Benralizumab, Mepolizumab and Reslizumab

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Coverage Policy

This coverage policy includes the following agents:
- Benralizumab (Fasenra®)
- Mepolizumab (Nucala®)
- Reslizumab (Cinqair®)

Asthma
Mepolizumab (Nucala®) is considered medically necessary for the treatment of asthma when ALL of the following criteria are met:
- Individual is 6 years of age or older
- Eosinophilic phenotype defined as EITHER of the following:
  - Blood eosinophils greater than or equal to 150 cells/mcl within the previous 6 weeks
  - History of blood eosinophils greater than or equal to 300 cells/mcl
- Diagnosis of severe asthma (*refer to definition*)
- Continued use of an inhaled corticosteroid AND another controller therapy (for example, long-acting beta-agonist, leukotriene receptor)
• Will not be used in combination with another antiasthmatic monoclonal antibody (for example, reslizumab [Cinqair®], benralizumab [Fasenra™], omalizumab [Xolair®])

Reslizumab (Cinqair®) is considered medically necessary for the treatment of asthma when ALL of the following criteria are met:
• Individual is an adult (18 years of age and older)
• Eosinophilic phenotype defined as blood eosinophil level of at least 400 cells/mcl
• Diagnosis of severe asthma (*refer to definition)
• Continued use of an inhaled corticosteroid AND another controller therapy (for example, long-acting beta-agonist, leukotriene receptor)
• Will not be used in combination with another antiasthmatic monoclonal antibody (for example, mepolizumab [Nucala®], benralizumab [Fasenra™], omalizumab [Xolair®])

Benralizumab (Fasenra®) is considered medically necessary for the treatment of asthma when ALL of the following criteria are met:
• Individual is 12 years of age or older
• Eosinophilic phenotype defined as EITHER of the following:
  o Blood eosinophils greater than or equal to 150 cells/mcl within the previous 6 weeks
  o History of blood eosinophils greater than or equal to 300 cells/mcl
• Diagnosis of severe asthma (*refer to definition)
• Continued use of an inhaled corticosteroid AND another controller therapy (for example, long-acting beta-agonist, leukotriene receptor)
• Will not be used in combination with another antiasthmatic monoclonal antibody (for example, reslizumab [Cinqair], omalizumab [Xolair], mepolizumab [Nucala])

*Severe asthma is defined as EITHER of the following:
• Inadequate control as defined by ONE of the following on high doses of inhaled corticosteroids with an additional controller (long-acting beta-agonist or leukotriene receptor antagonist/theophylline)
  o Poor symptom control: Asthma Control Questionnaire (ACT) consistently greater than 1.5 or Asthma Control Test less than 20
  o History of exacerbations meeting ONE of the following:
    ▪ Two (2) or more exacerbations requiring at least 3 days of systemic corticosteroids in the previous 12 months
    ▪ One (1) or more severe exacerbation (hospitalization, ICU stay or mechanical ventilation) in the previous 12 months
  o Demonstrated airflow limitation: 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)
• Dependence on (for at least 50% of the previous 12 months) or inadequate control with daily oral corticosteroids for maintenance

Initial authorization for benralizumab (Fasenra), mepolizumab (Nucala), or reslizumab (Cinqair) for the treatment of asthma is up to 12 months.

Benralizumab (Fasenra), mepolizumab (Nucala) or reslizumab (Cinqair) are considered medically necessary for continued use for the treatment of asthma when ALL of the following criteria are met:
• Evidence of beneficial clinical response
• Pretreatment clinical condition met the initial criteria for the specific drug
• Continued use of an inhaled corticosteroid AND another controller therapy (for example, long-acting beta-agonist, leukotriene receptor)
• Will not be used in combination with another antiasthmatic monoclonal antibody (for example, Cinqair, Fasenra, Nucala, Xolair)

Reauthorization is for up to 12 months
**EGPA (eosinophilic granulomatosis with polyangiitis)**

Mepolizumab (Nucala®) is considered medically necessary for the treatment of EGPA (eosinophilic granulomatosis with polyangiitis) when ALL of the following criteria are met:

