PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Nucala Prior Authorization Policy
- Nucala® (mepolizumab injection for subcutaneous use – GlaxoSmithKline)

REVIEW DATE: 02/17/2021

OVERVIEW

Nucala, an interleukin-5 antagonist monoclonal antibody, is indicated for the following uses:[1]

- **Asthma**, as add-on maintenance treatment of patients ≥ 6 years of age with severe disease and an eosinophilic phenotype. Limitations of Use: Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.
- **Eosinophilic granulomatosis with polyangiitis** (EGPA) [formerly known as Churg-Strauss Syndrome] in adult patients.
- **Hypereosinophilic syndrome** (HES) in patients ≥ 12 years of age who have had HES for ≥ 6 months without an identifiable non-hematologic secondary cause.

Clinical Efficacy

Asthma

The efficacy of Nucala was established in three studies in patients ≥ 12 years of age with severe asthma and eosinophilic inflammation despite therapy with an inhaled corticosteroid and another maintenance medication.[1-4] In general, patients were required to have elevated eosinophils at baseline (e.g., peripheral blood eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter at some time during the previous year). In patients with a history of frequent exacerbations (i.e., two or more asthma exacerbations requiring systemic corticosteroid therapy within the previous year), Nucala significantly reduced the rate of clinically significant asthma exacerbations per patient per year compared with placebo. Additionally, in a study of patients with asthma requiring maintenance treatment with oral corticosteroids, significantly more patients who received 24 weeks of Nucala therapy were able to reduce their oral corticosteroid dose compared with placebo. Use of Nucala in patients 6 to 11 years of age with severe eosinophilic asthma is supported by the clinical trials in adults and adolescents along with additional pharmacokinetic, pharmacodynamic, and safety studies conducted specifically in patients 6 to 11 years of age.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

One study evaluated the efficacy of Nucala in patients ≥ 18 years of age with relapsing or refractory EGPA who had received ≥ 4 weeks of a stable oral corticosteroid dose (i.e., prednisolone, prednisone).[5] Patients were also required to have a baseline relative eosinophil level of 10% or an absolute eosinophil level > 1,000 cells per microliter; however, the baseline mean absolute eosinophil level was approximately 175 cells per microliter across both treatment groups. While remission benefit of Nucala was demonstrated in the overall patient population, the magnitude of improvements observed with Nucala were larger in patients with baseline eosinophil levels ≥ 150 cells per microliter than in patients with lower baseline levels.

Hypereosinophilic Syndrome

One study evaluated the efficacy of Nucala in patients ≥ 12 years of age with hypereosinophilic syndrome for ≥ 6 months.[6] Patients with non-hematologic secondary hypereosinophilic syndrome and those with FIP1L1-PDGFRα kinase-positive hypereosinophilic syndrome were excluded. All patients had a baseline blood eosinophil count ≥ 1,000 cells per microliter and had experienced two or more hypereosinophilic flares within the previous 12 months. Additionally, all patients had been on stable therapy for their hypereosinophilic syndrome (e.g., oral corticosteroids, immunosuppressive agents, or cytotoxic therapy)

for 4 weeks or more prior to randomization. Over the 32-week treatment period, significantly fewer patients experienced one or more hypereosinophilic syndrome flares with Nucala compared with placebo.

Guidelines

Asthma Guidelines

The Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2020) proposes a step-wise approach to asthma treatment.[7] Nucala is listed as an option for add-on therapy in patients ≥ 6 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with an ICS/long-acting beta$_2$-agonist [LABA] combination with or without an additional controller). Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, nasal polyposis, and maintenance corticosteroids at baseline may predict a good asthma response to Nucala.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[8,9] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: FEV_1 < 80% predicted after appropriate bronchodilator withholding.

EGPA Guidelines

Current EGPA guidelines do not address Nucala or the other anti-interleukin (IL)-5 therapies. The 2016 European League Against Rheumatism (EULAR) recommendations for the management of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis address EGPA.[10] All patients should be managed in close collaboration with or at centers of expertise where specialists can provide appropriate interventions and monitoring. For remission-induction in patients with new onset organ- or life-threatening ANCA-associated vasculitis, a combination of corticosteroids and either cyclophosphamide or rituximab is recommended (Level 3 evidence, Grade C recommendation for EGPA specifically). For maintenance of remission of EGPA, a combination of low-dose corticosteroids and azathioprine should be used (Level 3 evidence, Grade C recommendation); maintenance therapy should be considered for 24 months at a minimum.

