

Medical Policy Bulletin

Title:

Interleukin-5 (IL-5) Antagonist (e.g., Cinqair®, Nucala®) and IL-5 Receptor Antagonist (e.g., Fasenra®)

Policy #:

MA08.024m

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

INDEX OF MEDICALLY NECESSARY INDICATIONS

This policy addresses numerous medically necessary indications for the use of benralizumab (Fasenra), mepolizumab (Nucala), and reslizumab (Cinqair) (listed in order of appearance within the Policy section). Please see below for the specific medical necessity criteria. (NOTE: Experimental/Investigational section below must also be reviewed.)

- Benralizumab (Fasenra)
 - Severe eosinophilic asthma
 - Relapsed or refractory eosinophilic granulomatosis with polyangiitis (EGPA)
- Mepolizumab (Nucala)
 - Severe eosinophilic asthma
 - Chronic rhinosinusitis with nasal polyps (CRSwNP)
 - Hypereosinophilic syndrome (HES)
 - Relapsed or refractory eosinophilic granulomatosis with polyangiitis (EGPA)
- Reslizumab (Cinqair)
 - Severe eosinophilic asthma

MEDICALLY NECESSARY

INITIAL THERAPY: BENRALIZUMAB (FASENRA)

Severe Eosinophilic Asthma

Benralizumab (Fasenra) is considered medically necessary and, therefore, covered for the treatment of severe eosinophilic asthma when all of the following criteria are met:

- The individual is 6 years of age or older.
- The blood eosinophil count at the initiation of treatment is at least:
 - 150 cells/ μ L, if dependent on concurrent daily oral corticosteroid therapy for at least 6 continuous months, or
 - 300 cells/ μ L, if naive of daily oral corticosteroid therapy
- The individual is currently receiving treatment that does not maintain adequate control of their asthma and benralizumab (Fasenra) is being used as additional maintenance therapy.
 - Current treatment must include high-dose inhaled corticosteroids (ICS), long-acting beta agonist (LABA), and, if required, additional asthma controller medication (e.g., oral corticosteroids, leukotriene inhibitor, theophylline), unless the individual is intolerant of or has a contraindication to these agents.
- Benralizumab (Fasenra) will not be used in combination with other biologics for asthma/allergic conditions (e.g., dupilumab [Dupixent], mepolizumab [Nucala], omalizumab [Xolair], reslizumab [Cinqair])

The dosage, frequency, and route of administration for benralizumab (Fasenra) is as follows:

- Adult and adolescent individuals 12 years of age and older: 30 mg administered once every 4 weeks for the first three doses, then once every 8 weeks thereafter, by subcutaneous injection.
- Pediatric Individuals 6 to 11 years of age, as follows according to body weight:
 - Less than 35 kg: 10 mg administered once every 4 weeks for the first three doses, then once every 8 weeks thereafter, by subcutaneous injection.
 - 35 kg or more: 30 mg administered once every 4 weeks for the first three doses, then once every 8 weeks thereafter, by subcutaneous injection.

Relapsed or Refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Benralizumab (Fasenra) is considered medically necessary and, therefore, covered for the treatment of EGPA when all of the following criteria are met:

- The individual is 18 years of age or older
- The individual has a documented diagnosis of EGPA for at least 6 months based on both of the following:
 - The individual has a history of asthma or a current asthma condition
 - The individual has eosinophilia, characterized by greater than 10% of leukocytes or an absolute eosinophil count greater than 1000 cells/ mm^3 (or $>1 \times 10^9/\text{L}$)
- The individual has symptoms despite treatment with oral corticosteroids, unless the individual is intolerant of or has a contraindication to these agents
- Presence of two or more of the following features typical of EGPA:
 - Biopsy showing histopathological evidence of one of the following:
 - Eosinophilic vasculitis
 - Perivascular eosinophilic infiltration
 - Eosinophil-rich granulomatous inflammation
 - Neuropathy
 - Pulmonary infiltrates
 - Sinonasal abnormality
 - Cardiomyopathy
 - Glomerulonephritis
 - Alveolar hemorrhage
 - Palpable purpura
 - Positive test for antineutrophil cytoplasmic antibody (ANCA)
- Benralizumab (Fasenra) will not be used in combination with other biologics for asthma/allergic conditions (e.g., dupilumab [Dupixent], mepolizumab [Nucala], omalizumab [Xolair], reslizumab [Cinqair])

The dosage, frequency, and route of administration for benralizumab (Fasenra) for the treatment of EGPA is 30 mg administered once every 4 weeks by subcutaneous injection.

INITIAL THERAPY: MEPOLIZUMAB (NUCALA)

Severe Eosinophilic Asthma

Mepolizumab (Nucala) is considered medically necessary and, therefore, covered for the treatment of severe eosinophilic asthma when all of the following criteria are met:

- The individual is 6 years of age or older.
- The individual has one of the following blood eosinophil counts:
 - Blood eosinophils of at least 150 cells/ μ L* during the 6 weeks prior to the initiation of treatment
 - Blood eosinophils of at least 300 cells/ μ L* in the past 12 months
- The individual is currently receiving treatment that does not maintain adequate control of their asthma and mepolizumab (Nucala) is being used as additional maintenance therapy.
 - Current treatment must include high-dose ICS (with or without oral corticosteroids) plus an additional controller (e.g., LABA, leukotriene inhibitor, theophylline) medication, unless the individual is intolerant of or has a contraindication to these agents.
- Mepolizumab (Nucala) will not be used in combination with other biologics for asthma/allergic conditions (e.g., benralizumab [Fasenra], dupilumab [Dupixent], omalizumab [Xolair], reslizumab [Cinqair])

The dosage, frequency, and route of administration for mepolizumab (Nucala) for the treatment of severe eosinophilic asthma is:

- Adults and adolescents aged 12 year and older: 100 mg administered once every 4 weeks by subcutaneous injection.
- Pediatric individuals aged 6 to 11 years: 40 mg administered once every 4 weeks by subcutaneous injection.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Mepolizumab (Nucala) is considered medically necessary and, therefore, covered as add-on maintenance therapy for CRSwNP when all of the following criteria are met:

