of EGPA-related symptoms

  **and**
- **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*; **or**
  - Patient has documented history of 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

  **and**
- Patient is not receiving the product in combination with **any** of the following:
  - **One** of the following:
    - For **Fasenra** reauthorization/continuation, another anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Nucala (mepolizumab)]

        - For **Nucala** reauthorization/continuation, another anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab)]
    - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
    - Anti-IgE therapy [e.g., Xolair (omalizumab)]
    - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the U. S. Food and Drug Administration-approved labeling; **and**
- Reauthorization will be for no more than 12 months

## Severe Asthma

### *Initial Therapy*

### 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 ≥ 150 cells/µL; **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®), or budesonide/formoterol (Symbicort®)]; **or**
    - Combination therapy including **both** of the following:
        - One maximally-dosed (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; **or**
    - 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)]
    - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the United States Food and Drug Administration (FDA)-approved labeling; **and**
- Prescribed by 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-treatment) peripheral blood eosinophil level ≥ 150 cells/µL; **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 maximally-dosed (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:
  - Physician attestation that the patient or caregiver is not competent or is physically unable to administer the Fasenra product FDA labeled for self-administration*; **or**
  - Patient has documented history of 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; **or**
  - 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)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

**and**

- Dosing for is in accordance with the U.S. FDA-approved labeling; **and**
- Prescribed by 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-treatment) peripheral blood eosinophil level ≥ 150 cells/µL; **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 maximally-dosed (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:
  - 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 documented history of 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)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the U.S. FDA-approved labeling; **and**
- Prescribed by 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; **or**
  - Decreased utilization of rescue medications; **or**
  - Increase in percent predicted FEV1 from pretreatment baseline; **or**
  - 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 maintenance medication [e.g., Advair/AirDuo (fluticasone/salmeterol), Breo Ellipta (fluticasone furoate/vilanterol), Symbicort (budesonide/ formoterol), Trelegy Ellipta (fluticasone)]; **and**
- Patient is not receiving the product in combination with **any** of the following:
  - **One** of the following:
    - For **Cinqair** reauthorization/continuation, another anti-interleukin 5 therapy [e.g., Fasenra (benralizumab), Nucala (mepolizumab)]
    - For **Fasenra** reauthorization/continuation, another anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Nucala (mepolizumab)]
    - For **Nucala** reauthorization/continuation, another anti-interleukin 5 therapy [e.g., Cinqair (reslizumab), Fasenra (benralizumab)]
  - Anti-IgE therapy [e.g., Xolair (omalizumab)]
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the United States Food and Drug Administration-approved labeling; **and**
- For **Fasenra** and **Nucala** reauthorization/continuation only:
  - **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*; **or**
    - Patient has documented history of 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 Nucala requests only: Patient is ≤ 11 years of age
- For **Cinqair** reauthorization/continuation only:
  - **One** of the following:
    - History of failure to a 4-month trial of Fasenra or Nucala; **or**
    - Contraindication or intolerance to Fasenra or Nucala

  **and**

- Reauthorization will be for no more than 12 months

## Hypereosinophilic Syndrome (HES)

### *Initial Therapy*

**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-PDGFRα kinase-positive

  **and**
- **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 documented history of 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 ≥ 1,000 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)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the United States Food and Drug Administration-approved labeling; **and**
- 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; **or**
  - Maintenance or reduction in background HES therapy requirements

  **and**
- **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 documented history of 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)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the United States Food and Drug Administration-approved labeling; **and**
- Reauthorization will be for no more than 12 months

## Chronic Rhinosinusitis With Nasal Polyps (CRSwNP)

### *Initial Therapy*

**Nucala for provider administration is proven and medically necessary for patients who meet the following criteria:**

- Diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) defined by **all** of the following:
  - **Two** or more of the following symptoms for longer than 12 weeks duration:
    - Nasal mucopurulent discharge
    - Nasal obstruction, blockage, or congestion
    - Facial pain, pressure, and/or fullness
    - Reduction or loss of sense of smell

