

**POLICY:** Immunologicals – Nucala<sup>®</sup> (mepolizumab injection for subcutaneous use – GlaxoSmithKline)

**APPROVAL DATE:** 02/20/2019; selected revision 09/25/2019

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## OVERVIEW

Nucala is indicated for add-on maintenance treatment of patients  $\geq 6$  years of age with severe asthma who have an eosinophilic phenotype.<sup>1</sup> Nucala is also indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA) [formerly known as Churg-Strauss Syndrome]. Nucala is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus. Nucala is a human interleukin (IL)-5 antagonist monoclonal antibody. IL-5 is the main cytokine involved in the growth, differentiation, recruitment, activation, and survival of eosinophils, a type of cell involved in the inflammation present in patients with asthma and EGPA.

## Clinical Efficacy

### *Asthma*

The efficacy of Nucala was established in three randomized, double-blind, placebo-controlled, multicenter pivotal studies in patients  $\geq 12$  years of age with severe asthma and eosinophilic inflammation despite therapy with an inhaled corticosteroid (ICS) and another maintenance medication.<sup>2-4</sup> In patients with a history of frequent exacerbations, Nucala significantly reduced the rate of clinically significant asthma exacerbations per patient per year compared with placebo. Exploratory subgroup analyses indicated that the efficacy of Nucala improved with larger elevations in blood eosinophil counts. In the oral corticosteroid (OCS) reduction study, eligible patients also required maintenance treatment with OCSs. In this study, significantly more patients receiving SC Nucala were able to reduce their oral glucocorticoid dose compared with placebo at Week 24.

Nucala for use 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.<sup>1</sup> Based on results from a pharmacokinetic/pharmacodynamic trial (n = 36) in the pediatric patient population, a dose of Nucala 40 mg SC every 4 weeks was found to result in a similar exposure as 100 mg SC administered to adults and adolescents.<sup>1,29</sup> Additionally, the safety profile of Nucala observed with pediatric patients in this trial was found to be similar to that observed in studies of adults and adolescents.<sup>1,30</sup>

### *EGPA*

The efficacy of Nucala was evaluated in one randomized, placebo-controlled, double-blind, Phase III study which involved patients  $\geq 18$  years of age with relapsing or refractory EGPA who had received  $\geq 4$  weeks of a stable corticosteroid dose.<sup>5</sup> 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. All patients had a diagnosis of asthma with eosinophilia. In this patient population, Nucala therapy resulted in significantly more accrued weeks of remission than placebo. Additionally, a higher percentage of patients receiving Nucala were in remission at both Week 36 and Week 48 compared with placebo. The magnitude of improvements observed were larger in patients with baseline eosinophil levels  $\geq 150$  cells per microliter than in patients with lower baseline levels.

## **Guidelines**

### *Asthma Guidelines*

The 2019 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a step-wise approach to asthma treatment.<sup>6</sup> Patients with persistent symptoms or exacerbations despite a medium-dose ICS/long-acting beta<sub>2</sub>-agonist (LABA) combination with or without an additional controller, GINA recommends referral of the patient to a specialist with expertise in the management of severe asthma for phenotypic assessment and add-on treatment. Nucala is listed as an option for add-on therapy in patients  $\geq 12$  years of age with difficult-to-treat, severe eosinophilic asthma. Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, and nasal polyposis may predict a good asthma response to Nucala.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014), 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.<sup>7</sup> Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control, frequent severe exacerbations, serious exacerbations, or airflow limitation. Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids.

### *EGPA Guidelines*

Current EGPA guidelines do not address Nucala or the other anti-IL-5 therapies. The 2016 European League Against Rheumatism (EULAR) recommendations for the management of ANCA-associated vasculitis address EGPA.<sup>8</sup> 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.<sup>9</sup> 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.