- Individual is 18 years of age or older
- Has diagnosis of asthma and hypereosinophilia [prior to corticosteroid therapy eosinophilia assessment: blood eosinophils ≥150 cells/microL (1.5 G/L) and/or ≥10 percent of leukocytes] AND at least two of the following:
  - Mononeuropathy (including multiplex) or polyneuropathy
  - Migratory or transient pulmonary opacities detected radiographically
  - Paranasal sinus abnormality
  - Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas
- Failure/inadequate response, contraindication per FDA label, intolerance, or not a candidate to oral prednisone greater than or equal to 7.5 mg/day for at least 4 weeks or equivalent
- Will not be used in combination with another antiasthmatic monoclonal antibody (for example, reslizumab [Cinqair®], benralizumab [Fasenra™], omalizumab [Xolair®])

Initial authorization for mepolizumab (Nucala) for EGPA is up to 12 months.

**Mepolizumab (Nucala) is considered medically necessary for continued use for EGPA when the following criteria are met:**

- Evidence of beneficial clinical response
- Pretreatment clinical condition met the initial criteria for the specific drug
- Will not be used in combination with another antiasthmatic monoclonal antibody (for example, Cinqair, Fasenra, Xolair)

Reauthorization is for up to 12 months

**Hypereosinophilic Syndrome**

Mepolizumab (Nucala®) is considered medically necessary for the treatment of hypereosinophilic syndrome (HES) when ALL of the following criteria are met:

- Individual is 12 years of age or older
- Individual has had hypereosinophilic syndrome for at least 6 months
- Documentation of FIP1L1-PDGFRA-negative disease
- According to the prescriber, the individual does NOT have an identifiable non-hematologic secondary cause of hypereosinophilic syndrome (for example, drug hypersensitivity, parasitic helminth infection, human immunodeficiency virus infection, non-hematologic malignancy)
- Prior to initiating therapy with any anti-interleukin-5 therapy, the individual has/had a blood eosinophil level of 1,000 cells per microliter or greater
  - Note: Examples of anti-interleukin-5 therapies include Nucala, Cinqair, and Fasenra.
- Documented failure/inadequate response, intolerance, contraindication per FDA label or not a candidate to at least one other treatment for hypereosinophilic syndrome for a minimum of 4 weeks (for example, systemic corticosteroids, hydroxyurea, cyclosporine, imatinib, methotrexate, tacrolimus, azathioprine)
- Symptoms of end organ (skin, lung, GI, heart, or nervous system) involvement as documented by at least two symptomatic flares in the last 12 months
  - Note: Documentation of chronic end organ damage can be accepted if acute flares are absent
- Prescribed by or in consultation with an allergist, immunologist, pulmonologist, hematologist or rheumatologist
- Will not be used in combination with another antiasthmatic monoclonal antibody (for example, Cinqair, Fasenra, Xolair)

Initial authorization for mepolizumab (Nucala) for hypereosinophilic syndrome is up to 12 months.

Mepolizumab (Nucala) is considered medically necessary for continued use for hypereosinophilic syndrome when the following criteria are met:
• Evidence of beneficial clinical response (for example, reduction in number of disease flares, reduction in total steroid use, reduction in absolute eosinophil count)
• Pretreatment clinical condition met the initial criteria for the specific drug
• Will not be used in combination with another antiasthmatic monoclonal antibody (for example, Cinqair, Fasenra, Xolair)

Reauthorization is for up to 12 months

Benralizumab (Fasenra), mepolizumab (Nucala) or reslizumab (Cinqair) are considered experimental, investigational or unproven for ANY other use including the following:
• Relief of acute bronchospasm or status asthmaticus
• Treatment of other eosinophilic conditions such as eosinophilic esophagitis, eosinophilic gastroenteritis, eosinophilic colitis
• Nasal polyposis
• Atopic dermatitis
• Chronic Obstructive Pulmonary Disease (COPD)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

