mepolizumab (Nucala®)

Medicare Advantage Medical Policy #MA-165
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Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Note that this authorization (if granted) is for the vial only. It is not for the syringe or the auto-injector. If this authorization is granted, it is only for the medical benefit.

Based on review of available data, the Health Plan may consider mepolizumab (Nucala®)‡ for add-on maintenance treatment of severe asthma (eosinophilic phenotype), OR for the treatment of patients with eosinophilic granulomatosis with polyangiitis (EGPA), OR for the treatment of hypereosinophilic syndrome (HES), OR for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP), OR for the add-on maintenance treatment of chronic obstructive pulmonary disease (COPD) to be **eligible for coverage.****

Asthma

Patient Selection Criteria

Coverage eligibility for mepolizumab (Nucala) will be considered for add-on maintenance treatment of severe asthma (eosinophilic phenotype) when the following criteria are met:

Initial Authorization:

I. Nucala is being used for the treatment of severe asthma (eosinophilic phenotype); AND
II. Patient is greater than or equal to 6 years of age; AND
III. Nucala is NOT being used in combination with other monoclonal antibodies typically used to treat asthma (e.g., reslizumab [Cinqair®]‡, omalizumab [Xolair®], benralizumab [Fasenra™], dupilumab [Dupixent®])‡; AND
IV. Nucala is dosed at 100 mg every 4 weeks for those 12 years of age and older OR 40 mg every 4 weeks for those 6 to 11 years of age; AND
V. Patient meets ONE of the following (a **or** b):
    a) Patient has a peripheral blood eosinophil count of ≥ 150 cells per microliter within the previous 6 weeks (prior to treatment with Nucala) OR a peripheral blood eosinophil count of ≥ 150 cells per microliter within 6 weeks prior to treatment with any monoclonal antibody that may alter blood eosinophil levels (e.g., reslizumab [Cinqair], omalizumab [Xolair], benralizumab [Fasenra], dupilumab [Dupixent]); OR
    b) Patient is dependent on systemic corticosteroids; AND

VI. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a **and** b):
   a) An inhaled corticosteroid (ICS), (e.g., fluticasone products [Arnuity™ Ellipta®, Armonair™ Respiclick®]‡, mometasone products [Asmanex® Twisthaler®, Asmanex® HFA]‡, flunisolide products [Aersopan™]‡, ciclesonide products [Alvesco®]‡, budesonide products [Pulmicort Flexhaler®]‡, beclomethasone products [QVAR®]‡); AND
   b) At least ONE of the following (1, 2, 3, **or** 4):
      1) Inhaled long-acting beta-agonist (LABA), (e.g., salmeterol products [Serevent® Diskus]‡, olodaterol products [Striverdi® Respimat®]‡, indacaterol products [Arcapta™ Neohaler™]‡); OR
      Note: Use of a combination inhaler containing both an ICS and a LABA would fulfil the requirement for both criteria a.) and b.) (e.g., fluticasone propionate and salmeterol inhalation powder/aerosol [Advair® Diskus/HFA, fluticasone/salmeterol generics, Wixela™ Inhub, AirDuo™ Respiclick]‡, budesonide and formoterol fumarate inhalation aerosol [Symbicort®]‡, fluticasone furoate and vilanterol inhalation powder [Breo® Ellipta®]‡, mometasone furoate and formoterol fumarate inhalation aerosol [Dulera®]‡).
      2) Inhaled long-acting muscarinic antagonist (LAMA), (e.g., tiotropium bromide inhalation spray [Spiriva® Respimat®, Spiriva Handihaler®, Stiolto® Respimat]‡, aclidinium products [Tudorza® Pressair®]‡, glycopyrrolate products [Seebri™ Neohaler, Bevespi™ Aerosphere, Utibron™ Neohaler]‡, umeclidinium products [Incruse® Ellipta, Anoro® Ellipta ‡]); OR
      3) Leukotriene receptor antagonist (LTRA), (e.g., montelukast tablets/granules [Singulair®, generics], zafirlukast tablets [Accolate®])‡; OR
      4) Theophylline (Theo-24, Uniphyl, TheoChron ER, generics); AND

VII. Patient's asthma continues to be uncontrolled as defined by ONE of the following (a, b, c, d, **or** e):
   a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
   b) Patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) visit in the previous year; OR
   c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
   d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
   e) Patient's asthma worsens upon tapering of oral corticosteroid therapy.