## **POLICY STATEMENT**

Prior authorization is recommended for medical benefit coverage of Nucala. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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. All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

## RECOMMENDED AUTHORIZATION CRITERIA

### FDA-Approved Indications

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- 1. Asthma.** Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):
  - A) Initial Therapy.** Approve Nucala for 6 months if the patient meets the following criteria (i, ii, iii, iv and v):
    - i.** Patient is  $\geq 6$  years of age; AND
    - ii.** Nucala is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND
    - iii.** Patient has a blood eosinophil level of  $\geq 150$  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 therapy include Nucala, Cinqair, and Fasenra.
    - iv.** 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/maintenance medication; AND  
Note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-interleukin-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an inhaled corticosteroid for at least 3 consecutive months. Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting beta<sub>2</sub>-agonist would fulfil the requirement for both criteria a and b. Examples of inhaled corticosteroids include Aerospan, Alvesco, ArmonAir RespiClick, Arnuity Ellipta, Asmanex Twisthaler/HFA, Flovent Diskus/HFA, Pulmicort Flexhaler, Qvar/Qvar RediHaler, and budesonide suspension for inhalation (Pulmicort Respules, generics). Examples of additional asthma controller/maintenance medications include long-acting beta<sub>2</sub>-agonists (e.g., Serevent Diskus); inhaled long-acting muscarinic antagonists (e.g., Spiriva Respimat); leukotriene receptor antagonists (e.g., montelukast tablets/granules [Singulair, generics], zafirlukast tablets [Accolate, generics]); theophylline (e.g., Theo 24, TheoChron ER, generics). Examples of combination inhaled corticosteroid/long-acting beta<sub>2</sub>-agonist inhalers include Advair Diskus/HFA (generic Wixela Inhub; authorized generics), AirDuo RespiClick (authorized generics), Breo Ellipta, Dulera, Symbicort.
  - v.** Patient's asthma is uncontrolled or was uncontrolled prior to starting any anti-interleukin therapy as defined by ONE of the following (a, b, c, d or e):
    - a)** The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
    - b)** The 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<sub>1</sub>)  $< 80\%$  predicted; OR
    - d)** Patient has an FEV<sub>1</sub>/forced vital capacity (FVC)  $< 0.80$ ; OR
    - e)** The patient's asthma worsens upon tapering of oral corticosteroid therapy; OR  
Note: Examples of anti-interleukin therapies include Nucala, Cinqair, and Fasenra.
- B) Patients Continuing Nucala Therapy.** Approve Nucala for 1 year if the patient meets the following criteria (i, ii, and iii):
  - i.** The patient has already received at least 6 months of therapy with Nucala; AND  
Note: Patients who have received  $< 6$  months of therapy or those who are 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

Note: Examples of an inhaled corticosteroid or an inhaled corticosteroid-containing combination inhaler include Flovent Diskus/HFA, ArmonAir RespiClick, Arnuity Ellipta, Asmanex Twisthaler/HFA, Aersopan, Alvesco, Pulmicort Flexhaler, budesonide suspension for inhalation (Pulmicort Respules, generics), Qvar/Qvar RediHaler, Advair Diskus/HFA (generic Wixela Inhub; authorized generics), AirDuo RespiClick (authorized generics), Breo Ellipta, Dulera, and Symbicort.

- iii. The patient has responded to Nucala 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 (ED)/urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

**Dosing.** Approve one of the following dosing regimens (A or B):

- A) For patients  $\geq 12$  years of age, approve 100 mg administered subcutaneously once every 4 weeks;  
OR  
B) For pediatric patients (6 to 11 years of age), approve 40 mg administered subcutaneously once every 4 weeks.

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**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 Nucala for 6 months if the patient meets ALL of the following conditions (i, ii, iii, and iv):
- i. Patient is  $\geq 18$  years of age; AND;
  - ii. Nucala is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist; AND
  - iii. Patient has tried therapy with a corticosteroid (e.g., prednisone) for a minimum of 4 weeks; AND
  - iv. Patient has/had a blood eosinophil level of  $\geq 150$  cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin-5 therapy; OR  
Note: Examples of anti-interleukin-5 therapies include Nucala, Cinqair, and Fasenna.
- B) Patients Continuing Nucala Therapy. Approve Nucala for 1 year if the patient meets the following criteria (i and ii)
- i. The patient has already received at least 6 months of therapy with Nucala; AND  
Note: Patients who have received  $< 6$  months of therapy or those who are restarting therapy with Nucala should be considered under criterion 2A (Eosinophilic Granulomatosis with Polyangiitis, Initial Therapy).
  - ii. The patient has responded to Nucala 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.