- The individual is 18 years of age or older
- The individual has undergone at least one surgery for the removal of nasal polyps within the previous 10 years
- The individual is diagnosed with recurrent, refractory, severe, bilateral, symptomatic CRSwNP characterized by all of the following:
 - Presence of the following symptoms of rhinosinusitis persisting at least 12 weeks:
 - Two or more: nasal blockage, obstruction, and congestion, or nasal discharge (anterior or posterior nasal drip)
 - One or more: nasal discharge (if not reported in bullet above), facial pain or pressure, and reduction or loss of smell
 - Nasal Polyp Score (NPS) of ≥ 5 of 8 (with NPS ≥ 2 for each nostril) at baseline, identified via one of the following visualization techniques: anterior rhinoscopy, nasal endoscopy, sinus computed tomography (CT), or magnetic resonance imaging (MRI)
 - Nasal obstruction symptoms (i.e., nasal obstruction, loss of smell, facial pain) with a visual analog scale (VAS) score of >5 of a maximum score of 10
- Documented failure, contraindication, or intolerance to at least an 8-week trial of intranasal corticosteroids
- Mepolizumab (Nucala) will be used in combination with intranasal corticosteroids, unless documented failure, contraindication, or intolerance.
- Mepolizumab (Nucala) will not be used in combination with other biologics for asthma/allergic conditions (e.g., benralizumab [Fasenra], dupilumab [Dupixent], omalizumab [Xolair], reslizumab [Cinqair])

The dosage, frequency, and route of administration for mepolizumab (Nucala) for the treatment of CRSwNP is: 100 mg administered once every 4 weeks by subcutaneous injection.

Hypereosinophilic Syndrome (HES)

Mepolizumab (Nucala) is considered medically necessary and, therefore, covered for the treatment of HES when all of the following criteria are met:

- The individual is 12 years of age or older

- The individual has a documented diagnosis of HES** for 6 or more months that is *FIP1L1-PDGFR*A-negative, and has all of the following characteristics:
 - Non-hematologic HES diagnosis without an identified secondary cause (i.e., other causes have been ruled out)
 - Blood eosinophil count of 1000 cells/ μ L (or 1×10^9 /L) or greater at the time mepolizumab (Nucala) will be initiated (baseline)
 - Signs and/or symptoms of organ involvement are present†
- There is documentation of uncontrolled HES characterized by two or more HES flares in the previous 12 months (Note: One or more of these flares are unrelated to a decrease in HES medication therapy in the preceding 4 weeks)
 - Flares are defined as worsening of HES-related symptoms or blood eosinophil count requiring medication escalation.
- The individual has a documented failure, contraindication, or intolerance to at least 4 weeks of one of the following conventional HES therapies (e.g., corticosteroids, immunosuppressive and/or cytotoxic therapy, such as hydroxyurea, interferon- α , vincristine, cyclosporine, imatinib, methotrexate, tacrolimus, azathioprine)
- Mepolizumab (Nucala) will not be used in combination with other biologics for asthma/allergic conditions (e.g., benralizumab [Fasenra], dupilumab [Dupixent], omalizumab [Xolair], reslizumab [Cinqair])

The dosage, frequency, and route of administration for mepolizumab (Nucala) for the treatment of HES is:

- Adults and adolescents aged 12 years and older: 300 mg (i.e., three separate 100-mg injections) administered once every 4 weeks by subcutaneous injection.

** Diagnosis of HES: Organ system involvement and/or dysfunction that could be directly related to a blood eosinophil count >1500 cells/ μ L (or $\geq 1.5 \times 10^9$ /L) on two or more occasions, and/or tissue eosinophilia, without a discernible secondary cause.

†Signs and/or symptoms of HES are highly variable, but may include dermatological, respiratory, gastrointestinal, central nervous system, and cardiovascular symptoms, such as, but not limited to: pruritus, skin rash, weakness, fatigue, cough, dyspnea, muscle inflammation, rhinitis, fever, asthma, abdominal pain, vomiting, diarrhea, arthritis, vertigo, paresthesia, speech or visual disturbances, congestive heart failure, cardiomyopathy, deep vein thrombosis, anemia.

Relapsed or Refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Mepolizumab (Nucala) is considered medically necessary and, therefore, covered for the treatment of EGPA when all of the following criteria are met:

- The individual is 18 years of age or older
- The individual has a documented diagnosis of EGPA for at least 6 months based on both of the following:
 - The individual has a history of asthma or a current asthma condition
 - The individual has eosinophilia, characterized by greater than 10% of leukocytes or an absolute eosinophil count greater than 1000 cells/ mm^3 (or $>1 \times 10^9$ /L)
- The individual has symptoms despite treatment with oral corticosteroids, unless the individual is intolerant of or has a contraindication to these agents
- Presence of two or more of the following features typical of EGPA:
 - Biopsy showing histopathological evidence of one of the following:
 - Eosinophilic vasculitis
 - Perivascular eosinophilic infiltration
 - Eosinophil-rich granulomatous inflammation
 - Neuropathy
 - Pulmonary infiltrates
 - Sinonasal abnormality
 - Cardiomyopathy
 - Glomerulonephritis
 - Alveolar hemorrhage
 - Palpable purpura
 - Positive test for antineutrophil cytoplasmic antibody (ANCA)
- Mepolizumab (Nucala) will not be used in combination with other biologics for asthma/allergic conditions (e.g., benralizumab [Fasenra], dupilumab [Dupixent], omalizumab [Xolair], reslizumab [Cinqair])

The dosage, frequency, and route of administration for mepolizumab (Nucala) for the treatment of EGPA is 300 mg (i.e., three separate 100-mg injections) administered once every 4 weeks by subcutaneous injection.