Re-Authorization

I. Patient received an initial authorization for the requested drug from the plan OR has provided documentation of authorization for an active course of treatment from previous health plan; AND
II. Nucala is being used for the treatment of severe asthma (eosinophilic phenotype); AND
III. Nucala is NOT being used in combination with other monoclonal antibodies typically used to treat asthma (e.g., reslizumab [Cinqair], omalizumab [Xolair], benralizumab [Fasenra], dupilumab [Dupixent]); AND

IV. Nucala is dosed at 100 mg every 4 weeks for those 12 years and older OR 40 mg every 4 weeks for those 6 to 11 years of age; AND
V. Patient continues to receive the medications required in criterion VI. in the "Initial Criteria"; AND
VI. Patient has responded to Nucala therapy as determined by the prescribing physician (e.g., decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, ED/urgent care, or physician visits due to asthma; decreased requirement for oral corticosteroid therapy.)

Eosinophilic Granulomatosis with Polyangiitis

Patient Selection Criteria

Coverage eligibility for mepolizumab (Nucala) will be considered for the treatment of EGPA when the following criteria are met:

Initial Authorization:

I. Patient has a diagnosis of EGPA; AND
II. Patient is 18 years of age or older; AND
III. Patient has tried and failed (e.g., intolerance or inadequate response) a corticosteroid (e.g., prednisone) for a minimum of 4 weeks unless there is clinical evidence or patient history that suggests the use of a corticosteroid for at least 4 weeks will be ineffective or cause an adverse reaction to the patient; AND
IV. Patient has/had a blood eosinophil level of ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin therapy (e.g., reslizumab [Cinqair], omalizumab [Xolair], benralizumab [Fasenra], dupilumab [Dupixent]); AND
V. Nucala is dosed at 300 mg every 4 weeks.

Re-Authorization

I. Patient received an initial authorization for the requested drug from the plan OR has provided documentation of authorization for an active course of treatment from previous health plan; AND
II. Patient has a diagnosis of EGPA; AND
III. Nucala is dosed at 300 mg every 4 weeks; AND
IV. Patient has responded to Nucala therapy as determined by the prescribing physician (e.g., reduced rate of relapse, corticosteroid dose reduction, reduced eosinophil levels).

Hypereosinophilic Syndrome

Patient Selection Criteria

Coverage eligibility for mepolizumab (Nucala) will be considered for the treatment of HES when the following criteria are met:

Initial Authorization:

I. Patient has a diagnosis of HES; AND
II. HES has been present for at least 6 months; AND

III. HES does NOT have an identifiable non-hematologic secondary cause (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy) AND patient does NOT have *FIP1L1-PDGFRα* kinase-positive HES; AND
IV. Patient is 12 years of age or older; AND
V. Patient has a blood eosinophil level of ≥ 1,000 cells per microliter prior to therapy; AND
VI. Patient has been on stable therapy for HES and will continue HES therapy (oral steroids, immunosuppressive agents, and/or cytotoxic agents); AND
VII. Patient has experienced at least 2 HES flares within the past 12 months (at least one of which is unrelated to a decrease in HES therapy in the 4 weeks prior to the flare). An HES flare is defined as HES related worsening of clinical symptoms or blood eosinophil counts requiring an escalation of therapy; AND
VIII. Nucala is dosed at 300 mg every 4 weeks.

Re-Authorization

I. Patient received an initial authorization for the requested drug from the plan OR has provided documentation of authorization for an active course of treatment from previous health plan; AND
II. Patient has a diagnosis of HES; AND
III. Nucala is dosed at 300 mg every 4 weeks; AND
IV. Patient has responded to Nucala therapy as determined by the prescribing physician (e.g., reduced rate of flares, improvement in symptoms, etc.).

Chronic Rhinosinusitis with Nasal Polyps

Patient Selection Criteria

Coverage eligibility for mepolizumab (Nucala) will be considered for the treatment of CRSwNP when the following criteria are met:

Initial Authorization

I. Patient has inadequately controlled chronic rhinosinusitis with nasal polyps; AND
II. Patient is 18 years of age or older; AND
III. Patient has recurrent polyposis after at least ONE surgical resection (unless resection is contraindicated); AND
IV. Patient's nasal polyposis has been confirmed as grade 3 or higher with nasal endoscopy; AND
V. Patient's polyposis recurrence occurred within 6 months of at least one high dose oral steroid taper after the most recent resection unless there is clinical evidence or patient history that suggests the use of a high dose oral steroid taper will be ineffective or cause an adverse effect to the patient; AND
VI. Patient meets BOTH of the following (a **and** b):
    a) Patient has received at least 4 weeks of therapy with an intranasal corticosteroid (e.g., fluticasone, mometasone, Xhance®)‡; AND
    b) Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Nucala (if the intranasal corticosteroid was tolerated); AND

VII. Requested drug is NOT being used in combination with other monoclonal antibodies typically used to treat nasal polyps (e.g., omalizumab [Xolair], dupilumab [Dupixent]); AND
VIII. Nucala is dosed at 100 mg every 4 weeks.