    **and**
  - **One** of the following findings using nasal endoscopy and/or sinus computed tomography (CT):
    - Purulent mucus or edema in the middle meatus or ethmoid regions; **or**
    - Polyps in the nasal cavity or the middle meatus; **or**
    - Radiographic imaging demonstrating mucosal thickening or partial or complete opacification of paranasal sinuses

    **and**
  - **One** of the following:
    - Presence of bilateral nasal polyposis; **or**
    - Patient has previously required surgical removal of bilateral nasal polyps

    **and**
  - **One** of the following:
    - Patient has required prior sinus surgery; **or**
    - Patient has required systemic corticosteroids (e.g., prednisone, methylprednisolone) for CRSwNP in the previous 2 years; **or**
    - Patient has been unable to obtain symptom relief after trial of **two** of the following classes of agents:
      - Nasal saline irrigations
      - Intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone)
      - Antileukotriene agents (e.g., montelukast, zafirlukast, zileuton)

  **and**
- Patient will receive Nucala as add-on maintenance therapy in combination with intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone); **and**
- **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 documented history of 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 5 therapy [e.g., Cinqair (resilizumab), Fasenra (benralizumab)]
  - Anti-IgE therapy [e.g., Xolair (omalizumab)]
  - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Prescribed by an allergist/immunologist/otolaryngologist/pulmonologist; **and**
- Initial authorization will be for no more than 6 months

### *Reauthorization/Continuation of Care Criteria*

**Nucala for the treatment of CRSwNP for continued use will be approved based on all of the following criteria:**

- Documentation of positive clinical response to Nucala therapy; **and**
- Patient will continue to receive Nucala as add-on maintenance therapy in combination with intranasal corticosteroids (e.g., fluticasone, mometasone, triamcinolone); **and**

- **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 documented history of 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 ≤ 11 years of age

  **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)]
  - Thymic stromal lymphopoietin (TSLP) inhibitor [e.g., Tezspire (tezepelumab)]

  **and**
- Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization will be for no more than 12 months

### Unproven and Not Medically Necessary

**Cinqair, Fasenra, and Nucala are unproven and not medically necessary for 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

## Applicable Codes

The following list(s) of procedure 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 |
| J31.0 | Chronic rhinitis |
| J32.0 | Chronic maxillary sinusitis |
| J32.1 | Chronic frontal sinusitis |
| J32.2 | Chronic ethmoidal sinusitis |
| J32.3 | Chronic sphenoidal sinusitis |
| J32.4 | Chronic pansinusitis |
| J32.8 | Other chronic sinusitis |
| J32.9 | Chronic sinusitis, unspecified |
| J33.0 | Polyp of nasal cavity |
| J33.1 | Polypoid sinus degeneration |
| J33.8 | Other polyp of sinus |
| J33.9 | Nasal polyp, unspecified |

| 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 |
| J82.81 | 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 sustained 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 [lymphocytic variant HES (L-HES) and HES of unknown etiology] appear to be equally distributed between the sexes. Patients with HES usually have more than 1,500 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.[16-18]

Chronic rhinosinusitis with nasal polyps is an inflammatory condition involving the paranasal sinuses and linings of the nasal passages, which persists for 12 weeks or longer, and affects approximately 2-4% of the population. Symptoms include mucopurulent drainage, nasal obstruction, facial pain/pressure/fullness and decreased sense of smell. CRSwNP cannot be cured in most patients and therapy is intended to reduce symptoms and improve quality of life. Standard treatment includes therapies to minimize inflammation such as intranasal corticosteroids and antileukotriene agents. If intranasal and oral corticosteroids fail to reduce polyp tissue sufficiently and the patient has persistent blockage, sinus surgery or therapy with a biologic recommended. Mepolizumab binds to IL-5, inhibiting the production of eosinophils, thereby reducing inflammation.[1,21,22]