INITIAL THERAPY: RESLIZUMAB (CINQAIR)

Severe Eosinophilic Asthma

Reslizumab (Cinqair) is considered medically necessary and, therefore, covered for the treatment of severe eosinophilic asthma when all of the following criteria are met:

- The individual is 18 years of age or older
- Blood eosinophils of at least 400 cells/ μL * at the initiation of treatment (within 3–4 weeks of the first dose)
- The individual is currently receiving treatment that does not maintain adequate control of their asthma and reslizumab (Cinqair) is being used as additional maintenance therapy.
 - Current treatment must include high-dose ICS (with or without oral corticosteroids) plus an additional controller (e.g., LABA, leukotriene inhibitor, theophylline) medication, unless the individual is intolerant of or has a contraindication to these agents.
- Reslizumab (Cinqair) will not be used in combination with other biologics for asthma/allergic conditions (e.g., benralizumab [Fasenra], dupilumab [Dupixent], mepolizumab [Nucala], omalizumab [Xolair])

The dosage, frequency, and route of administration of reslizumab (Cinqair) is 3 mg/kg once every 4 weeks by intravenous infusion.

*Note: 1 μL is equal to 1 cubic millimeter (mm^3).

CONTINUATION THERAPY

Severe Eosinophilic Asthma, Relapsed or Refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Benralizumab (Fasenra), mepolizumab (Nucala), reslizumab (Cinqair) are considered medically necessary and, therefore, covered during continuation therapy for individuals when there is documentation of clinical improvement in respiratory function (e.g., oral corticosteroid elimination or reduction, exacerbation elimination or reduction, reduced absenteeism from school or work) and when they will not be used in combination with other biologics for asthma/allergic conditions (e.g., benralizumab [Fasenra], dupilumab [Dupixent], mepolizumab [Nucala], omalizumab [Xolair], reslizumab [Cinqair]).

Hypereosinophilic Syndrome (HES)

Mepolizumab (Nucala) is considered medically necessary and, therefore, covered during continuation therapy for individuals when there is documentation of oral corticosteroid elimination or reduction and/or clinical improvement in HES-related signs and/or symptoms[†] and when they will not be used in combination with other biologics for asthma/allergic conditions (e.g., benralizumab [Fasenra], dupilumab [Dupixent], mepolizumab [Nucala], omalizumab [Xolair], reslizumab [Cinqair]).

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Mepolizumab (Nucala) is considered medically necessary and, therefore, covered during continuation therapy for individuals, when both of the following criteria are met:

- Documentation of clinical improvement or stabilization of the disease (e.g., reduction in the size of nasal polyps; improvement in nasal discharge, facial pain or pressure, and loss of smell)
- Mepolizumab (Nucala) will not be used in combination with other biologics for asthma/allergic conditions (e.g., benralizumab [Fasenra], dupilumab [Dupixent], mepolizumab [Nucala], omalizumab [Xolair], reslizumab [Cinqair])

EXPERIMENTAL/INVESTIGATIONAL

All other uses for benralizumab (Fasenra), mepolizumab (Nucala), reslizumab (Cinqair) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may

include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

There is no Medicare coverage determination addressing interleukin-5 (IL-5) antagonist (e.g., reslizumab [Cinqair], mepolizumab [Nucala]), and IL-5 receptor antagonist (e.g., benralizumab [Fasenra]); therefore, the Company policy is applicable.

BLACK BOX WARNINGS

RESLIZUMAB (CINQAIR)

Refer to the specific manufacturer's prescribing information for any applicable Black Box Warnings.

NASAL POLYP SCORE (NPS)

Nasal polyp score (NPS) is a measurement of the extent/severity of nasal polyps based on evaluation by nasal endoscopy and scored (range, 0–4 per nostril: 0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 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 turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity) for a total NPS (range, 0–8).

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, interleukin-5 (IL-5) antagonist (e.g., reslizumab [Cinqair], mepolizumab [Nucala]) and IL-5 receptor antagonist (e.g., benralizumab [Fasenra]) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

For Medicare Advantage members, certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when interleukin-5 (IL-5) antagonist (e.g., Cinqair, Nucala) and IL-5 receptor antagonist (e.g., Fasentra) are covered under a member's medical benefit (Part B benefit). It does not address instances when interleukin-5 (IL-5) antagonist (e.g., Cinqair, Nucala) and IL-5 receptor antagonist (e.g., Fasentra) are covered under a member's pharmacy benefit (Part D benefit).

Coverage for (IL-5) antagonist (e.g., reslizumab [Cinqair], mepolizumab [Nucala]) and IL-5 receptor antagonist (e.g., benralizumab [Fasenra]) may be reviewed for coverage through applicable Part D benefits. Individual benefits must be verified.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Benralizumab (Fasentra) was approved by the FDA on November 14, 2017, for the add-on maintenance treatment of individuals with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Supplemental approvals for benralizumab (Fasentra) have since been issued by the FDA.

Mepolizumab (Nucala) was approved by the FDA on November 4, 2015, for the add-on maintenance treatment of individuals with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Supplemental approvals for mepolizumab (Nucala) have since been issued by the FDA.

Reslizumab (Cinqair) was approved by the FDA on March 23, 2016, for the add-on maintenance treatment of individuals with severe asthma aged 18 years and older with an eosinophilic phenotype.

PEDIATRIC USE

BENRALIZUMAB (FASENRA)

The safety and efficacy for the treatment of eosinophilic asthma in pediatric individuals younger than 6 years have not been established. The safety and effectiveness for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) in pediatric individuals younger than 18 years have not been established.

MEPOLIZUMAB (NUCALA)

The safety and effectiveness for the treatment of eosinophilic asthma in pediatric individuals younger than 6 years have not been established. The safety and effectiveness for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) and eosinophilic granulomatosis with polyangiitis (EGPA) in pediatric individuals younger than 18 years have not been established. The safety and effectiveness for the treatment of hypereosinophilic syndrome (HES) in pediatric individuals younger than 12 years have not been established.

RESLIZUMAB (CINQAIR)

Reslizumab (Cinqair) is not indicated for use in pediatric individuals less than 18 years of age. The safety and effectiveness in pediatric individuals (aged 17 years and younger) have not been established.