In 2015, a Consensus Task Force comprised of experts from Europe and the United States published recommendations for the evaluation and management of EGPA.[11] These recommendations are similar to the EULAR guidance and also conclude that EGPA should be managed in collaboration with, or in, centers specializing in the management of small- and medium-sized-vessel vasculitides. In general, it is appropriate to use corticosteroids to induce EGPA remission; these medications are the cornerstone of therapy for EGPA.

Hypereosinophilia Guidelines

The 2019 World Health Organization (WHO)-defined eosinophilic disorders update on diagnosis, risk stratification, and management notes that corticosteroids remain the cornerstone of therapy for several forms of HES.[12] Use of anti-IL-5 approaches for the treatment of HES remains investigational. This document was published prior to the approval of Nucala for HES. However, it is recommended that patients

with idiopathic HES and end organ damage as well as those with lymphocyte-variant HES should consider enrollment into an anti-IL-5/anti-IL-5 receptor antibody clinical trial (as second-line therapy).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nucala. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nucala as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Nucala to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nucala is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Asthma.** Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient has a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin-5 therapy; AND
       Note: Examples of anti-interleukin-5 therapies include Nucala, Cinqair® (reslizumab injection for intravenous use), and Fasenra® (benralizumab injection for subcutaneous use).
     - **iii.** Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
       - **a)** An inhaled corticosteroid; AND
       - **b)** At least one additional asthma controller or asthma maintenance medication; AND

       Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting $beta_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, anti-interleukin-5 therapies (e.g., Cinqair, Fasenra, Nucala), and theophylline. Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting $beta_2$-agonist would fulfil the requirement for both criteria a and b.
     - **iv.** Patient has asthma that is uncontrolled or was uncontrolled at baseline 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(s) requiring hospitalization or an Emergency Department 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)** The patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND

       Note: "Baseline" is defined as prior to receiving any Nucala or other anti-interleukin-5 therapies (i.e., Fasenra or Nucala).
     - **v.** The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
- **i.** Patient has already received at least 6 months of therapy with Nucala; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 1A (Asthma, Initial Therapy).
- **ii.** Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND
- **iii.** Patient has responded to therapy as determined by the prescriber.
  Note: Examples of a response to Nucala therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department/urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

2. Eosinophilic Granulomatosis with Polyangiitis (EGPA) [formerly known as Churg-Strauss Syndrome]. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following conditions (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has/had a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin-5 therapy; AND
  Note: Examples of anti-interleukin-5 therapies include Nucala, Cinqair, and Fasenra.
- **iii.** Patient has tried therapy with a corticosteroid (e.g., prednisone) for a minimum of 4 weeks; AND
- **iv.** The medication is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.

B) Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i and ii):
- **i.** Patient has already received at least 6 months of therapy with Nucala; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 2A (Eosinophilic Granulomatosis with Polyangiitis, Initial Therapy).
- **ii.** Patient has responded to therapy as determined by the prescriber.
  Note: Examples of a response to Nucala therapy are reduced rate of relapse, corticosteroid dose reduction, and reduced eosinophil levels.

3. Hypereosinophilic Syndrome. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 8 months if the patient meets the following conditions (i, ii, iii, iv, v, vi, and vii):
- **i.** Patient is ≥ 12 years of age; AND;
- **ii.** Patient has had hypereosinophilic syndrome for ≥ 6 months; AND
- **iii.** Patient has FIP1L1-PDGFRα-negative disease; AND
- **iv.** Patient does NOT have an identifiable non-hematologic secondary cause of hypereosinophilic syndrome according to the prescriber; AND
  Note: Examples of secondary causes of hypereosinophilic syndrome include drug hypersensitivity, parasitic helminth infection, human immunodeficiency virus infection, non-hematologic malignancy.
- **v.** Patient has/had a blood eosinophil level ≥ 1,000 cells per microliter prior to treatment with any anti-interleukin-5 therapy; AND
  Note: Examples of anti-interleukin-5 therapies include Nucala, Cinqair, and Fasenra.

vi. Patient has tried at least one other treatment for hypereosinophilic syndrome for a minimum of 4 weeks; AND
Note: Treatments for hypereosinophilic syndrome include systemic corticosteroids, hydroxyurea, cyclosporine, imatinib, methotrexate, tacrolimus, and azathioprine.

vii. Nucala is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.

B) Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i and ii):

i. Patient has already received at least 8 months of therapy with Nucala; AND
Note: A patient who has received < 8 months of therapy or who is restarting therapy with Nucala should be considered under criterion 3A (Hypereosinophilic Syndrome, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Nucala therapy are decreased number of flares, improved fatigue, reduced corticosteroid requirements, and decreased eosinophil levels.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nucala is not recommended in the following situations:

1. **Atopic Dermatitis.** Nucala is not indicated for the treatment of atopic dermatitis.[1] In one small study, intravenous (IV) mepolizumab significantly reduced peripheral blood eosinophil counts in patients with moderate to severe atopic dermatitis.[13,14] However, mepolizumab IV therapy did not result in clinical success as assessed by Physician's Global Assessment of Improvement scores compared with placebo. Other clinical outcomes were also not significantly improved with mepolizumab IV. Another small study evaluated subcutaneous Nucala in patients with moderate to severe atopic dermatitis.[15] Following 16 weeks of therapy, Nucala did not demonstrate efficacy, with 11% (n = 2/11) of patients meeting the primary endpoint of treatment success with Nucala vs. 0 with placebo.

2. **Chronic Obstructive Pulmonary Disease (COPD).** Nucala is not indicated for the treatment of COPD.[1] Two Phase III studies, METREX (n = 836) and METREO (n = 675) evaluated Nucala in patients with COPD who had a history of moderate or severe exacerbations despite treatment with inhaled triple therapy (inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta$_2$-agonist).[16] METREX included patients regardless of eosinophil counts, but did include a subgroup of patients who were considered to have an eosinophilic phenotype (eosinophil count ≥ 150 cells/microliter) [n = 462]. METREO only included patients with an eosinophilic phenotype (defined as an eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter within the previous year). Overall, lower COPD exacerbation rates were observed with Nucala vs. placebo; however, none of these reductions were statistically significant in either the METREX overall modified intent to treat (mITT) population or the METREO mITT population (which included all eosinophilic phenotype patients). In the subgroup of patients in the METREX study with an eosinophilic phenotype, the COPD exacerbation rates were statistically lower with Nucala vs. placebo, as was the difference in the time to first exacerbation. In July 2018, the FDA's Pulmonary Allergy Drugs Advisory Committee voted against approval of Nucala as an add-on treatment to inhaled corticosteroid-based maintenance treatments to reduce flare-ups in patients with COPD.[17] The Committee had concerns about the defining criteria for the eosinophilic phenotype of COPD as well as the lack of data on patient asthma history. Subsequently, in September 2018, the FDA rejected the approval of Nucala for COPD citing the need for additional clinical data. Current COPD guidelines from the Global Initiative for Chronic Lung Disease (GOLD) [2021] note the mixed data with Nucala.[18] The guidelines state that further

studies are needed to determine if Nucala may have a role in a highly selected subgroup of patients with eosinophilic COPD.

3. **Concurrent use of Nucala with another Anti-Interleukin Monoclonal Antibody.** The efficacy and safety of Nucala used in combination with other anti-interleukin monoclonal antibodies (e.g., Cinqair, Fasenra, Dupixent® [dupilumab subcutaneous injection]) have not been established.

4. **Concurrent use of Nucala with Xolair® (omalizumab injection for subcutaneous use).** Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody indicated for use in patients ≥ 6 years of age with moderate to severe persistent asthma and who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.[19] Xolair is also indicated for chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H_1 antihistamine treatment and for nasal polyps, as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids. The efficacy and safety of Nucala used in combination with Xolair have not been established. A small number of case reports detailing combination use of Nucala and Xolair are available for both FDA-approved and off-label uses.[20-22] Further investigation is warranted.

5. **Eosinophilic Esophagitis, Eosinophilic Gastroenteritis, or Eosinophilic Colitis.** Nucala is not indicated for the treatment of eosinophilic esophagitis, eosinophilic gastroenteritis or eosinophilic colitis.[1] A few small studies have reported IV mepolizumab to be efficacious in these conditions.[23-25] Of note, Nucala is not approved for IV administration.[1] Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) only recommend using anti-interleukin-5 therapies in the context of a clinical trial.[26] Further research is warranted to determine if Nucala has a place in therapy in the treatment of these conditions.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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