# Clinical Evidence

## Proven

### *Eosinophilic Granulomatosis With Polyangiitis (EGPA)*

Benrazlizumab is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).[11]

In a multicenter, double-blind, phase 3, randomized, active-controlled noninferiority trial, Wechsler et al, evaluated the efficacy and safety of benrazlizumab as compared with mepolizumab for eosinophilic granulomatosis with polyangiitis (EGPA). Patients were required to have asthma, eosinophilia (1,000 cells/uL or > 10% of leukocytes) and a history of relapsing or refractory disease. Additionally, patients were being treated with background prednisolone/prednisone with or without immunosuppressive therapy. Patients with relapsing or refractory EGPA who were receiving standard care were randomly assigned in a 1:1 ratio to receive benralizumab (30 mg) or mepolizumab (300 mg) subcutaneously every 4 weeks for 52 weeks. The primary end point was remission at weeks 36 and 48 with a prespecified non-inferiority margin of -25 percentage points. The secondary end points were accrued duration of remission, time to first relapse, oral glucocorticoid use, eosinophil count, and safety. 140 patients were randomized with 70 assigned to each group. The adjusted percentage of patients with remission at weeks 36 and 48 for the benralizumab and mepolizumab group was 59% and 56%, respectively [difference, 3 percentage points; 95% confidence interval (CI), -13 to 18; p = 0.73 for superiority], demonstrating noninferiority of benralizumab to mepolizumab. Accrued duration of remission and time to first relapse were similar in both groups. Complete withdrawal of oral glucocorticoids during weeks 48 through 52 was not statistically significant for those who received benralizumab or mepolizumab. Adverse events occurred in 90% of the patients in the benralizumab group and 96% in the mepolizumab group, while serious adverse events were reported in 6% and 13%, respectively. The authors concluded that benrazlizumab was noninferior to mepolizumab for the induction or remission in patients with relapsing or refractory EGPA.

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

In a post hoc analysis of the phase III clinical trial, Steinfeld et al. investigated the clinical benefit of mepolizumab in patients with EGPA that factors in remission, oral glucocorticoid (OGC) dose reduction, and EGPA relapses.[14] The post hoc clinical benefit was defined as: remission at any time (2 definitions used), 50% or greater OGC dose reduction during weeks 48 to 52, or no EGPA relapses. The 2 remission definitions were Birmingham Vasculitis Activity Score of 0 plus OGC dose of 4 mg/d or less (remission 1/clinical benefit 1) or 7.5 mg/d or less (remission 2/clinical benefit 2). Clinical benefit was assessed in all patients and among subgroups with a baseline blood eosinophil count of less than 150 cells/μL, baseline OGC dosage of greater than 20 mg/d, or weight of greater than 85 kg. With mepolizumab versus placebo, 78% versus 32% of patients experienced clinical benefit 1, and 87% versus 53% of patients experienced clinical benefit 2 (both p < .001). Significantly more patients experienced clinical benefit 1 with mepolizumab versus placebo in the blood eosinophil count less than 150 cells/μL subgroup (72% vs. 43%, p = .033) and weight greater than 85 kg subgroup (68% vs. 23%, p = .005); in the OGC greater than 20 mg/d subgroup, results were not significant but favored mepolizumab (60% vs. 36%, p = .395). The authors concluded that the majority of patients with EGPA experienced benefit with mepolizumab.