**FDA Approved Indications**

### FDA Approved Indications

<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cinqair</strong> (reslizumab)</td>
<td>Cinqair is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype [see Clinical Studies (14)].</td>
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<tr>
<td></td>
<td>Limitation of Use:</td>
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<tr>
<td></td>
<td>• Cinqair is not indicated for treatment of other eosinophilic conditions.</td>
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<tr>
<td></td>
<td>• Cinqair is not indicated for the relief of acute bronchospasm or status asthmaticus [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td><strong>Fasenra</strong> (benralizumab)</td>
<td>Fasenra is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype [see Clinical Studies (14)].</td>
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<tr>
<td></td>
<td>Limitations of use:</td>
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<tr>
<td></td>
<td>• FASENRA is not indicated for treatment of other eosinophilic conditions.</td>
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<tr>
<td></td>
<td>• FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.</td>
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<tr>
<td><strong>Nucala</strong> (mepolizumab)</td>
<td><strong>Maintenance Treatment of Severe Asthma</strong></td>
</tr>
<tr>
<td></td>
<td>NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype</td>
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<tr>
<td></td>
<td>Limitations of Use</td>
</tr>
<tr>
<td></td>
<td>NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.</td>
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<tr>
<td></td>
<td><strong>Eosinophilic Granulomatosis with Polyangiitis</strong></td>
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<tr>
<td></td>
<td>NUCALA is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).</td>
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<td></td>
<td><strong>Hypereosinophilic Syndrome</strong></td>
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</table>
NUCALA 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.

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<td></td>
<td>older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-</td>
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<td></td>
<td>hematologic secondary cause.</td>
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**Recommended Dosing**

<table>
<thead>
<tr>
<th>FDA Recommended Dosing</th>
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</thead>
<tbody>
<tr>
<td><strong>Cinqair (reslizumab)</strong></td>
<td>Cinqair is for intravenous infusion only. Do not administer as an intravenous push or bolus.</td>
</tr>
<tr>
<td></td>
<td>The recommended dosage regimen is 3 mg/kg once every 4 weeks administered by intravenous infusion over 20-50 minutes [see Dosage and Administration (2.2)].</td>
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<tr>
<td></td>
<td>Discontinue the infusion immediately if the patient experiences a severe systemic reaction, including anaphylaxis [see Contraindications (4), Warnings and Precautions (5.1)].</td>
</tr>
<tr>
<td><strong>Fasenra (benralizumab)</strong></td>
<td><strong>Recommended Dosage</strong></td>
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<tr>
<td></td>
<td>Fasenra is for subcutaneous use only.</td>
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<tr>
<td></td>
<td>The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.</td>
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<tr>
<td></td>
<td><strong>Preparation and Administration</strong></td>
</tr>
<tr>
<td></td>
<td>FASENRA is intended for use under the guidance of a healthcare provider. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended [see Warnings and Precautions (5.1)].</td>
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<tr>
<td></td>
<td>Administer FASENRA into the thigh or abdomen. The upper arm can also be used if a healthcare provider or caregiver administers the injection.</td>
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<tr>
<td></td>
<td><strong>Prefilled Syringe</strong></td>
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<td></td>
<td>The prefilled syringe is for administration by a healthcare provider.</td>
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<tr>
<td></td>
<td><strong>Autoinjector</strong></td>
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<tr>
<td></td>
<td>FASENRA PEN is intended for administration by patients/caregivers. Patients/caregivers may inject after proper training in subcutaneous injection technique, and after the healthcare provider determines it is appropriate.</td>
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<tr>
<td><strong>Nucala (mepolizumab)</strong></td>
<td><strong>Recommended Dosage</strong></td>
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<tr>
<td></td>
<td>Nucala is for subcutaneous use only.</td>
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<td></td>
<td><strong>Severe Asthma</strong></td>
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<td></td>
<td>Adults and Adolescents Aged 12 Years and Older</td>
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<td></td>
<td>The recommended dosage of Nucala in adults and adolescents aged 12 years and older is 100 mg administered once every 4 weeks by SC injection into the upper arm, thigh, or abdomen.</td>
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<td></td>
<td>Pediatric Patients Aged 6 to 11 Years</td>
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<tr>
<td></td>
<td>The recommended dosage of Nucala in children aged 6 to 11 years is 40 mg administered once every 4 weeks by SC injection into the upper arm, thigh, or abdomen.</td>
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</table>
## Eosinophilic Granulomatosis with Polyangiitis

The recommended dosage of Nucala is 300 mg administered once every 4 weeks by SC injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen. It is recommended that the individual 100-mg injections be administered at least 5 cm (approximately 2 inches) apart if more than 1 injection is administered at the same site. Preparation of the 300-mg dose for treatment of EGPA requires the reconstitution of 3 separate 100-mg vials or administration of 3 prefilled autoinjectors or 3 prefilled syringes as described below [see Dosage and Administration (2.3, 2.4)].