Description

Asthma is a chronic respiratory disorder characterized by variable and recurring symptoms of airflow obstruction, bronchial hyper-responsiveness, and airway inflammation that can be triggered by environmental allergens, upper respiratory infections, or other stimuli. Eosinophilic asthma is a phenotype of asthma that is associated with tissue and sputum eosinophilia, thickening of the basement membrane zone, and often corticosteroid responsiveness. Sputum cell counts range from 1% to 3% of eosinophils. Reducing the sputum eosinophil count has been shown to be an effective method for preventing severe asthma exacerbations and hospitalizations.

Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly known as the Churg–Strauss syndrome) is a type of vasculitis of the small- and medium-sized arteries. Symptoms of EGPA include allergic rhinitis, asthma, and peripheral blood eosinophilia. Any organ can be affected, but EGPA more commonly affects the lung and skin. Initial treatment begins with systemic glucocorticoids. Immunosuppressants, such as methotrexate, azathioprine, rituximab, and IVIG may be added to control this disease.

Hypereosinophilic syndrome (HES) is a heterogeneous group of rare disorders that are associated with persistently elevated eosinophil levels in blood and/or tissues. Seventy-five percent of the cases are idiopathic, with other causes identified as myeloproliferative neoplasms/disorders (myeloproliferative HES), increased production of interleukin-5 (IL-5) (lymphocytic HES), or a variation of an unknown gene (familial HES). This syndrome is often diagnosed in individuals between 20 and 50 years of age. The clinical presentation of the disease is highly variable depending on the location and severity, but dermatological, respiratory, gastrointestinal, central nervous system, and cardiovascular symptoms are frequently affected. The goal of treatment is the long-term reduction of blood and tissue eosinophil levels to reverse and prevent end-organ damage. The standard of care for treatment consists of glucocorticoids and cytotoxic/immunosuppressive therapy.

Chronic rhinosinusitis with nasal polyps (CRSwNP), also known as nasal polyps, is a severe type of chronic rhinosinusitis that affects about 15% of adults. Individuals present with symptoms for 12 weeks or longer with nasal polyps (benign growths) in the nasal sinus tissue, nasal and sinus inflammation, nasal drainage, nasal congestion, facial pressure or pain, and a decrease in sense of smell. Although the exact mechanism is unknown, elevated IgE activates inflammatory cells such as mast cells, basophils, and eosinophils. Diagnosis is based on symptoms and evidence of nasal polyps by visualization via anterior rhinoscopy, nasal endoscopy, sinus computed tomography (CT), or magnetic resonance imaging (MRI). Options for treatment include saline lavage of sinuses, short-term oral corticosteroids, intranasal corticosteroids, and functional endoscopic sinus surgery; however, nasal polyps can regrow despite corticosteroids and surgery.

BENRALIZUMAB (FASENRA)

Interleukin-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils, a type of white blood cell that contributes to the development of allergic conditions. Benralizumab (Fasenra) is a humanized monoclonal antibody (IgG1 kappa) produced by recombinant DNA technology in Chinese

hamster ovary cells that directly binds to the alpha subunit of IL-5 receptor (IL-5Ra) expressed on the surface of eosinophils and basophils. Benralizumab (Fasenra) recruits natural killer (NK) cells to induce cell death (apoptosis) of eosinophils and basophils, reducing their quantity in the body.

SEVERE ASTHMA WITH EOSINOPHILIC PHENOTYPE

Individuals 12 Years and Older

On November 14, 2017, benralizumab (Fasenra) was approved by the US Food and Drug Administration (FDA) for the add-on maintenance treatment of individuals with severe asthma with an eosinophilic phenotype, aged 12 years and older.

The safety and efficacy of benralizumab (Fasenra) was studied in three phase 3 trials.

TRIALS 1 AND 2

The Efficacy and Safety Study of Benralizumab Added to High-dose Inhaled Corticosteroid Plus LABA in Patients with Uncontrolled Asthma (SIROCCO) trial (a 48-week trial) and Efficacy and Safety Study of Benralizumab in Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β 2 Agonist (CALIMA) (a 56-week trial) were both phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter studies in 2511 subjects. Individuals were between 12 and 75 years of age with asthma for at least 1 year, and at least two exacerbations of asthma (requiring a new or increased dose of oral corticosteroids) within the year while taking medium- to high-dose inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) with or without oral corticosteroids and additional asthma controllers. Individuals were randomly assigned (1:1:1) to receive the add-on treatment of one of the following:

- benralizumab (Fasenra) 30 mg every 4 weeks (Q4W)
- benralizumab (Fasenra) 30 mg every 4 weeks for three doses, then every 8 weeks thereafter (Q8W)
- placebo every 4 weeks

Subjects were stratified 2:1 according to blood eosinophil counts of at least 300 cells/ μ L and less than 300 cells/ μ L. The primary endpoint was annual exacerbation rate ratio versus placebo, which is the total number of exacerbations times 365.25 divided by total duration of follow-up within the treatment group (days).

In the SIROCCO trial, subjects with blood eosinophil counts of at least 300 cells/ μ L who received benralizumab (Fasenra) had a statistically significant reduction in the annual exacerbation rate ratio by 45% (Q4W) and 51% (Q8W) compared with placebo. Subjects with blood eosinophil counts of less than 300 cells/ μ L who received benralizumab (Fasenra) Q4W also had a statistically significant reduction in the annual exacerbation rate ratio compared with placebo (30%), although Q8W did not (17%). Adverse events were similar between all treatment groups.

In the CALIMA trial, subjects with blood eosinophil counts of at least 300 cells/ μ L who received benralizumab (Fasenra) had a statistically significant reduction in the annual exacerbation rate ratio by 36% (Q4W) and 28% (Q8W) compared with placebo. Although not a primary endpoint, subjects with blood eosinophil counts of less than 300 cells/ μ L who received benralizumab (Fasenra) also had a statistically significant reduction in the annual exacerbation rate ratio by 36% (Q4W) and 40% (Q8W) compared with placebo. Adverse events were similar between all treatment groups.