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 6 years and older, and with an eosinophilic phenotype.[11]

The efficacy of benralizumab was established for the add-on maintenance treatment of severe asthma, and with an eosinophilic phenotype, in two randomized, double-blind, parallel-group, placebo-controlled, exacerbation trials, SIROCCO (NCT01928771) and CALIMA (NCT01914757), for 48 and 56 weeks in duration, respectively. The primary endpoint for the SIROCCO and CALIMA trials was the rate of asthma exacerbations in patients with baseline blood eosinophil counts greater than or equal to 300 cells/μL who were taking high-dose ICS and LABA. SIROCCO and CALIMA included 2,510 patients, 12 years of age and older, for 48 and 56 weeks in duration, respectively. All patients had a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months, ACQ-6 score of 1.5 or more at screening, and reduced lung function at baseline despite regular treatment with either high dose ICS in the SIROCCO trial, or with medium or high dose ICS in the CALIMA trial, plus a long-acting beta agonist (LABA) with or without oral corticosteroids (OCS) and additional asthma controller medications. Patients were stratified by geography, age, and blood eosinophils count (300 cells/μL or < 300 cells/μL). Benralizumab, administered once every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter as add-on to background treatment, was evaluated compared to placebo. In SIROCCO, 35% of patients receiving benralizumab experienced an asthma exacerbation compared to 51% on placebo, while in the CALIMA trial 40% of patients receiving benralizumab experienced an asthma exacerbation compared to 51% on placebo. Additionally, the ZONDA (NCT02075255) trial and another 12-week lung function trial (NCT02322775) demonstrated the efficacy of benralizumab for the reduction of oral corticosteroid use and effect on lung function. The ZONDA trial was a randomized, double-blind, parallel-group, OCS reduction trial in 220 adult patients with asthma. All patients in the trial required treatment with daily OCS (7.5 to 40 mg per day) in addition to regular use of high-dose ICS and LABA with or without additional controller(s). Baseline median OCS dose was similar across all treatment groups. Patients were required to have blood eosinophil counts greater than or equal to 150 cells/μL and a history of at least one exacerbation in the past 12 months. The baseline median OCS dose was 10 mg (range: 8 to 40 mg) for all 3 treatment groups (placebo, benralizumab every 4 weeks, and benralizumab every 4 weeks for the first 3 doses, and then once every 8 weeks). The primary endpoint in the ZONDA trial the was percent reduction from baseline of the final OCS dose during Weeks 24 to 28, while maintaining asthma control (see definition of asthma control in trial description). Compared to placebo, patients receiving benralizumab achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. The median percent reduction in daily OCS dose from baseline was 75% in patients receiving benralizumab (95% CI: 60, 88) compared to 25% in patients receiving placebo (95% CI: 0, 33).

Mepolizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype.[1]

Mepolizumab was studied under the asthma development program in patients aged 12 years and older in 3 different double-blind, randomized, placebo-controlled trials: 1 dose-ranging and exacerbation trial, along with 2 different confirmatory trials. In all trials, mepolizumab was administered every 4 weeks as adjunct to existing background therapy which was continued throughout the trials. The dose-ranging and exacerbation trial was 52-weeks in duration for patients with severe asthma and a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without oral corticosteroids (OCS). Enrolled patients were required to have at least 1 of the following 4 pre-specified criteria in the previous 12 months: blood eosinophil count ≥ 300 cells/μL, sputum eosinophil count ≥ 3%, exhaled nitric oxide concentration ≥ 50 ppb, or deterioration of asthma control after ≤ 25% reduction in regular maintenance ICS/OCS. Three different intravenous doses of mepolizumab (75, 250, and 750 mg) were administered once every 4 weeks and evaluated compared with placebo. Results from this trial and the pharmacodynamic study supported the evaluation of mepolizumab 75 mg IV and 100 mg subcutaneous in the subsequent trials. Two confirmatory trials studied 711 patients with severe asthma, requiring blood eosinophils of ≥ 150 cells/μL at screening or blood eosinophils of ≥ 300 cells/μL within 12 months of enrollment. Trial 2 was a 32-week placebo- and active-controlled trial in patients with severe asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS. Patients received mepolizumab 75 mg IV (n = 191), mepolizumab 100 mg (n = 194), or placebo (n = 191) once every 4 weeks for 32 weeks. Trial 3 was 24-weeks in duration to evaluate OCS reduction in patients with severe asthma who required daily OCS in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control. Patients received mepolizumab 100 mg (n = 69) or placebo (n = 66) once every 4 weeks for 24 weeks. Efficacy was evaluated for trials 1 and 2 using an endpoint of the frequency of exacerbations defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. Compared with placebo, patients receiving mepolizumab 100 mg or 75 mg experienced significantly fewer exacerbations. Additionally, there were fewer exacerbations requiring hospitalization and/or emergency department visits and exacerbations requiring only in-patient hospitalization with mepolizumab 100 mg when compared with placebo. Trial 3 evaluated the effect of mepolizumab 100 mg on maintenance OCS reduction. Endpoint measurement was the percent reduction of OCS dose during Weeks 20 to 24 compared with baseline dose, while maintaining asthma