Re-Authorization

I. Patient has received an initial authorization for the requested drug from the plan OR has provided documentation of authorization for an active course of treatment from previous health plan; AND
II. Patient will continue to use an intra-nasal corticosteroid (e.g., fluticasone, mometasone, Xhance) in combination with Nucala (if the intra-nasal corticosteroid was tolerated); AND
III. Requested drug is NOT being used in combination with other monoclonal antibodies typically used to treat nasal polyps (e.g., omalizumab [Xolair], dupilumab [Dupixent]); AND
IV. Patient has responded to requested therapy as determined by the prescribing physician (e.g., decrease in nasal polyps, decreased congestion/obstruction, etc.); AND
V. Nucala is dosed at 100 mg every 4 weeks.

Chronic Obstructive Pulmonary Disease

Based on review of available data, the Health Plan may consider mepolizumab (Nucala) for the treatment of chronic obstructive pulmonary disease to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for mepolizumab (Nucala) for the treatment of chronic obstructive pulmonary disease will be considered when the patient selection criteria are met:

Initial Authorization

I. Patient has a diagnosis of chronic obstructive pulmonary disease (COPD) confirmed by post-bronchodilator $FEV_1/FVC < 0.7$ on spirometry; AND
II. Nucala will be used as add-on maintenance treatment; AND
III. Nucala will not be used in combination with ensifentrine (Ohtuvayre™)‡ or dupilumab (Dupixent); AND
IV. Patient is 18 years of age or older; AND
V. Nucala is dosed at 100 mg every 4 weeks; AND
VI. Patient meets one of the following (a **or** b):
    a) Patient has a blood eosinophil level of greater than or equal to 300 cells per microliter within the previous 6 weeks; OR
    b) Patient had a blood eosinophil level greater than or equal to 300 cells per microliter prior to treatment with Nucala or another monoclonal antibody therapy (e.g., dupilumab [Dupixent], reslizumab [Cinqair], benralizumab [Fasenra], tralokinumab-ldrm [Adbry]) that may alter blood eosinophil levels; AND
VII. Patient meets ONE of the following (a **or** b):
    a) Patient has received at least 3 consecutive months of combination therapy with ALL of the following (1, 2, **and** 3):
        1) Inhaled long-acting beta 2-agonist (LABA) (e.g., Serevent® Diskus [salmeterol xinafoate], Striverdi® Respimat [olodaterol], Brovana®

[arformoterol tartrate, generic], and Perforomist® [formoterol fumarate])‡; AND

2) Inhaled long-acting muscarinic antagonist (LAMA) (e.g., Incruse® Ellipta [umeclidinium], Spiriva® HandiHaler [tiotropium bromide], Spiriva® Respimat [tiotropium bromide], Tudorza® Pressair [aclidinium bromide], and Yupelri®‡ [revefenacin])‡; AND
3) Inhaled corticosteroid (ICS)(e.g., Advair Diskus [fluticasone propionate and salmeterol], Breo Ellipta [fluticasone furoate and vilanterol], Symbicort [budesonide and formoterol fumarate]); OR

Note: Use of a combination inhaler containing an ICS, a LABA, and a LAMA would fulfill the requirement for criterion a.) (e.g., Breztri Aerosphere™‡ [budesonide, glycopyrrolate, and formoterol fumarate], Trelegy Ellipta [fluticasone furoate, umeclidinium, and vilanterol])

b) Patient meets BOTH of the following (1 **and** 2):
1) Patient has received at least 3 consecutive months of combination therapy with an inhaled LABA and an inhaled LAMA; AND
2) According to the prescriber, the patient has a contraindication to the use of an inhaled corticosteroid; AND

Note: Use of a combination inhaler containing a LAMA and LABA would fulfill the requirement for criterion b.) (e.g., Anoro™‡ Ellipta [umeclidinium and vilanterol], Bevespi Aerosphere™‡ [glycopyrrolate and formoterol fumarate], Duaklir®‡ Pressair [aclidinium bromide and formoterol fumarate], Stiolto®‡ Respimat [tiotropium bromide and olodaterol])

VIII. Patient meets ONE of the following (a **or** b):
a) Patient experienced two or more COPD exacerbations requiring treatment with a systemic corticosteroid with or without an antibiotic in the previous 12 months; OR
b) Patient experienced one or more COPD exacerbation(s) requiring hospitalization in the previous 12 months.