A subanalysis of the SIROCCO and CALIMA trials was performed to compare the primary endpoint in those with blood eosinophil counts of at least 150 cells/ μ L versus less than 150 cells/ μ L. The Q4W group was not included in the analysis. In those with blood eosinophil counts of at least 150 cells/ μ L, the benralizumab (Fasenra) Q8W had a statistically significant reduction in the annual exacerbation rate ratio by 42% (SIROCCO) and 36% (CALIMA) compared with placebo. In those with blood eosinophil counts less than 150 cells/ μ L, the benralizumab (Fasenra) Q8W had favorable, but not statistically significant reduction in the annual exacerbation rate ratio by 24% (SIROCCO) and 35% (CALIMA) compared with placebo.

A pooled analysis of the SIROCCO and CALIMA trials was performed to compare the primary endpoint analyzed by blood eosinophil counts of at least ≥ 0 , ≥ 150 , ≥ 300 , or ≥ 450 cells/ μ L. Researchers found that those with higher baseline blood eosinophil counts treated with benralizumab (Fasenra) had an increased degree of improvement in annual exacerbation rate ratio, compared to those with lower baseline blood eosinophil counts. When annual exacerbation rate ratio was stratified by blood eosinophil counts (i.e., < 150 , 150–299, 300–449, ≥ 450 cells/ μ L), those with counts < 150 cells/ μ L who had benralizumab (Fasenra) Q4W or Q8W, had favorable, but not statistically significant reductions in the annual exacerbation rate ratio compared to placebo. Similarly, in those with baseline blood eosinophil counts of 150 to 299 cells/ μ L, Q8W, had favorable but not statistically significant reduction in the

annual exacerbation rate ratio compared to placebo.

TRIAL 3

The Efficacy and Safety Study of Benralizumab to Reduce OCS Use in Patients With Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus LABA and Chronic OCS Therapy (ZONDA) trial assessed the safety and efficacy of benralizumab (Fasenra) as an oral glucocorticoid-sparing therapy in this 28-week, randomized, double-blind, parallel-group, placebo-controlled, Phase 3 trial. Participants were 220 adults who required oral glucocorticoid to manage their severe eosinophilic asthma. Inclusion criteria included blood eosinophil counts of 150 cells/ μ L or more, one exacerbation of asthma in the previous 12 months, and were on a regimen containing high-dose ICS, LABA, oral glucocorticoid therapy for at least 6 months (equivalent to prednisone 7.5–40 mg/d), and, if needed, additional asthma controller (e.g., leukotriene inhibitor, theophylline) medication.

During the run-in phase (Week –8), the dose of the oral glucocorticoid was reduced to the minimum dose required to control asthma. At Week 0, individuals were randomly assigned (1:1:1) similarly to the prior trials, benralizumab (Fasenra) Q4W, Q8W, or placebo every 4 weeks for 28 weeks. During weeks 0 to 4, the oral glucocorticoid dose remained unchanged. Weeks 4 to 24 was the oral glucocorticoid reduction phase during which daily doses were reduced every 4 weeks by 2.5 to 5 mg; in those who had worsening asthma, the dose was increased to the most recent effective dose and maintained. During weeks 24 to 28, the oral glucocorticoid dose was maintained.

The primary end point was the percentage reduction in the oral glucocorticoid dose from baseline (randomization at week 0) to the final dose at the end of the maintenance phase (week 28) while asthma control was maintained. Results showed a statistically significant median reduction from baseline of 75% in those who received benralizumab (Fasenra) Q4W or Q8W, as compared with a reduction of 25% in those who received placebo ($P < 0.001$ for both comparisons). Approximately 85% of the subjects had a median blood eosinophil count 300 cells/ μ L or higher; however, the results were not stratified to median blood eosinophil counts of both 150 to 299 and 300 or higher cells/ μ L.

Individuals 6 to 11 Years and of Age

On April 5, 2024, benralizumab (Fasenra) was approved by the FDA for the add-on maintenance treatment of individuals with severe asthma with an eosinophilic phenotype, aged 6 years and older.

The effectiveness is extrapolated from three clinical trials (SIROCCO, CALIMA, and ZONDA) with support from pharmacokinetic analysis and pharmacodynamic response in pediatric individuals aged 6 to 11 years compared to adults and adolescents. The pharmacokinetic, pharmacodynamic, and safety data were assessed in a 48-week, open-label, trial (PK/PD and Long Term Safety Study of Benralizumab in Children With Severe Eosinophilic Asthma [TATE]) conducted in 28 individuals aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype; data were similar with those observed in older individuals from SIROCCO, CALIMA, and ZONDA trials.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

Benralizumab (Fasenra) was approved by the FDA on September 17, 2024, for the treatment of adults with EGPA (formerly known as Churg–Strauss syndrome).

The safety and effectiveness of benralizumab (Fasenra) was studied in a multicenter, double-blind, phase 3, randomized, active-controlled noninferiority trial (MANDARA) of 140 adults with relapsing/refractory EGPA on oral corticosteroid (OCS) with or without immunosuppressive therapy. Individuals had a history or presence of asthma, a blood eosinophil level of 10% or an absolute eosinophil count of more than 1000 cells per cubic millimeter, and the presence of two or more criteria that are typical of EGPA (biopsy showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation; neuropathy; pulmonary infiltrates; sinonasal abnormality; cardiomyopathy; glomerulonephritis; alveolar hemorrhage; palpable purpura; or antineutrophil cytoplasmic antibody [ANCA], MPO, and/or PR3 positivity). Individuals were randomly assigned (1:1) to receive benralizumab (Fasenra) 30 mg SC every 4 weeks or mepolizumab (Nucala) 300 mg SC every 4 weeks. Starting at Week 4, the OCS dose was tapered at the discretion of the investigator. The primary endpoint was remission (defined as a Birmingham Vasculitis Activity Score [BVAS] of 0 and an oral glucocorticoid dose of ≤ 4 mg per day) at weeks 36 and 48. The study demonstrated benralizumab (Fasenra) is noninferior to mepolizumab (Nucala) since the adjusted percentage of individuals with remission at 36 and 48 weeks was 59% in the benralizumab (Fasenra) arm when compared to 56% in the mepolizumab (Nucala) arm. The safety profile of each arm was similar.

