



MEDICAL MUTUAL®

Nucala® (mepolizumab) injection for subcutaneous use

Prior Approval Criteria

December 2015

OVERVIEW

Nucala, an interleukin (IL)-5 antagonist monoclonal antibody (IgG1κ), is indicated for add-on maintenance treatment of patients with severe asthma aged ≥ 12 years who have an eosinophilic phenotype. Limitations of Use: Nucala is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus. Nucala is a human IL-5 antagonist; IL-5 is the main cytokine involved in the growth, differentiation, recruitment, activation, and survival of eosinophils. The most important factor in the pathogenesis of asthma is inflammation, which involves multiple mediators and cell types, including eosinophils. By inhibiting the signaling of IL-5, Nucala decreases the production and survival of eosinophils. However, the exact mechanism of action of Nucala in asthma has not been established. Nucala is not indicated for intravenous (IV) use; it should be administered as a 100 mg subcutaneous (SC) injection once every 4 weeks by a healthcare professional

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nucala. All approval durations are noted below. Note: 1 month is equal to 30 days.

RECOMMENDED AUTHORIZATION CRITERIA

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

Food and Drug Administration (FDA)-Approved Indications

- 1. Severe Asthma, add on maintenance in patients with eosinophilic phenotype.** Approve initial use of Nucala for 6 months if the patient meets the following criteria (A, B, C, D and E):
 - A)** Patient is ≥ 12 of age; AND
 - B)** Nucala is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND
 - C)** Patient has a peripheral blood eosinophil count of ≥ 150 cells per microliter within the previous 6 weeks (prior to treatment with Nucala); AND
 - D)** Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (i and ii):
 - i.** An inhaled corticosteroid (ICS) [e.g. Flovent® HFA {fluticasone inhalation aerosol}, Flovent® Diskus® {fluticasone inhalation powder}, Arnuity™ Ellipta® {fluticasone furoate inhalation powder}, Asmanex® Twisthaler® {mometasone inhalation powder}, Asmanex® HFA {mometasone inhalation aerosol}, Aersopan™ {flunisolide HFA inhalation

aerosol}, Alvesco[®] {ciclesonide inhalation aerosol}, Pulmicort Flexhaler[®] {budesonide inhalation powder}, QVAR[®] {beclomethasone HFA inhalation aerosol}]; AND

ii. At least ONE of the following (1, 2, 3 or 4):

1. Inhaled long-acting beta-agonist (LABA) [e.g., Serevent[®] Diskus[®] {salmeterol xinafoate inhalation powder}]; OR

NOTE: Use of a combination inhaler containing both an ICS and a LABA would fulfil the requirement for both criteria i and ii. (e.g., Advair[®] Diskus/HFA [fluticasone propionate and salmeterol inhalation powder/aerosol], Symbicort[®] [budesonide and formoterol fumarate inhalation aerosol], Breo[®] Ellipta[®] [fluticasone furoate and vilanterol inhalation powder], and Dulera[®] [mometasone furoate and formoterol fumarate inhalation aerosol])

2. Inhaled long-acting muscarinic antagonist (LAMA) [e.g., Spiriva[®] Respimat[®] {tiotropium bromide inhalation spray}]; OR

3. Leukotriene receptor antagonist (LTRA) [e.g. montelukast tablets/granules {Singulair[®], generics}, Accolate[®] {zafirlukast tablets}]; OR

4. Theophylline (Theo-24, Uniphyll, TheoChron ER, generics); AND

E) Patient's asthma continues to be uncontrolled as defined by ONE of the following (i, ii, iii, iv or v):

i. The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

ii. The patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) visit in the previous year; OR

iii. Patient has a forced expiratory volume in 1 second (FEV₁) < 80% predicted; OR

iv. Patient has an FEV₁/forced vital capacity (FVC) < 0.80; OR

v. The patient's asthma worsens upon tapering of oral corticosteroid therapy.