Re-Authorization

I. Patient has received an initial authorization for the requested drug from the plan OR has provided documentation of authorization for an active course of treatment from previous health plan; AND
II. Patient has received at least 6 months of therapy with the requested drug; AND
III. Patient has had a clinically meaningful beneficial response to Nucala therapy as compared to their baseline status (before Nucala therapy) as evidenced by ONE or more of the following:
a) Reduced COPD symptoms
b) Reduced COPD exacerbations
c) Reduced COPD-related hospitalizations
d) Reduced emergency department or urgent care visits
e) Improved lung function parameters; AND
IV. Nucala is dosed at 100 mg every 4 weeks.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of mepolizumab (Nucala) for severe asthma when the patient has NOT been on the pre-requisite medications for at least 3 consecutive months to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of mepolizumab (Nucala) for EGPA when the patient has NOT tried and failed a corticosteroid for a minimum of 4 weeks to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of mepolizumab (Nucala) for HES when the patient has NOT been on stable therapy for HES OR will NOT continue HES therapy to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of mepolizumab (Nucala) for HES when the patient has NOT experienced at least 2 HES flares within the past 12 months to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of mepolizumab (Nucala) for CRSwNP when the patient has NOT met any of the following criteria to be **not medically necessary:****

- Patient has recurrent polyposis after at least ONE surgical resection (unless resection is contraindicated)
- Patient's nasal polyposis has been confirmed as grade 3 or higher with nasal endoscopy
- Patient's polyposis recurrence occurred within 6 months of at least one high dose oral steroid taper after the most recent resection
- Patient has received at least 4 weeks of therapy with an intranasal corticosteroid (e.g., fluticasone, mometasone, Xhance)

Based on review of available data, the Health Plan considers the use of mepolizumab (Nucala) for COPD when the patient has NOT met any of the following criteria to be **not medically necessary:****

- Patient has tried and failed at least three months of therapy with a combination of a LABA, LAMA, and ICS OR a combination of a LAMA and LAMA when an ICS is contraindicated
- Patient experienced two or more COPD exacerbations requiring treatment with a systemic corticosteroid with or without an antibiotic in the previous 12 months OR patient experienced one or more COPD exacerbation(s) requiring hospitalization in the previous 12 months
- For continuation requests: Patient has received at least 6 months of therapy with the requested drug

Based on review of available data, the Health Plan considers the continued use of mepolizumab (Nucala) when the patient has NOT responded to Nucala therapy as determined by the prescribing physician to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of mepolizumab (Nucala) when the patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) to be **investigational.***

Based on review of available data, the Health Plan considers the use of mepolizumab (Nucala) for indications other than the add-on maintenance treatment of severe asthma (eosinophilic phenotype), OR the treatment of EGPA, OR the treatment of HES, OR the add-on maintenance treatment of CRSwNP, OR the add-on maintenance treatment of COPD to be **investigational.***

Background/Overview

Nucala is an interleukin-5 (IL-5) antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 6 years and older (with an eosinophilic phenotype), for the treatment of adults with EGPA, for the treatment of adult and pediatric patients aged 12 years and older with HES for greater than or equal to 6 months without an identifiable non-hematologic secondary cause, for the add-on maintenance treatment of adult patients with CRSwNP, and for the add-on maintenance treatment of COPD. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Nucala binds to IL-5, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inflammation is an important component in the pathogenesis of asthma, CRSwNP, COPD, EGPA, and HES. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Nucala, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of action in asthma, CRSwNP, COPD EGPA, and HES has not been definitively established. Nucala is provided in 100 mg lyophilized powder in a single-dose vial for reconstitution as well as a 100 mg/mL single dose prefilled autoinjector or single dose prefilled syringe. Nucala is also available in a 40 mg/0.4 ml prefilled syringe. The Nucala 100 mg/ml vial should be reconstituted and administered by a healthcare professional, however the autoinjector and prefilled syringe can be self-administered. The 40 mg/0.4 ml prefilled syringe must be administered by a healthcare provider or the patient caregiver. The dosing of Nucala is 100 mg administered subcutaneously (SC) once every 4 weeks in severe asthma for those 12 years of age and older and 40 mg subcutaneously once every 4 weeks for those 6-11 years of age. For those 6-11 years of age with eosinophilic asthma, only the vial or 40 mg/0.4 ml prefilled syringe should be used for dosing. For EGPA and HES, Nucala is

dosed at 300 mg administered subcutaneously once every 4 weeks. For CRSwNP and COPD, Nucala is dosed at 100 mg administered subcutaneously once every 4 weeks.