control. Patients were stratified based on their change in OCS use during the trial with the following categories: 90% to 100% decrease, 75% to < 90% decrease, 50% to < 75% decrease, > 0% to < 50% decrease, and no improvement. Compared with placebo, patients receiving mepolizumab 100 mg achieved statistically significant reductions in daily maintenance OCS dose, while maintaining asthma control. Sixteen (23%) patients in the group receiving mepolizumab 100 mg versus 7 (11%) in the placebo group had a 90% to 100% reduction in their OCS dose. Twenty-five (36%) patients in the group receiving mepolizumab 100 mg versus 37 (56%) in the placebo group were classified as having no improvement for OCS dose. Additionally, 54% of patients receiving mepolizumab 100 mg achieved at least a 50% reduction in the daily prednisone dose compared with 33% of patients receiving placebo (95% CI for difference: 4%, 37%).

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]

The efficacy of resilizumab was demonstrated in 4 different randomized, double-blind, placebo-controlled studies (studies I-IV) 16 to 52 weeks in duration involving 981 patients 12 years of age and older. Background asthma therapy was continued in all subjects throughout the duration of the studies. Studies I and II were 52-week studies involving 953 patients with a diagnosis of asthma and a blood eosinophil count of at least 400/μL, and at least 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. The majority of patients (82%) were on medium-high dose inhaled corticosteroids plus an ICS/LABA at baseline. Maintenance OCS were allowed, of which 106 (11%) patients were on OCS at baseline. Reslizumab 3 mg/kg administered once every 4 weeks for a total of 13 doses was evaluated compared with placebo. Study III was a 16-week study in 315 patients with a blood eosinophil count of at least 400/μL at screening. Maintenance OCS were not allowed. Reslizumab 3 mg/kg or 0.3 mg/kg administered once every 4 weeks for a total of 4 doses was evaluated compared with placebo. Study IV was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count of less than 400/mcL). Maintenance OCS were not allowed. Reslizumab 3 mg/kg administered once every 4 weeks for a total of 4 doses was evaluated compared with placebo. The primary endpoint for Studies I and II was the frequency of asthma exacerbations for each patient during the 52-week treatment period, defined as 1) either the use of a systemic corticosteroid, or ≥ 2-fold an increase in the use of ICS for 3 or more days, and/or 2) asthma-related emergency treatment. Studies I and II demonstrated significant reductions in the rate of all asthma exacerbations in patients receiving reslizumab 3 mg/kg every 4 weeks compared to placebo. Exacerbations requiring the use of an OCS as well as exacerbations resulting in hospitalization or an emergency room visit were each reduced with reslizumab 3 mg/kg. The effect of reslizumab 3 mg/kg administered once every 4 weeks on FEV1 over time relative to placebo was assessed in all 4 studies, but was the primary endpoint in Study III and IV, the 16-week lung function studies. Study III also studied a lower resilizumab dose (0.3 mg/kg), which produced significant but numerically smaller changes in FEV1, and blood eosinophil reduction compared with the 3 mg/kg dose. Study IV was the only study to test reslizumab 3 mg/kg in asthma patients unselected for blood eosinophils (measured 3 to 4 weeks prior to dosing), which found no association of treatment effect (i.e., difference between reslizumab and placebo in the change in FEV1 at Week 16) and baseline blood eosinophils.