2. Patient has been started on Nucala (re-authorization). Approve for 1 year if the patient meets the following criteria (A, B, C and D):

A) Patient is ≥ 12 years of age; AND

B) Nucala is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND

C) Patient continues to receive therapy with BOTH of the following (i and ii):

i. An inhaled corticosteroid (ICS); AND

ii. At least ONE of the following (1, 2, 3 or 4):

1. Inhaled long-acting beta-agonist (LABA); OR

NOTE: Use of a combination inhaler containing both an ICS and a LABA would fulfil the requirement for both criteria i and ii.

2. Inhaled long-acting muscarinic antagonist (LAMA); OR

3. Leukotriene receptor antagonist (LTRA); OR

4. Theophylline; AND

D) The patient has responded to Nucala therapy as determined by the prescribing physician (e.g., decreased asthma exacerbations; decreased asthma symptoms;

decreased hospitalizations, emergency department (ED)/urgent care, or physician visits due to asthma; decreased requirement for oral corticosteroid therapy).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Nucala has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Atopic Dermatitis (AD)

In one small (n = 40) randomized, placebo-controlled, parallel group study, mepolizumab 750 mg IV once weekly for 2 weeks significantly reduced peripheral blood eosinophil counts in patients with moderate to severe atopic dermatitis. However, mepolizumab IV therapy did not result in clinical success as assessed by the Physician's Global Assessment of Improvement (PGA) compared with placebo (P = 0.115). Clinical outcomes (as measured by Scoring Atopic Dermatitis [SCORAD]), pruritus scoring, and serum thymus and activation-regulated chemokine (TARC) values were also not significantly improved with mepolizumab IV vs. placebo. In the same patient population, mepolizumab IV also did not significantly reduce the macroscopic outcome of the atopy patch test, an in vivo model that is used to study the induction of eczema by inhalant allergens in patients with atopic dermatitis. There are no studies evaluating the use of SC Nucala in patients with atopic dermatitis.

2. Chronic Obstructive Pulmonary Disease

The safety and efficacy of Nucala have not been established in patients with COPD. There are currently two Phase III studies underway evaluating SC Nucala as an adjunct treatment in COPD management and in patients with severe COPD and recurrent exacerbations; a third Phase III study is evaluating IV Nucala in patients with COPD with eosinophilic bronchitis. Results are anticipated in 2016.

3. Concurrent use of Nucala with Xolair® (omalizumab injection for subcutaneous use).

Xolair is a recombinant humanized immunoglobulin G (IgG)1 κ monoclonal indicated for use in adults and adolescents (aged \geq 12 years) 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. The efficacy and safety of Nucala in combination with Xolair have not been established.

4. Eosinophilic Esophagitis (EoE), Eosinophilic Gastroenteritis, or Eosinophilic Colitis.

Nucala is not indicated for the treatment of eosinophilic conditions other than asthma. In an open-label, Phase I/II study of mepolizumab IV in four adult patients with EoE, dysphagia, and esophageal strictures, three IV infusions of mepolizumab were found to decrease peripheral blood eosinophil counts (by 6.4-fold from baseline) and percent of CCR3+ cells (by 7.9-fold). Mean esophageal eosinophil counts decreased from 46 cells/hpf to 6 cells/hpf and maximal esophageal eosinophil counts decreased from 153 cells/high-power field (hpf) to 28 cells/hpf following mepolizumab IV therapy. One small (n = 11), Phase II, randomized, double-blind, placebo-controlled study that assessed the efficacy of mepolizumab 750 mg IV (administered once weekly for 2 weeks) compared with placebo in patients with EoE experiencing frequent episodes of dysphagia (\geq 1 episode per week). At 4