Asthma
Asthma is a respiratory disorder characterized by increased responsiveness of the trachea and bronchi to various stimuli resulting in the narrowing of the airways, along with mucous secretion. Symptoms vary in severity and intensity and include wheezing, cough and dyspnea. Attacks can be triggered by exercise, allergens, irritants and viral infections. Based on symptoms, the four levels of asthma severity are:

- Mild intermittent (comes and goes) - you have episodes of asthma symptoms twice a week or less, and you are bothered by symptoms at night twice a month or less; between episodes, however, you have no symptoms and your lung function is normal.
- Mild persistent asthma - you have asthma symptoms more than twice a week, but no more than once in a single day. You are bothered by symptoms at night more than twice a month. You may have asthma attacks that affect your activity.
- Moderate persistent asthma - you have asthma symptoms every day, and you are bothered by nighttime symptoms more than once a week. Asthma attacks may affect your activity.
- Severe persistent asthma - you have symptoms throughout the day on most days, and you are bothered by nighttime symptoms often. In severe asthma, your physical activity is likely to be limited.

Treatment of asthma is based on a step up and step down approach based on the asthma severity and symptoms. Medications include short acting beta agonists for fast relief. Long term treatment centers around the use of ICSs and possible addition of medications such as long-acting beta agonists, LTRAs, inhaled long acting muscarinic antagonists, or theophylline.

Eosinophilic Granulomatosis with Polyangiitis
EGPA is a rare, idiopathic vasculitis that affects small to medium sized vessels. The prevalence of this condition is estimated to be around 11 to 14 cases per million persons. There are three phases of EGPA: allergic phase, eosinophilic phase, and a vasculitic phase. The allergic phase includes the development of asthma, allergic rhinitis, and sinusitis. During the eosinophilic phase, there is an increase in the eosinophil count and eosinophilic infiltration (typically in the lungs heart, and gastrointestinal system). During the vasculitis phase, patients experience necrotizing vasculitis as well as extravascular granulomatosis and symptoms including fever, malaise, and weight loss. Cardiac sequelae are the main cause of death in these patients as one of the most detrimental manifestations of EGPA are cardiac related (myocardial infarction, pericarditis, or congestive heart failure). Corticosteroids are the primary treatment of EGPA with most patients requiring continuous therapy (although still experiencing relapse). Other medications used include cyclophosphamide, azathioprine, methotrexate, etc.; however, no large randomized trials have been performed to effectively guide therapy beyond the use of corticosteroids. Current guidelines do not address newer interleukin products for EGPA.

Hypereosinophilic Syndrome
HES is a rare heterogenous disorder characterized by persistent hypereosinophilia which can lead to organ dysfunction due to the eosinophil infiltration into the tissues. Due to the complex classification of HES, it is difficult to assess incidence and prevalence, but some estimates point to roughly 5,000 HES patients in the United States. The exact mechanism of this condition is unknown. There are known mechanisms due to mutations in certain genes, such as PFGFRA. Clinical manifestations of this condition are wide-ranging. Symptoms can include fatigue, cough, dyspnea, rhinitis, anemia, rash, fever, myalgia, angioedema, abdominal pain, diarrhea, other gastrointestinal distress, pleural effusion, and cardiac manifestations including valvular disease, endomyocardial fibrosis, or pericarditis. Dermatological symptoms have also been reported in patients. Multiple signs of organ damage/dysfunction can potentially be associated with HES including fibrosis, thrombosis, erythema, angioedema, or neuropathy without a clear link to a root cause. Treatment options for patients with HES include corticosteroids or cytotoxic agents (e.g., hydroxyurea, cyclophosphamide) or immunomodulators (e.g., cyclosporine) as second-line agents.

Chronic Rhinosinusitis with Nasal Polyps
Chronic rhinosinusitis is an inflammatory condition involving the nasal sinuses and the lining of the nasal passages. Chronic rhinosinusitis often involves nasal drainage, nasal obstruction, facial pain and/or pressure and decreased sense of smell. Chronic rhinosinusitis with nasal polyposis is characterized by the presence of bilateral nasal polyps in the middle meatus. As imagined, these polyps lead to worsening nasal congestion, pressure, drainage, etc. Various treatment modalities for chronic rhinosinusitis include, but are not limited to, intranasal saline, intranasal steroids, oral steroids, surgery, non-sedating antihistamines, anti-leukotriene agents, and for those who have failed these more traditional therapies, a biologic agent such as Dupixent or Nucala.