## *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]

## *Chronic Rhinosinusitis With Nasal Polyps*

Mepolizumab is indicated for add-on maintenance treatment of adult patients 18 years and older with chronic rhinosinusitis with nasal polyps (CRSwNP) and an inadequate response to nasal corticosteroids.

A total of 407 adult patients with CRSwNP were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 52-week trial (NCT03085797). Patients received Nucala 100 mg or placebo administered subcutaneously once every 4 weeks while continuing nasal corticosteroid therapy. Patients must have received background nasal corticosteroid for = 8 weeks pre-screening. Patients had recurrent and symptomatic CRSwNP and had at least 1 surgery for the removal of nasal polyps within the previous 10 years. Patients were required to have nasal obstruction symptoms with a visual analog scale (VAS) score of > 5 out of a maximum score of 10. Patients were also required to have an endoscopic bilateral nasal polyp score (NPS) of = 5 out of 8 with NPS = 2 in each nasal cavity. Patients reported nasal obstruction VAS scores daily by placing a single mark on a continuous line labeled from 0 (none) to 100 (as bad as you can imagine). The distance along the line was converted to a 0-to-10-point scale for scoring. For NPS, polyps on each side of the nose were graded on a categorical scale (0 = no polyps, 1 = small polyps in the middle meatus not reaching below the inferior border of the middle concha, 2 = polyps reaching below the lower border of the middle turbinate, 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha, 4 = large polyps causing almost complete congestion/obstruction of the inferior meatus) for a total score of 0 to 8. Sinus CT scans were not performed at baseline nor during treatment to evaluate for sinus opacification.

The co-primary endpoints were changed from baseline to Week 52 in total endoscopic NPS (0 to 8 scale) as graded by independent blinded assessors and change from baseline in nasal obstruction VAS score (0 to 10 scale) during Weeks 49 to 52. The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52 in this trial. Other secondary endpoints were changed from baseline in loss of smell VAS score during Weeks 49 to 52, and proportion of patients requiring systemic steroids for nasal polyps up to Week 52. All VAS scores were collected daily by the patients and reported on a 0 to 10 scale (0 = none, 10 = as bad as you can imagine).

Patients who received Nucala 100 mg had a statistically significant improvement (decrease) in bilateral NPS at Week 52 and nasal obstruction VAS score from Weeks 49 to 52 at the end of the 52-week treatment period. The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52. The proportion of patients who had surgery was significantly reduced by 57% (hazard ratio: 0.43, 95% CI: 0.25, 0.76) in the group treated with Nucala 100 mg compared with the placebo group (Figure 2). By Week 52, 18 (9%) patients who received Nucala 100 mg had surgery compared with 46 (23%) patients in the placebo group. For patients who received Nucala 100 mg, statistically significant improvement was observed in loss of smell compared to placebo and improvements were also observed in the individual VAS symptom scores compared with patients in the placebo group in the 4-weeks prior to the end of the 52-week treatment period. Treatment with Nucala 100 mg significantly reduced the need for systemic steroids for nasal polyps vs. placebo up to Week 52 (odds ratio: 0.58, 95% CI: 0.36, 0.92). In patients who received Nucala 100 mg, 52 (25%) required = 1 course of systemic steroids compared with 74 (37%) in the placebo group throughout the 52-week treatment period.[1]

## *Professional Societies*

### Global Initiative for Asthma

The Global Initiative for Asthma (GINA, 2023) defines uncontrolled, difficult-to-treat and severe asthma as follows:[6]

- Uncontrolled asthma is asthma with poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma) and/or frequent exacerbations (≥ 2/year) requiring OCS, or serious exacerbations (≥ 1/year) requiring hospitalization.
- Difficult-to-treat asthma is asthma that is uncontrolled despite prescribing of medium- or high-dose ICS with a second controller (usually a LABA) or maintenance OCS, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.
- Severe asthma is asthma that is uncontrolled despite adherence with maximal optimized high-dose ICS-LABA treatment and management of contributory factors, or that worsens when high-dose treatment is decreased. Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed.