MEPOLIZUMAB (NUCALA)

Mepolizumab (Nucala) is a humanized IL-5 antagonist monoclonal antibody (IgG1 kappa) produced by recombinant DNA technology in Chinese hamster ovary cells. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils, a type of white blood cell that contributes to the development of inflammation, which is an important component in the pathogenesis of asthma, CRSwNP, EGPA, and HES. Mepolizumab (Nucala) binds to IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface.

SEVERE ASTHMA WITH EOSINOPHILIC PHENOTYPE Individuals 12 Years and Older

On November 4, 2015, mepolizumab (Nucala) was approved by the FDA for the add-on maintenance treatment of individuals with severe asthma with an eosinophilic phenotype, aged 12 years and older.

A total of 1327 subjects with asthma were evaluated in three randomized, placebo-controlled multicenter trials of 24 to 52 weeks duration. Of these, 1192 subjects had a history of two or more exacerbations in the year prior to enrollment despite regular use of high-dose IHS plus an additional controller(s), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose IHS plus an additional controller(s) to maintain asthma control. All subjects had markers of eosinophilic airway inflammation and blood eosinophils of at least 150 cells/ μ L at initiation of treatment or blood eosinophils of at least 300 cells/ μ L in the last 12 months. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab (Nucala) was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received mepolizumab (Nucala) by subcutaneous route for at least 24 weeks. Compared with placebo, individuals with severe asthma receiving mepolizumab (Nucala) had fewer exacerbations requiring hospitalization and/or emergency department visits, and a longer time to the first exacerbation. In addition, individuals with severe asthma receiving mepolizumab (Nucala) experienced greater reductions in their daily maintenance oral corticosteroid dose, while maintaining asthma control, compared with individuals receiving placebo. Treatment with mepolizumab (Nucala) did not result in a significant improvement in lung function, as measured by the volume of air exhaled by individuals in one second.

Serious adverse events that occurred in more than one individual and in a greater percentage of individuals treated with mepolizumab (Nucala) (n=263) than placebo (n=257) included one event, herpes zoster (two vs. 0 individuals, respectively). Approximately 2% of individuals withdrew from clinical trials due to adverse events (e.g., headache, injection site reaction) compared with 3% of individuals receiving placebo.

Pediatric Individuals 6 Years and Older

On September 12, 2019, mepolizumab (Nucala) was approved by the FDA for the add-on maintenance treatment of pediatric individuals with severe asthma with an eosinophilic phenotype, aged 6 years and older.

Use of mepolizumab (Nucala) in children aged 6 to 11 years with severe asthma with an eosinophilic phenotype is thought to be supported by trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in children ages 6 to 11 years. A single, open-label clinical trial was conducted in 36 children ages 6 to 11 years with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial. Based on the pharmacokinetic data from this trial, a dose of 40 mg subcutaneously (SC) every 4 weeks was determined to have similar exposure to adults and adolescents administered at a dose of 100 mg SC.

The efficacy of mepolizumab (Nucala) in children aged 6 to 11 years is extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks in children aged 6 to 11 years compared with adults and adolescents. The safety profile and pharmacodynamic response observed in this trial for children aged 6 to 11 years were similar to that seen in adults and adolescents.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSwNP)

On July 29, 2021, mepolizumab (Nucala) was approved by the FDA for the add-on maintenance therapy of CRSwNP in adults with inadequate response to nasal corticosteroids.

The safety and efficacy of mepolizumab (Nucala) were evaluated in a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter, 52-week trial of 407 adults with CRSwNP. Inclusion criteria consisted of individuals with recurrent, refractory, severe, bilateral, symptomatic CRSwNP with at least one surgery for the

removal of nasal polyps within the previous 10 years, nasal corticosteroid use for 8 weeks or longer pre-screening, nasal obstruction symptoms with a visual analog scale (VAS) score of greater than 5 out of a maximum score of 10, endoscopic bilateral nasal polyp score (NPS) of 5 or higher out of 8 with NPS 2 or higher in each nasal cavity, individual-reported nasal obstruction VAS scores which consisted of two or more different symptoms for at least 12 weeks before screening (nasal blockage, obstruction, and congestion, or nasal discharge [anterior or posterior nasal drip]), with one or more of the following symptoms: nasal discharge, facial pain or pressure, and reduction or loss of smell. In this study, individuals received mepolizumab (Nucala) 100 mg or placebo administered subcutaneously once every 4 weeks while continuing nasal corticosteroid therapy. Results of the study confirmed that individuals who received mepolizumab (Nucala) had a statistically significant improvement (decrease) in bilateral NPS at Week 52 compared to baseline ($P<0.0001$), and improvement in nasal obstruction VAS score from Weeks 49 to 52 compared to baseline ($P<0.0001$). The proportion of individuals who had on-treatment adverse events was similar between the two groups (169 [82%] in the mepolizumab (Nucala) group and 168 [84%] in the placebo group).

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

Mepolizumab (Nucala) was approved by the FDA on December 17, 2017, for the treatment of adults with EGPA (formerly known as Churg–Strauss syndrome).

The safety and efficacy of mepolizumab (Nucala) was studied in 136 adults with relapsing or refractory EGPA in a phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter trial over 52 weeks. Participants had a history or presence of asthma, a blood eosinophil level of 10% or an absolute eosinophil count of more than 1000 cells per cubic millimeter, and the presence of two or more criteria that are typical of EGPA (biopsy showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation; neuropathy; pulmonary infiltrates; sinonasal abnormality; cardiomyopathy; glomerulonephritis; alveolar hemorrhage; palpable purpura; or antineutrophil cytoplasmic antibody [ANCA] positivity).

Participants received 300 mg mepolizumab (Nucala) or placebo subcutaneously every 4 weeks. They were required to be on a stable dose of oral corticosteroids 4 weeks prior to baseline; doses could be tapered during the study. If required, those who were taking immunosuppressives were required to remain at a stable dose 4 weeks prior to baseline and continue throughout the study.