Chronic Obstructive Pulmonary Disease
COPD is a chronic lung condition that is characterized by respiratory symptoms stemming from abnormalities in the airways, which often cause bronchitis and bronchiolitis, and/or from the alveoli, which often causes emphysema. Common symptoms of COPD include dyspnea, wheezing, chest tightness, and a cough that may or may not present with sputum production. Diagnosis of COPD is confirmed with spirometry demonstrating that airflow limitation is either irreversible or only partially reversible as defined by a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio less than 0.7. Treatment regimens are typically based on an assessment of symptoms and exacerbation history. Long-acting bronchodilators, including long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and combination products containing both of these classes are the mainstay of maintenance treatment for this condition. Inhaled corticosteroids in combination with a LABA and LAMA are considered for those who have a blood eosinophil level ≥ 300 cells/microliter. Daliresp®‡ (roflumilast), an oral PDE4 inhibitor, systemic corticosteroids, antibiotics, and mucolytics may also be considered in select patients. Nucala is the second biologic, after Dupixent, approved to treat COPD.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Nucala was approved in late 2015 for add-on maintenance treatment of patients with severe asthma aged 12 years and older, with an eosinophilic phenotype. In late 2017, Nucala was approved for the treatment of adults with EGPA. In 2019, the asthma indication was expanded to include patients aged 6 years and older. In 2020, Nucala was approved for the treatment of patients 12 years of age or older with HES. In 2021, Nucala was approved for the add-on maintenance treatment of adult patients with CRSwNP. In 2025, Nucala was approved for the add-on maintenance treatment of adult patients with COPD.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Asthma - 12 Years of Age and Older

The safety and efficacy of Nucala was studied in three randomized, double-blind, randomized, placebo-controlled trials. One trial was a dose ranging and exacerbation trial and the other two were confirmatory trials. Nucala was given as add-on therapy in all trials and patients continued taking their other asthma medications throughout the trial.

Trial 1 was a 52-week dose-ranging and exacerbation-reduction trial in subjects with asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICSs plus an additional controller(s) with or without oral corticosteroids. Three IV doses of Nucala (75, 250, and 750 mg) administered once every 4 weeks were evaluated compared with placebo. Results from this trial and the pharmacodynamic study supported the evaluation of mepolizumab 75 mg IV (intravenous) and 100 mg subcutaneously in the subsequent trials. Nucala is not indicated for IV use and should only be administered by the subcutaneous route.

A total of 711 subjects with asthma were studied in the 2 confirmatory trials (Trials 2 and 3). In these 2 trials subjects were required to have blood eosinophils of greater than or equal to 150 cells/mcL at screening (within 6 weeks of dosing) or blood eosinophils of greater than or equal to 300 cells/mcL within 12 months of enrollment. Trial 2 was a 32-week placebo- and active-controlled trial in subjects with asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICSs plus an additional controller(s) with or without oral corticosteroids. Subjects received mepolizumab 75 mg IV (n = 191), Nucala 100 mg subcutaneously (n = 194), or placebo (n = 191) once every 4 weeks for 32 weeks.

The primary endpoint for Trials 1 and 2 was the frequency of exacerbations defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or ED visits. For

subjects on maintenance oral corticosteroids, an exacerbation requiring oral corticosteroids was defined as the use of oral/systemic corticosteroids at least double the existing dose for at least 3 days. Compared with placebo, subjects receiving Nucala 100 mg subcutaneously or mepolizumab 75 mg IV experienced significantly fewer exacerbations. Additionally, compared with placebo, there were fewer exacerbations requiring hospitalization and/or ED visits and exacerbations requiring only in-patient hospitalization with Nucala. In Trial 2, the exacerbation rate was 1.74 in the placebo group vs. 0.83 in the Nucala group (rate ratio of 0.47, 95% confidence interval [CI 0.35, 0.64]). In Trial 2, the exacerbation rate requiring hospitalization/ED visit was 0.20 in the placebo group vs. 0.08 in the Nucala group (rate ratio of 0.39, 95% CI [0.18, 0.83]). In Trial 2, the exacerbation rate requiring hospitalization was 0.10 in the placebo group vs. 0.03 in the Nucala group (rate ratio of 0.31, 95% CI [0.11, 0.91]).