The Global Initiative for Asthma (GINA, 2023) recommends add-on biologic therapy for treatment of adults, adolescents and children with uncontrolled severe asthma despite optimized maximal therapy as follows:[1]

- Add-on anti-immunoglobulin E (anti-IgE) treatment (omalizumab) for patients aged ≥ 6 years with severe allergic asthma (Evidence A)
- Add-on anti-interleukin 5/5R treatment (subcutaneous mepolizumab for patients aged ≥ 6 years; intravenous reslizumab for ages ≥ 18 years; subcutaneous benralizumab for ages ≥ 12 years) with severe eosinophilic asthma (Evidence A)
- Add-on anti-interleukin-4R α treatment (subcutaneous dupilumab) for patients aged ≥ 6 years with severe eosinophilic/Type 2 asthma, or for adults or adolescents requiring treatment with maintenance OCS (Evidence A)
- Add-on anti-thymic stromal lymphopoietin (anti-TSLP) treatment [subcutaneous tezepelumab for patients aged ≥ 12 years with severe asthma (Evidence A)]

The Global Initiative for Asthma (GINA, 2023) recommends that low dose oral corticosteroids (≤ 7.5 mg/day prednisone equivalent) should only be considered as last resort in adult patients with severe asthma with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 5 treatment, and after exclusion of other contributory factors and other add-on treatments including biologics where available and affordable (Evidence D). Oral corticosteroids are often associated with substantial side effects (Evidence A).

## 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 100 mg 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 first European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines on severe asthma were published in 2014. Severe asthma was defined 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] Emphasis was placed on the necessity to confirm the diagnosis of asthma and exclude other conditions that may mimic asthma. In addition, the guidelines recognized that severe asthma is a heterogeneous condition consisting of phenotypes such as severe eosinophilic asthma, and specific recommendations were made on the use of sputum eosinophil count and exhaled nitric oxide fraction ($F_{ENO}$) to guide therapy. Recommendations were also made for the use of methotrexate, macrolide antibiotics, antifungal agents, bronchial thermoplasty and the anti-IgE antibody omalizumab in severe asthma.

In 2020, the European Respiratory Society (ERS)/American Thoracic Society (ATS) published updated guidelines for the management of asthma.[23] Six specific and important questions were formulated using the PICO (Patient population, Intervention, Comparison and Outcome) format. The GRADE (Grading of Recommendations, Assessment, Development

and Evaluation) approach was used to assess the strength of evidence and develop recommendations. These recommendations are summarized below:

- An anti-interleukin (IL)-5 and anti-IL-5 receptor $\alpha$ for severe uncontrolled adult eosinophilic asthma phenotypes
- A blood eosinophil cut-point ≥ 150 $\mu L^{-1}$ to guide anti-IL-5 initiation in adult patients with severe asthma
- Specific eosinophil (≥ 260 $\mu L^{-1}$) and exhaled nitric oxide fraction (≥ 19.5 ppb) cut-offs to identify adolescents or adults with the greatest likelihood of response to anti-IgE therapy
- Inhaled tiotropium for adolescents and adults with severe uncontrolled asthma despite Global Initiative for Asthma (GINA) step 4-5 or National Asthma Education and Prevention Program (NAEPP) step 5 therapies
- A trial of chronic macrolide therapy to reduce asthma exacerbations in persistently symptomatic or uncontrolled patients on GINA step 5 or NAEPP step 5 therapies, irrespective of asthma phenotype
- Anti-IL-4/13 for adult patients with severe eosinophilic asthma and for those with severe corticosteroid-dependent asthma regardless of blood eosinophil levels

### 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 6 years and older, who have an eosinophilic phenotype. Fasenra is also indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).Fasenra is not indicated for the treatment of other eosinophilic conditions or for acute bronchospasm or status asthmaticus.[11]