weeks, mepolizumab therapy resulted in a significant reduction in esophageal eosinophilia (54% reduction) compared with placebo (5% reduction) [P = 0.03]. Another study evaluated three infusions of either 0.55 mg/kg, 2.5 mg/kg, or 10 mg/kg mepolizumab IV administered every 4 weeks in pediatric patients with EoE (n = 59). No placebo comparator was used. Peak eosinophil counts were reduced to < 5 cells/hpf in 8.8% of the patients; no differences between the three doses of mepolizumab IV were observed. In total, 31.6% of patients experienced reduced peak eosinophil counts of < 20 cells/hpf and in 89.5% of patients, mepolizumab IV reduced mean eosinophil counts to < 20 per hpf. The American College of Gastroenterology clinical guideline for the diagnosis and management of esophageal eosinophilia and EoE state that further studies utilizing anti-IL-5 therapies are needed to define their role in EoE. They note two trials of mepolizumab IV, but highlight that while eosinophil counts declined, the majority of patients did not achieve complete histologic resolution and in adults symptoms did not improve. A 2014 updated food allergy practice parameter from the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology (JCAAI) Joint Task Force addressed the treatment of EoE, but also noted that biologic therapies, including anti-IL-5 therapy, have had varying success and are not recommended for routine use in patients with EoE. There are no data to support the use of Nucala in patients with eosinophilic gastroenteritis or eosinophilic colitis. Further research is warranted to determine if Nucala has a place in therapy in the treatment of these conditions.

5. Eosinophilic Granulomatosis with Polyangiitis (EGPA) [formerly known as Churg-Strauss Syndrome].

Nucala is not indicated for the treatment of eosinophilic conditions other than asthma. In one open-label, single-arm, pilot study (n = 7), four monthly doses of mepolizumab IV resulted in reduced eosinophil counts and reduction of systemic corticosteroid requirements in all patients. In a second, Phase II, uncontrolled trial, mepolizumab 750 mg IV every 4 weeks (total of nine doses) resulted in complete remission in 8 out of 9 patients with EGPA. A randomized, placebo-controlled study of SC Nucala in patients with EGPA is ongoing; however, results are not yet available. Further data will assist in determining the role of Nucala in this patient population.

6. Hypereosinophilic Syndrome (HES), idiopathic

Nucala is not indicated for the treatment of eosinophilic conditions other than asthma. One small (n = 4) open-label trial of three IV doses of mepolizumab (10 mg/kg; maximum dose of 750 mg) every 4 weeks in patients with HES found mepolizumab IV significantly lowered peripheral blood eosinophil counts, even in the setting of continued systemic glucocorticoid therapy. This effect was sustained for up to 12 weeks following the last dose of mepolizumab IV. Another randomized, double-blind, placebo-controlled, multicenter, Phase II trial (published) [n = 85] evaluated mepolizumab IV therapy in patients with HES (negative for the FIP1L1-PDGFR α fusion gene). Mepolizumab 750 mg IV for 36 months resulted in significantly more patients reducing their prednisone dose \leq 10 mg per day compared with placebo (84% of patients vs. 43% of patients, P < 0.001). In an open-label extension of this study (mean exposure to mepolizumab of 251 weeks), 62% of patients were prednisone-free without other hypereosinophilic syndrome medications for \geq 12 weeks.

Dosing intervals of IV mepolizumab varied in the extension study; the most common dosing interval was every 9 to 12 weeks. SC Nucala has not been studied in this patient population. IV mepolizumab is available from the manufacturer on a compassionate use basis for patients with life-threatening HES who have failed prior therapies.

7. Nasal Polyps

There are limited data regarding the use of Nucala in patients with nasal polyps. One small (n = 30), randomized, double-blind study compared mepolizumab 750 mg IV (every 28 days for two doses) with placebo for the treatment of severe nasal polyposis. At Week 8, mepolizumab IV was found to significantly improve the change in the total polyp score from baseline compared with placebo (60% improvement vs. 10% improvement, respectively; P = 0.018). Non-significant improvements in patients' loss of smell, postnasal drip, and congestion were observed with mepolizumab IV at Week 8 vs. the placebo group; rhinorrhea remained at the same level regardless of treatment. No studies of SC Nucala have been conducted in this patient population. Additional, well-controlled trials are needed to determine the role of Nucala in the treatment of nasal polyposis.

8. 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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