Trial 3 was a 24-week oral corticosteroid-reduction trial in subjects with asthma who required daily oral corticosteroids in addition to regular use of high-dose ICSs plus an additional controller(s) to maintain asthma control. The purpose of Trial 3 was to evaluate the effect of Nucala on reducing the use of maintenance oral corticosteroids. Subjects in Trial 3 were not required to have a history of exacerbations in the prior year. Subjects received Nucala 100 mg subcutaneously (n = 69) or placebo (n = 66) once every 4 weeks for 24 weeks. The primary endpoint was the percent reduction of oral corticosteroid dose during Weeks 20 to 24 compared with baseline dose, while maintaining asthma control. Compared with placebo, subjects receiving Nucala achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. Sixteen (23%) subjects in the group receiving Nucala versus 7 (11%) in the placebo group had a 90%to 100% reduction in their oral corticosteroid dose. Twenty-five (36%) subjects in the group receiving Nucala versus 37 (56%) in the placebo group were classified as having no improvement for oral corticosteroid dose. Additionally, 54% of subjects treated with Nucala achieved at least a 50% reduction in the daily prednisone dose compared with 33% of subjects treated with placebo (95% CI for difference: 4%, 37%).

Change from baseline in mean FEV_1 was measured in all 3 trials. Compared with placebo, Nucala did not provide consistent improvements in mean change from baseline in FEV_1.

Asthma – 6 to 11 Years of Age
Use of Nucala in children aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype, is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in children aged 6 to 11 years. A single, open-label clinical trial was conducted in 36 children aged 6 to 11 years (mean age: 8.6 years, 31% female) with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial (Trial 2). Based upon the pharmacokinetic data from this trial, a dose of 40 mg subcutaneously every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg subcutaneously. The efficacy of 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.

Eosinophilic Granulomatosis with Polyangiitis
The 52-week study for EGPA was randomized, placebo-controlled, multicenter, and included 136 subjects. Subjects received 300 mg of Nucala or placebo once every 4 weeks while continuing their stable oral corticosteroid therapy. At week 4, the oral corticosteroids were tapered at the discretion of the investigator. The co-primary endpoints were the total accrued duration of remission over the 52-week treatment period, defined as Birmingham Vasculitis Activity Score (BVAS) = 0 (no active vasculitis) plus prednisolone or prednisone dose less than or equal to 4 mg/day, and the proportion of subjects in remission at both week 36 and 48 of treatment.

Subjects receiving 300 mg of Nucala achieved a significantly greater accrued time in remission compared with placebo. A significantly higher proportion of subjects receiving 300 mg of Nucala achieved remission at both Week 36 and Week 48 compared with placebo. In addition, significantly more subjects receiving 300 mg of Nucala achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week study treatment period compared with placebo (19% for 300 mg of Nucala versus 1% for placebo; OR 19.7; 95% CI:2.3, 167.9). Additionally, a statistically significant benefit for these endpoints was demonstrated using remission defined as BVAS = 0 plus prednisolone/prednisone ≤7.5 mg/day.

The time to first relapse (defined as worsening related to vasculitis, asthma, or sino-nasal symptoms requiring an increase in dose of corticosteroids or immunosuppressive therapy or hospitalization) was significantly longer for subjects receiving 300 mg of Nucala compared with placebo with a hazard ratio of 0.32 (95% CI: 0.21, 0.5). Additionally, subjects receiving 300 mg of Nucala had a reduction in rate of relapse compared with subjects receiving placebo (rate ratio 0.50; 95% CI: 0.36, 0.70 for 300 mg of Nucala compared with placebo). The incidence and number of relapse types (vasculitis, asthma, sino-nasal) were numerically lower with mepolizumab compared with placebo.

Subjects receiving 300 mg of Nucala had a significantly greater reduction in average daily oral corticosteroid dose compared with subjects receiving placebo during Weeks 48 to 52

Hypereosinophilic Syndrome
A total of 108 adult and adolescent patients aged 12 years and older with HES for at least 6 months were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 32-week trial. Patients with non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy) or *FIP1L1-PDGFRα* kinase-positive HES were excluded from the trial. Patients received 300 mg of Nucala or placebo subcutaneously once every 4 weeks while continuing their stable HES therapy. Patients entering the trial had experienced at least 2 HES flares within the past 12 months and a blood eosinophil count of 1,000 cells/mcL or higher during screening. Historical HES flares for the trial entry criteria were defined as HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy. Patients must have been on stable HES therapy for the 4 weeks prior to randomization. HES therapy

could include chronic or episodic oral corticosteroids (OCS), immunosuppressive, or cytotoxic therapy. The efficacy of Nucala in HES was established based upon the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES or increasing eosinophils (on at least 2 occasions), resulting in the need to increase steroids or increase/add cytotoxic or immunosuppressive HES therapy.