**Preparation and Administration of Nucala for Injection Vial** - Nucala should be reconstituted and administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended [see Warnings and Precautions (5.1)].

**Preparation and Administration of Nucala Injection Prefilled Autoinjector and Prefilled Syringe** - Nucala injection is intended for use under the guidance of a healthcare provider. The Nucala injection prefilled autoinjector and prefilled syringe are only for use in adults and adolescents aged 12 years and older. A patient may self-inject or the patient caregiver may administer Nucala injection subcutaneously after the healthcare provider determines it is appropriate. Provide proper training in SC injection technique and on the preparation and administration of Nucala injection prior to use according to the “Instructions for Use”.

## Hypereosinophilic Syndrome

The recommended dosage of Nucala is 300 mg administered once every 4 weeks by subcutaneous injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen [see Dosage and Administration (2.4, 2.5)]. Administer individual 100-mg injections at least 5 cm (approximately 2 inches) apart.

### Drug Availability

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug Availability</th>
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</thead>
<tbody>
<tr>
<td>Cinqair (reslizumab)</td>
<td>100 mg/10 mL (10 mg/mL) solution in single-use vials</td>
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</tbody>
</table>
| Fasenra (benralizumab) | • Single-Dose Prefilled Syringe Carton contains one 30 mg/mL single-dose prefilled syringe  
                          | • Single-Dose Autoinjector FASENRA PEN Carton contains one 30 mg/mL single-dose autoinjector |
| Nucala (mepolizumab) | For injection: 100 mg white to off-white lyophilized powder in a single-dose vial for reconstitution.  
                           | Injection: 100 mg/mL as a clear to opalescent, colorless to pale yellow to pale brown solution in a single-dose prefilled autoinjector or a single-dose prefilled glass syringe. |

### General Background

#### Pharmacology

Mepolizumab and reslizumab are interleukin-5 antagonists. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. IL-5 antagonists, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the
mechanism of action in asthma has not been definitively established. (GlaxoSmithKline, 2015; Teva Respiratory, 2016)

Benralizumab is a humanized afucosylated, monoclonal antibody (IgG1, kappa) that directly binds to the alpha subunit of the human interleukin-5 receptor (IL-5Ra) with a dissociation constant of 11 pM. The IL-5 receptor is expressed on the surface of eosinophils and basophils. In an *in vitro* setting, the absence of fucose in the Fc domain of benralizumab facilitates binding (45.5 nM) to FcγRIII receptors on immune effector cells, such as natural killer (NK) cells, leading to apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC). (AstraZeneca, 2018)

**Eosinophilic Granulomatosis with Polyangiitis**

Previously named Churg-Strauss Syndrome, eosinophilic granulomatosis with polyangiitis (EGPA), is a systemic necrotizing vasculitis that affects vessels of small to medium-size. EGPA is typically associated with severe asthma and eosinophilia (Groh 2015, Schwartz 2016).

Steroid conversion calculators are available online.