The first primary end point was the total accrued weeks of remission, defined as a Birmingham Vasculitis Activity Score (BVAS, version 3) of 0 on a scale from 0 to 63 (with 0 meaning no disease activity and higher scores indicating greater disease activity) and the receipt of prednisolone or prednisone at a dose of 4 mg or less per day over the 52-week period. Those who received mepolizumab (Nucala) had a greater percentage of participants who had remission over the 52-week period, measured at 0 weeks, 0 to less than 12 weeks, 12 to less than 24 weeks, 24 to less than 36 weeks, and for at least 36 weeks (odds ratio [OR], $P<0.001$). The second primary end point was the percentage of participants who had remission at both week 36 and week 48. Those who received mepolizumab (Nucala) had a statistically significant greater percentage of participants achieving remission at both 36 and 48 weeks (32% vs 3%) (OR, $P<0.001$). There was no significant differences between the two groups in the occurrence of adverse reactions; however, there was a greater percentage of serious adverse events in those in the placebo group (26%) when compared to the mepolizumab (Nucala) group (18%). This observation could be related to relapsing disease.

HYPEREOSINOPHILIC SYNDROME (HES)

Mepolizumab (Nucala®) was approved by the FDA on September 25, 2020, for the treatment of adult and pediatric individuals aged 12 years and older with HES for 6 months or longer without an identifiable nonhematologic secondary cause.

The safety and efficacy of mepolizumab (Nucala) was studied in 108 adults and adolescents aged 12 years and older with *FIP1L1-PDGFR*A–negative HES for at least 6 months in a phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter trial over 32 weeks. Participants had experienced uncontrolled HES, defined as two or more flares in the previous 12 months and a blood eosinophil count at or higher than 1000 cells/ μ L at screening. Flares were defined as worsening of HES-related symptoms or blood eosinophil count requiring HES therapy escalation. Participants had been receiving stable background HES therapy (e.g., oral corticosteroids, immunosuppressive and/or cytotoxic therapy, such as hydroxyurea, cyclosporine, imatinib, methotrexate, tacrolimus, and azathioprine) for at least 4 weeks before and including randomization. HES diagnosis was based on organ system involvement and/or dysfunction that could be directly related to a blood eosinophil count higher than 1500 cells/ μ L on at least two occasions, and/or tissue eosinophilia, without a discernible secondary cause. Historical flares were defined as a worsening of HES-related clinical symptoms or a blood eosinophil count requiring an escalation in

therapy; at least one flare within the past 12 months had to be unrelated to a decrease in HES therapy in the preceding 4 weeks.

Participants received 300 mg mepolizumab (Nucala) or placebo subcutaneously every 4 weeks while continuing their stable HES therapy. The primary outcome was the proportion of participants with at least one flare, defined as worsening of HES-related symptoms necessitating HES therapy escalation or two or more courses of blinded rescue oral corticosteroids during the study. Participants who withdrew early from the study were included in this result as well. Those who received mepolizumab (Nucala) had a statistically significant reduction (50%; $P=0.002$), in the occurrence of HES flares (28%) compared to the placebo group (56%). There were no significant differences between the two groups in the occurrence of adverse reactions.

RESLIZUMAB (CINQAIR)

On March 23, 2016, reslizumab (Cinqair) was FDA-approved for the add-on maintenance treatment of individuals with severe asthma with an eosinophilic phenotype who are aged 18 years and older. Reslizumab (Cinqair) is a humanized IL-5 antagonist monoclonal antibody produced by recombinant technology in murine myeloma nonsecreting 0 (NS0) cells.

Reslizumab (Cinqair) approval was based on four randomized, double-blind, placebo-controlled studies. Studies I and II were 52-week studies in 953 individuals with severe asthma who were required to have a blood eosinophil count of at least 400 cells/ μ L, and at least one asthma exacerbation requiring systemic corticosteroid use over the past 12 months. The majority of individuals (82%) were on medium-high dose IHS plus a long-acting beta agonist (ICS/LABA) at baseline. Maintenance oral corticosteroids were allowed. The primary endpoint was the frequency of asthma exacerbations. In both studies, individuals on reslizumab (Cinqair) had a statistically significant reduction in the rate of all asthma exacerbations (episodes requiring systemic corticosteroid use and exacerbations resulting in hospitalization and/or emergency room visit) compared to the placebo. The forced expiration volume in 1 second (FEV_1) was also observed during the studies. Improvements were observed at four weeks after the first dose of reslizumab (Cinqair) and maintained through Week 52.

Study 3 was a 16-week study on 315 individuals with severe asthma with a blood eosinophil count of at least 400 cells/ μ L at screening. Maintenance oral corticosteroids were not allowed. Individuals received 3 mg/kg or 0.3 mg/kg of reslizumab (Cinqair) once every 4 weeks for a total of four doses compared to placebo. Reslizumab (Cinqair) at 3 mg/kg is the recommended dose. The primary endpoint was FEV_1 . Improvements in FEV_1 were observed at 4 weeks following the first dose of reslizumab (Cinqair).

Study 4 was a 16-week study on 496 individuals with severe asthma. Baseline blood eosinophil levels were not taken into account for selection. The majority of the participants had a blood eosinophil level of less than 400 cells/ μ L at screening. Maintenance oral corticosteroids were not allowed. Individuals were randomly assigned to receive either reslizumab (Cinqair) 3 mg/kg once every 4 weeks or placebo for a total of four doses. The primary endpoint was FEV_1 . There was no association of treatment effect and baseline blood eosinophils observed in asthma individuals unselected for blood eosinophils. In the subgroup of individuals with eosinophil count at least 400 cells/ μ L, the treatment of reslizumab (Cinqair) was associated with a significant improvement in FEV_1 compared to the placebo.