The trial compared the proportion of patients who experienced a HES flare or withdrew from the trial in the Nucala and placebo treatment groups. Over the 32-week treatment period, the incidence of HES flare over the treatment period was 56% for the placebo group and 28% for the group treated with Nucala (50% reduction).

Chronic Rhinosinusitis with Nasal Polyps

A total of 407 adult patients with CRSwNP were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 52-week trial. Patients received Nucala 100 mg or placebo administered subcutaneously once every 4 weeks while continuing nasal corticosteroid therapy. Patients must have received background nasal corticosteroid for ≥8 weeks pre-screening. Patients had recurrent and symptomatic CRSwNP, and had at least 1 surgery for the removal of nasal polyps within the previous 10 years. Patients were required to have nasal obstruction symptoms with a visual analog scale (VAS) score of >5 out of a maximum score of 10. Patients were also required to have an endoscopic bilateral nasal polyp score (NPS) of ≥5 out of 8 with NPS ≥2 in each nasal cavity. Patients reported nasal obstruction VAS scores daily by placing a single mark on a continuous line labeled from 0 (none) to 100 (as bad as you can imagine). The distance along the line was converted to a 0 to 10 point scale for scoring. For NPS, polyps on each side of the nose were graded on a categorical scale (0 = no polyps, 1 = small polyps in the middle meatus not reaching below the inferior border of the middle concha, 2 = polyps reaching below the lower border of the middle turbinate, 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha, 4 = large polyps causing almost complete congestion/obstruction of the inferior meatus) for a total score of 0 to 8. The co-primary endpoints were change from baseline to Week 52 in total endoscopic NPS (0 to 8 scale) as graded by independent blinded assessors and change from baseline in nasal obstruction VAS score (0 to 10 scale) during Weeks 49 to 52.

Patients who received Nucala 100 mg had a statistically significant improvement (decrease) in bilateral NPS (-0.87 in the Nucala group vs. 0.06 in the placebo group) at Week 52 and nasal obstruction VAS score (-4.40 in the Nucala group vs. -2.54 in the placebo group) from Weeks 49 to 52 at the end of the 52 week treatment period.

Chronic Obstructive Pulmonary Disease

The efficacy of Nucala as add-on maintenance treatment for adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype was evaluated in two randomized, double-blind, placebo-controlled, multicenter trials. The two trials enrolled a total of 1640 adults who were randomized to receive Nucala 100 mg or placebo administered subcutaneously every 4 weeks for a treatment duration of 52 to 104 weeks in the first trial or 52 weeks in in the second trial. While 1640 adults were enrolled in the two clinical trials, the

efficacy population consisted of 1266 adults. Both trials enrolled patients with a diagnosis of COPD with moderate to very severe airflow limitation (post-bronchodilator FEV1/FVC ratio < 0.7 and post-bronchodilator FEV1 of 20% to 80% predicted) and at least 2 moderate or 1 severe COPD exacerbation in the previous year despite receiving triple inhaled therapy. In the first trial, patients were required to have a minimum blood eosinophil count of 300 cell/mcL at screening. In the second trial, there was no minimum blood eosinophil count requirement, but randomization was stratified by baseline blood eosinophil count: ≥ 150 cell/mcL at screening or ≥ 300 cell/mcL in the previous 12 months, or blood eosinophil count < 150 cells/mcL at screening with no evidence of blood eosinophil count ≥ 300 cell/mcL in the previous 12 months. Due to insufficient data from the second trial for patients with low eosinophil counts (< 150 cells/mcL) and no prior elevation (≥ 300 cells/mcL), those patients were excluded from the efficacy analysis. The final efficacy population included 804 patients from the first trial and 462 of those from the second trial who had elevated eosinophil counts either at screening or within the previous 12 months.

The primary endpoint for both trials was the annualized rate of moderate or severe exacerbations during the 52 to 104-week and 52-week treatment periods, respectively. Moderate exacerbations are defined per protocol as clinically significant exacerbations that require treatment with oral/systemic corticosteroids and/or antibiotics. Severe exacerbations are defined per protocol as clinically significant exacerbations that require in-patient hospitalization (i.e., ≥ 24 hours) or result in death.

In both trials, Nucala demonstrated a statistically significant reduction in the annualized rate of moderate or severe exacerbations compared with placebo when added to triple inhaled therapy.

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Policy History

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Current Effective Date: 02/01/2026
11/18/2025 UM Committee review and approval. New Policy.
Next Scheduled Review Date: 11/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J2182
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: All codes listed on the Medical Policy require prior authorization. This ensures appropriate utilization and alignment with current clinical guidelines.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.