**Professional Societies/Organizations Guidelines**

**Severe Asthma**

**Global Initiative for Asthma (GINA)**

GINA published updated guidelines in 2018 for asthma management and prevention. GINA 2018 recommends for patients with severe asthma that are uncontrolled on Step 4 treatment (for example, 2 or more controllers plus as needed reliever medication), phenotyping into categories is suggested such as: severe allergic, aspirin-exacerbated or eosinophilic asthma. Omalizumab is recommended as the preferred treatment option for the management of patients at Step 5. Similarly, add-on anti-IL-5 therapy (including: benralizumab, mepolizumab, reslizumab) is recommended for patients aged greater than or equal to 12 years that have severe eosinophilic asthma uncontrolled on Step 4 treatment. (GINA 2018)

GINA guidelines state there are recognizable clusters of demographic, pathophysiological or clinical manifestations that are frequently titled asthma phenotypes. In more severe asthma patients, phenotype guided treatments are available. But, these cluster types do not have a strong correlation with an exact pathological processes or a treatment response and more research is necessary to understand the utility of classification of phenotype for the asthma patient. Phenotype-guided add-on treatment is listed under management of severe disease and patients with severe eosinophilic asthma may benefit from anti-IL5 therapy however no consenses is given to the specific levels at which to treat (GINA 2018)

**National Heart, Lung, and Blood Institute (NHLBI)**

NHLBI guidelines/National Asthma Education and Prevention Program state that pharmacologic therapy is based on a stepwise approach where medications are increased until the asthma is controlled and then decreased when it is possible in order to minimize treatment related adverse effects. According to the 2007 NHLBI guidelines, the level of asthma control is based on (1) symptoms reported over the past 2 to 4 weeks, (2) current level of FEV₁ and FEV₁/forced vital capacity [FVC] values, (3) the number of exacerbations requiring oral corticosteroids each year. NHLBI guidelines state omalizumab is used as adjunctive therapy in patients 12 years and older who experience allergies and severe persistent asthma that is not controlled adequately with the combination of high-dose ICS and LABA therapy (NHLBI 2007).

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

The ERS/ATS defines severe asthma as those individuals who require treatment with GINA step 4 or 5 medications (high-dose ICS and LABA or leukotriene receptor antagonist or theophylline) for the previous year or systemic corticosteroids for at least 50% of the previous year to prevent the condition from becoming uncontrolled or which remains uncontrolled despite the therapy. (Chung, 2014) Uncontrolled asthma is defined as having at least one of the following: poor symptom control (using standardized measures); frequent severe exacerbations (requiring 2 or more bursts (greater than 3 days) or corticosteroids in the previous year); serious
exacerbations (at least one hospitalization, intensive care unit stay or mechanical ventilation in the previous year); or airflow limitation. (Chung, 2014) Controlled asthma that worsens when tapering high doses of inhaled corticosteroids, systemic corticosteroids, or other biologic therapies also meets the definition of severe asthma. (Chung, 2014)

**Eosinophilic Granulomatosis with Polyangiitis**
The EGPA (Churg-Strauss) Consensus Task Force and American Society for Apheresis guidelines recommend glucocorticoids alone for those patients without life-threatening and/or organ-threatening EGPA. However, for patients with life-threatening and/or organ-threatening EGPA, both a glucocorticoid and an immunosuppressant are recommended for treatment, as well as maintenance therapy with either azathioprine or methotrexate. In addition, IVIG can be considered for (1) refractory EGPA or (2) treatment while pregnant (Groh 2015, Schwartz 2016).

Note: These guidelines have not been updated to include mepolizumab and its place in therapy; however, EGPA Consensus Task Force recommendations do state mepolizumab holds promise for this diagnosis based on available pilot studies (Groh 2015).

**Hypereosinophilia Guidelines**
The 2019 World Health Organization (WHO)-defined eosinophilic disorders update on diagnosis, risk stratification, and management notes that corticosteroids remain the cornerstone of therapy for several forms of hypereosinophilic syndrome. (Shomali, 2019) Use of anti-IL-5 approaches for the treatment of HES remains investigational. This document was published prior to the approval of Nucala for hypereosinophilic syndrome. However, it is recommended that patients with idiopathic hypereosinophilic syndrome and end organ damage as well as those with lymphocyte-variant hypereosinophilic syndrome should consider enrollment into an anti-IL-5/anti-IL-5 receptor antibody clinical trial (as second-line therapy).