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

N/A

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

HCPCS Level II Code Number(s)

J0517 Injection, benralizumab, 1 mg
J2182 Injection, mepolizumab, 1 mg
J2786 Injection, reslizumab, 1 mg

Revenue Code Number(s)

N/A

Policy History

Revisions From MA08.024m:

06/13/2025	<p>This version of the policy will become effective 06/13/2025.</p> <p>This policy has been updated to communicate the Company's coverage position for the medically necessary use of benralizumab (Fasenra) for the treatment of adults with eosinophilic granulomatosis with polyangiitis (EGPA). Additionally, the pediatric dosage and frequency were included for benralizumab (Fasenra) for the treatment of severe eosinophilic asthma.</p> <p>All of the ICD-10 CM codes have been removed from this policy, since they are informational. Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.</p>
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Revisions From MA08.024l:

12/16/2024	<p>This version of the policy will become effective 12/16/2024.</p> <p>This policy has been updated to communicate the Company's coverage position for the Medically Necessary use of benralizumab (Fasenra) for the treatment of severe eosinophilic asthma in pediatric individuals 6 to 11 years of age.</p> <p>The following ICD-10 CM code has been deleted from this policy: I77.82 Antineutrophilic cytoplasmic antibody (ANCA) vasculitis</p>
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Revisions From MA08.024k:

05/07/2024	<p>This policy has been reissued in accordance with the Company's annual review process.</p>
10/01/2022	<p>This version of the policy will become effective 10/01/2022.</p> <p>The following ICD-10 code has been added to this policy: I77.82 Antineutrophilic cytoplasmic antibody [ANCA] vasculitis</p>

Revisions From MA08.024j:

05/23/2022	<p>This version of the policy will become effective 05/23/2022.</p> <p>This policy has been updated to communicate the Company's coverage position for the Medically Necessary use of mepolizumab (Nucala) for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP).</p> <p>The following ICD-10 CM codes were added: D72.110 Idiopathic hypereosinophilic syndrome [IHES]</p>
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	D72.111 Lymphocytic Variant Hypereosinophilic Syndrome [LHES] J33.0 Polyp of nasal cavity J33.1 Polypoid sinus degeneration J33.8 Other polyp of sinus J33.9 Nasal polyp, unspecified
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Revisions From MA08.024i:

10/04/2021	This version of the policy will become effective 10/04/2021. The following criterion was added to each drug and indication for Initial and Continuation Therapy. <ul style="list-style-type: none"> • <i>Fasenra, Nucala, and Cinqair</i> "will not be used in combination with other biologics for asthma/allergic conditions (e.g., benralizumab [Fasenra], dupilumab [Dupixent], mepolizumab [Nucala], omalizumab [Xolair], reslizumab [Cinqair])" Clarification of a six-week timeframe for blood eosinophil count measurements for mepolizumab (Nucala).
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Revisions From MA08.024h:

01/01/2021	This policy was updated to communicate the Company's coverage position for the newly FDA-approved indication for mepolizumab (Nucala) for the treatment of hypereosinophilic syndrome (HES) in individuals ages 12 years and older. The following ICD-10 CM code was added to this policy: D72.119 Hypereosinophilic syndrome [HES], unspecified
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Revisions From MA08.024g:

10/01/2020	This policy has been identified for the ICD-10 CM code update, effective 10/01/2020. The following ICD-10 CM code was deleted from this policy: J82 Pulmonary eosinophilia, not elsewhere classified The following ICD-10 CM code was added to this policy: J82.83 Eosinophilic asthma
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Revisions From MA08.024f:

12/16/2019	This policy was updated to reflect the coverage criteria of Nucala for eosinophilic asthma for ages 6 years and older, in accordance with FDA-approval. Coverage criteria regarding timeframes was revised for Nucala for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA). Parameters were outlined for all agents' Continuation Therapy criteria.
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Revisions From MA08.024e:

01/01/2019	This policy has been identified for the HCPCS code update, effective 01/01/2019. The following HCPCS code has been added to this policy: J0517 Injection, benralizumab, 1 mg The following HCPCS codes have been removed from this policy: C9466 Injection, benralizumab, 1 mg J3590 Unclassified biologics
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Revisions From MA08.024d:

04/09/2018	<p>This policy has undergone a routine review, and the medical necessity criteria have been revised as follows:</p> <p>The coverage criteria was included for the newly FDA-approved drug, benralizumab (Fasenra™) for the treatment of severe asthma with an eosinophilic phenotype.</p> <p>The coverage criteria was also included for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) with mepolizumab (Nucala®).</p>
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Revisions From MA08.024c:

08/02/2017	This policy has been reissued in accordance with the Company's annual review process.
01/01/2017	<p>This policy has been identified for the HCPCS code update, effective 01/01/2017.</p> <p>The following HCPCS code has been termed from this policy: C9473 Injection, mepolizumab, 1 mg</p> <p>The following NOC code has been removed from this policy and is replaced by the following HCPCS code: REMOVED: J3590 Unclassified biologics REPLACED WITH: CJ2182 Injection, mepolizumab, 1 mg AND J2786 Injection, reslizumab, 1 mg</p>

Revisions From MA08.024b:

06/15/2016	This version of the policy will become effective 06/15/2016. This policy has been updated to include the addition of Reslizumab (Cinqair®), a new FDA-approved drug. The name of the policy was changed from mepolizumab (Nucala®) to Interleukin-5 Antagonist for Severe Eosinophilic Asthma (e.g. Nucala®, Cinqair®).
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Revisions From MA08.024a:

04/01/2016	<p>This policy has been identified for the HCPCS code update, effective 04/01/2016.</p> <p>The following HCPCS code has been added to this policy:</p> <p>Healthcare Common Procedure Coding System (HCPCS) C Series Codes can only be reported for outpatient facility services. Professional providers should not report HCPCS C Series Codes for professional services regardless of where those services are performed: C9473 Injection, mepolizumab, 1 mg</p>
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Revisions From MA08.024:

01/01/2016	New policy number MA08.024 was issued to communicate medical necessity criteria for mepolizumab (Nucala).
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Version Effective Date:
06/13/2025
Version Issued Date:
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Version Reissued Date:
N/A