### 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 relief of acute bronchospasm or status asthmaticus. Nucala is also indicated for the treatment of adult patients 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, and for add-on maintenance treatment of adult patients 18 years and older with chronic rhinosinusitis with nasal polyps (CRSwNP).[1]

## References


1. Nucala® [prescribing information]. Research Triangle Park, NC; GlaxoSmithKline, LLC; March 2023.
2. Cinqair® [prescribing information]. Frazer, PA; Teva Respiratory, LLC; June 2020.
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 18, 2024.
5. Institute for Clinical and Economic Review (ICER). Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. November 13, 2018. Available at https://icer.org/wp-content/uploads/2020/10/Asthma-Revised-Report-FOR-PUBLICATION-11.13.2018.pdf. Accessed April 18, 2024.
6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Available at http://www.ginasthma.org. Accessed April 18, 2024.
7. 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.
8. 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.
9. Centers for Disease Control and Prevention. Asthma. Available at http://www.cdc.gov. Accessed April 18, 2024.
10. National Heart, Lung and Blood Institute. Explore Asthma. Available at http://www.nhlbi.nih.gov. Accessed April 18, 2024.
11. Fasenra® [prescribing information]. Wilmington, DE; AstraZeneca Pharmaceuticals LP; September 2024.
12. FitzGerald JM, Bleecker 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.
13. Goldman M, Hirsch I, Zangrilli JG, et al. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: sub analyses of the Phase III SIROCCO and CALIMA studies. Curr Med Res Opin. 2017 Sep;33(9):1605-1613.
14. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med 2017; 376: 1921-32.
15. Steinfeld J, Bradford ES, Brown J, et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol. 2019 Jun;143(6):2170-2177.
16. Crane MM, Chang cm, Kobayashi MG, Weller PF. Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence. J Allergy Clin Immunol. 2010;126(1):179.
17. Roufosse F, Klion A, Weller P. Hypereosinophilic syndromes: Clinical manifestations, pathophysiology, and diagnosis. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com. Accessed April 18, 2024.
18. Hypereosinophilic Syndrome (HES). American Academy of Allergy, Asthma & Immunology. Available at http://www.aaaai.org. Accessed June 13, 2023.
19. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol. 2016;6:S22-S209.
20. Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. Ann Allergy Asthma Immuno. 2014;113:347-385.
21. Hamilos DL. Chronic rhinosinusitis: management. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com. Accessed on April 18, 2024.
22. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, Smith SG, Martin N, Mayer B, Yancey SW, Sousa AR, Chan R, Hopkins C; SYNAPSE study investigators. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021 Apr 16:S2213-2600(21)00097-7. doi: 10.1016/S2213-2600(21)00097-7. Epub ahead of print. PMID: 33872587.
23. Hamilos DL, Holbrook EH. Chronic rhinosinusitis: Clinical manifestations, pathophysiology, and diagnosis. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com. Accessed on April 18, 2024.
24. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2020 Jan 2;55(1):1900588. doi: 10.1183/13993003.00588-2019. PMID: 31558662.
25. Wechsler ME, Nair P, Terrier B, Walz B, Bourdin A, Jayne DRW, Jackson DJ, Roufosse F, Börjesson Sjö L, Fan Y, Jison M, McCrae C, Necander S, Shavit A, Walton C, Merkel PA; MANDARA Study Group. Benralizumab versus

Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis. N Engl J Med. 2024 Mar 7;390(10):911-921. doi: 10.1056/NEJMoa2311155. Epub 2024 Feb 23. PMID: 38393328.

# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 08/01/2025 | **Application**<br>***Arizona***<br>• Added instruction to use the drug-specific criteria found within the state's Medicaid clinical policy, if available for the specific product, otherwise this medical benefit drug policy applies<br>**Supporting Information**<br>• Archived previous policy version CS2025D0055U |

# 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.