**Clinical Efficacy**

**Comparative Trials**
Cockle et al performed a systematic review and indirect treatment comparison in patients with severe asthma with the goal of assessing effectiveness and tolerability of mepolizumab versus omalizumab as add-on therapy to standard of care. Studies included were double-blind, randomized, greater than or equal to 12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history and receiving a high-dose ICS plus greater than or equal to 1 additional controller medication. Two patient populations were examined: 1) both treatments (as an overlap population) and 2) either treatment (as a trial population). For the overlap population: no differences were shown between mepolizumab and omalizumab treatment. However, there were trends favoring mepolizumab, with median estimated rate ratios of 0.66 for the clinically significant exacerbation rate and 0.19 for the exacerbations that required hospitalization rate.

For the results of the trial population analysis, mepolizumab was shown to be associated with an estimated median rate ratio of 0.63 corresponding to a reduction of 37% in the clinically significant exacerbations rate compared to omalizumab. However, there were no difference between the two treatments for the rate of exacerbations resulting in hospitalization; but note that the median rate ratio of 0.58 demonstrated a trend for mepolizumab over omalizumab treatment. Lastly, the two treatments had comparable effects on lung function, and similar tolerability profiles. (Cockle 2017)

Nachef et al conducted a systematic review that was unable to detect differences in efficacy when comparing asthma patients with add-on therapy with mepolizumab or omalizumab in those who were not well controlled on ICS therapy. This analysis included randomized controlled trials and cohort studies with a duration of greater than or equal to 12 weeks (included: 18 omalizumab studies (N=4854) and 4 mepolizumab studies (N=1620)). The network meta-analysis did not find significant differences in FEV1 between the two groups. Both treatments reduced the annualized asthma exacerbations rates by ~ 50% when compared against placebo. The authors did state that they were unable to identify significant differences in efficacy, however, there was high heterogeneity among the identified clinical trials and major differences found in inclusion criteria within the studies (Nachef 2017)
Farne et al conducted a systematic review of mepolizumab, reslizumab, and benralizumab. The systematic review included 13 studies (N=6000) in patients with asthma poorly controlled by ICS (majority had severe eosinophilic asthma). All of the IL-5 antagonists reduced asthma exacerbations by about 50% and improved FEV₁ (by 0.08 L to 0.11 L). Although there was not an increase in serious adverse events with any IL-5 antagonist, more patients discontinued their medication due to adverse events with benralizumab (36 out of 1599) than placebo (9 out of 998) (Farne 2017)

- Benralizumab (Fasenra)
The SIROCCO trial was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 study in (N=1205) patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs. The patients who were enrolled were assigned randomly to placebo, benralizumab 30 mg every 4 weeks, or benralizumab 30 mg every 8 weeks. Benralizumab compared to placebo reduced the annual asthma exacerbation rate over the 48 weeks timeframe when administered every 4 weeks (rate ratio, 0.55; P<0.0001) or every 8 weeks (rate ratio, 0.49; P<0.0001). Benralizumab, at both doses, significantly improved pre-bronchodilator FEV₁ at week 48 versus the placebo arm. Benralizumab every 8 weeks improved asthma symptoms, but not every 4 weeks, when compared against placebo. (Bleecker 2016)

The CALIMA trial (N=1306) was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 study evaluating benralizumab as add-on therapy (to high-dose ICS and LABA) in patients with severe, uncontrolled asthma and an elevated blood eosinophil counts. Patients were randomly assigned to benralizumab 30 mg every 4 weeks, benralizumab 30 mg every 8 weeks or placebo. Significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (rate ratio, 0.64; P=0.0018) and every 8 weeks (rate ratio, 0.72; P=0.0188) when compared against placebo. In addition, benralizumab patients had significantly improved pre-bronchodilator FEV₁ and total asthma symptom scores when compared against placebo. (Fitzgerald 2016)

The BISE trial (N=211) was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 study evaluating benralizumab in mild to moderate persistent asthma patients. Patients had been receiving either low-dose to medium-dose ICS or low-dose ICS plus a LABA and were randomized to either benralizumab 30 mg every 4 weeks or placebo. The results demonstrated benralizumab resulted in an 80 mL (P=0.04) greater improvement in pre-bronchodilator FEV₁ after 12 weeks when compared against placebo. However, note that despite this improvement, this result in lung function does not warrant benralizumab use in mild to moderate asthma patients because benralizumab did not reach the 10% minimum clinically important improvement mark. (Ferguson 2017)

The ZONDA (N=220) trial was a randomized, multicenter, double-blind, placebo-controlled, 28-week study that assessed if benralizumab was effective as an oral glucocorticoid-sparing treatment in patients on oral steroids in managing severe asthma associated with eosinophilia. Patients were randomly assigned to benralizumab 30 mg every 4 weeks, benralizumab 30 mg every 8 weeks, or placebo. The results demonstrated that both benralizumab doses significantly reduced the median final oral glucocorticoid doses (from baseline) by 75% compared to placebo at a 25% reduction. Benralizumab administered every 4 weeks also demonstrated an annual exacerbation rate 55% lower than seen compared to placebo. Benralizumab administered every 8 weeks demonstrated a 70% lower rate than compared to placebo. (Nair 2017)

- Mepolizumab (Nucala)

Severe Asthma
The DREAM trial included 621 patients aged 12 to 74 years with severe refractory asthma per American Thoracic Society (ATS) criteria for at least 12 months and taking high-dose inhaled corticosteroids and an additional controller medication. Patients were included if they had at least 2 exacerbations requiring oral or systemic corticosteroids in the previous 12 months. Eosinophilic airway inflammation was defined as either having elevated peripheral blood eosinophils at least 300/mcL, sputum eosinophils at least 3%, exhaled nitric oxide at least 50 parts per billion, or having deterioration of asthma control following at 25% reduction of maintenance inhaled or oral steroids. Patients were randomized to either 75 mg, 250 mg, or 750 mg of intravenous mepolizumab or placebo for a 52-week treatment period. Mepolizumab demonstrated a significant reduction in the number of clinically significant asthma exacerbations per year. (Pavord, 2012)
The MENSA trial evaluated 32 weeks of treatment with mepolizumab 75 mg intravenous, 100 mg subcutaneously or placebo in 576 patients with severe eosinophilic asthma. Individuals were included if they were on a high-dose inhaled corticosteroid along with another controller medication for at least 12 months, had at least 2 exacerbations requiring systemic corticosteroids in the past year, and had blood eosinophils of at least 150 cells/mcL at screen or 300 cells/mcL or greater during the previous year. Both doses of mepolizumab were significantly more effective compared to placebo at reducing the number of asthma exacerbations. (Ortega, 2014)

The SIRIUS trial evaluated 135 individuals with severe eosinophilic asthma given mepolizumab 100 mg subcutaneously or placebo every 4 weeks through week 20. Patients enrolled had at least a 6 month history of requiring systemic corticosteroids (5-35 mg/day of prednisone equivalent) in addition to high-dose inhaled corticosteroid and an additional controller medication for the past 12 months. Two or more exacerbations requiring corticosteroids in the previous 12 months and blood eosinophils of at least 150 cells/mcL at screening or 300 cells/mcL during the previous criteria were required for inclusion. Mepolizumab significantly reduced the oral maintenance glucocorticoid dose compared to placebo. (Bel, 2014)

**Eosinophilic Granulomatosis with Polyangiitis**

Wechsler et al conducted a 52 week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial that evaluated mepolizumab’s efficacy and safety as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) in relapsing or refractory EGPA. Inclusion criteria included 1) at least 18 years of age and also 2) diagnosis of relapsing or refractory EGPA at least 6 months previously, and had been taking a stable dose of prednisolone or prednisone (≥ 7.5 to ≤ 50.0 mg per day, with or without additional immunosuppressive therapy) for at least 4 weeks before the baseline visit. Results showed for mepolizumab and placebo groups, respectively that (1) Percentage of patients with ≥24 weeks of accrued remission: 28% vs 3% (OR, 5.91; P<0.001), (2) Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; P<0.001), (3) Annualized relapse rate: 1.14 vs 2.27 (rate ratio, 0.50; P<0.001), (4) Percentage of patients able to reduce their daily dose of concomitant prednisolone or prednisone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; P<0.001). (Wechsler, 2017)

**Hypereosinophilic Syndrome**

One Phase III study evaluated the efficacy of Nucala in patients ≥ 12 years of age with hypereosinophilic syndrome for ≥ 6 months. (Roufosse, 2020) Patients with non-hematologic secondary hypereosinophilic syndrome and those with FIP1L1-PDGFRα kinase-positive hypereosinophilic syndrome were excluded. All patients had a baseline blood eosinophil count ≥ 1,000 cells per microliter and had experienced two or more hypereosinophilic flares within the previous 12 months. Additionally, all patients had been on stable therapy for their hypereosinophilic syndrome (e.g., oral corticosteroids, immunosuppressive agents, or cytotoxic therapy) for 4 weeks or more prior to randomization. Over the 32-week treatment period, significantly fewer patients experienced one or more hypereosinophilic syndrome flares with Nucala compared with placebo. Nucala also resulted in a delayed time to first flare. Several secondary endpoints were also improved, including measurements of fatigue.

- **Reslizumab (Cinqair)**

Reslizumab 3 mg/kg intravenous every 4 weeks was evaluated in two 52-week trials (Study 3082 and 3083). Individuals enrolled were 12-75 years of age, had a blood eosinophil level of at least 400 cells/mcL during the screening period, and were receiving at least medium dose inhaled corticosteroid with or without another controller drug. Individuals were included if they had at least 1 asthma exacerbation in the previous year that required systemic corticosteroid use for at least 3 days. Reslizumab significantly decreased the frequency of asthma exacerbations compared to placebo in both trials. (Castro, 2015)

Study 3081 evaluated the change from baseline in FEV₁ of reslizumab and placebo at 16 weeks. Individuals enrolled were 12-75 years old, had a blood eosinophil level of at least 400 cells/mcL, had inadequately controlled asthma per the Asthma Control Questionnaire, and were receiving at least medium dose inhaled corticosteroid. Patients receiving systemic corticosteroids were excluded. The overall change in FEV₁ was significantly improved with reslizumab 3 mg/kg compared to placebo. The improvement was evident as early as 4 weeks and maintained through the study. (Bjermer, 2016)
Study 3084 was a 16-week trial evaluating reslizumab and placebo and change in FEV\textsubscript{1} from baseline. This trial did not require a specific baseline eosinophil count. Adults with inadequately controlled asthma on at least a medium dose of inhaled corticosteroid and not receiving systemic corticosteroids were included. There was not a significant difference between reslizumab and placebo in the mean change in FEV\textsubscript{1} from baseline to week 16. The study was not powered to assess differences in subgroups based on eosinophil levels. (Corren, 2016)

**Off Label Uses**

AHFS Drug Information 2019 Edition does not support any off-label uses of benralizumab (Fasenra), mepolizumab (Nucala) or reslizumab (Cinqair).

**Experimental, Investigational, Unproven Uses**

The FDA product information notes that these agents are not indicated for the relief of acute bronchospasm and status asthmaticus or for the treatment of other eosinophilic conditions (with the exception of Nucala in EGPA).

Clinical trials have investigated benralizumab, mepolizumab and reslizumab for atopic dermatitis (Oldhoff, 2005), COPD (Brightling, 2014; Nair, 2016; Pavord, 2017), and other eosinophilic conditions including eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis (Assa’ad, 2011; Spergel, 2012; Straumann, 2010), nasal polyposis (Gevaert, 2006; Gevaert, 2011). At this time, however, there are insufficient published data to demonstrate the safety and efficacy of the use of mepolizumab or reslizumab for these indications. Some of the studies did not demonstrate any clinical improvement and others were limited by small and/or heterogeneous patient populations; short-term follow-ups; lack of a control group; potential reporting and publication bias; and heterogeneity of inclusion criteria and outcome measures.

**Coding/Billing Information**

**Note:**

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

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<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<td>C9466</td>
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<tr>
<td>J2786</td>
<td>Injection, reslizumab, 1 mg</td>
</tr>
<tr>
<td>J3590</td>
<td>Unclassified biologics</td>
</tr>
</tbody>
</table>

**References**


32. Teva Respiratory, LLC. Cinqair (reslizumab) injection, for intravenous use [product information]. Frazer, PA: Teva Respiratory, LLC; March 2016.