**Dosing.** Approve 300 mg administered subcutaneously once every 4 weeks.

### **Conditions Not Recommended for Approval**

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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).** There are no studies evaluating the use of SC Nucala in patients with atopic dermatitis. In one small randomized, placebo-controlled, parallel group study (published) [n = 40], mepolizumab 750 mg IV once weekly for 2 weeks significantly reduced peripheral blood eosinophil counts in patients with moderate to severe atopic dermatitis.<sup>10</sup> However, mepolizumab IV therapy did not result in clinical success as assessed by Physician's Global Assessment of Improvement scores compared with placebo. Clinical outcomes (as measured by Scoring Atopic Dermatitis [SCORAD] index), 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.<sup>11</sup>
- 2. Chronic Obstructive Pulmonary Disease (COPD).** Nucala is not indicated for the treatment of COPD.<sup>1</sup> Two Phase III studies, METREX (n = 836) and METREO (n = 675) [both published] evaluated Nucala in patients with COPD who had a history of moderate or severe exacerbations despite treatment with inhaled triple therapy (ICS/LAMA/LABA).<sup>12</sup> METREX included patients regardless of eosinophil counts, but did include a subgroup of patients who were considered to have an eosinophilic phenotype (eosinophil count  $\geq 150$  cells/microliter) [n = 462]. METREO only included patients with an eosinophilic phenotype (defined as an eosinophil count  $\geq 150$  cells/microliter at screening or  $\geq 300$  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 in the METREX study with an eosinophilic phenotype, the difference between Nucala and placebo was statistically significant (mean annual exacerbation rate of 1.40 vs. 1.71, respectively; rate ratio: 0.82; P = 0.04). Difference in the time to first exacerbation was also only significant in the eosinophilic phenotype subgroup of the METREX study. No other secondary endpoints were significantly improved with Nucala in either study. 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 chronic obstructive pulmonary disease (COPD).<sup>13</sup> 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.
- 3. Concurrent use of Nucala with another Anti-Interleukin (IL) Monoclonal Antibody.** The efficacy and safety of Nucala used in combination with other anti-IL monoclonal antibodies (e.g., Cinqair, Dupixent® [dupilumab subcutaneous injection], Fasentra) have not been established.
- 4. Concurrent use of Nucala with Xolair® (omalizumab injection for subcutaneous use).** Xolair is a recombinant humanized immunoglobulin G (IgG)1 $\kappa$  monoclonal antibody indicated for use in adults and adolescents (aged  $\geq 6$  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.<sup>14</sup> The efficacy and safety of Nucala used in combination with Xolair have not been established. One case report describes the combination use of Nucala and Xolair for a patient

with severe eosinophilic asthma and elevated IgE levels.<sup>15</sup> A second case report details the use of this combination for refractory allergic bronchopulmonary aspergillosis, an off-label use.<sup>16</sup> Further investigation is warranted.

- 5. Eosinophilic Esophagitis (EoE), Eosinophilic Gastroenteritis, or Eosinophilic Colitis.** Nucala is not indicated for the treatment of eosinophilic EoE, eosinophilic gastroenteritis or eosinophilic colitis.<sup>1</sup> 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).<sup>17</sup> 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 ( $\geq$  one episode per week).<sup>18</sup> At 4 weeks, mepolizumab therapy resulted in a significant reduction in esophageal eosinophilia (54% reduction) compared with placebo (5% reduction). 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).<sup>19</sup> 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. The American College of Gastroenterology clinical guideline (2013) 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.<sup>20</sup> 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.<sup>21</sup> 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.
- 6. Hypereosinophilic Syndrome (HES), Idiopathic.** Nucala is not indicated for the treatment of hypereosinophilic syndrome.<sup>1</sup> In addition to one small open-label trial, one 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 $\alpha$  fusion gene).<sup>22,23</sup> 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.<sup>24</sup> 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.<sup>25</sup>
- 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.<sup>26</sup> At Week 8, mepolizumab IV was found to significantly improve the change in the total polyp score from baseline compared with placebo. 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. A second randomized, double-blind, placebo-controlled study (n = 105) involved adult patients with recurrent nasal polyposis who required surgery.<sup>27</sup> Patients received either mepolizumab 750 mg IV or placebo Q4W for 6 doses in addition to topical corticosteroids. At Week

25, significantly more patients who received mepolizumab no longer required surgery compared with placebo (30% vs. 10%, respectively). The nasal polyposis visual analog scale (VAS) score and the endoscopic nasal polyp score were also significantly improved with mepolizumab along with several other secondary endpoints. No studies of SC Nucala have been conducted in this patient population. In June 2017, a Phase III study of Nucala in patients with severe bilateral nasal polyps began; results are not yet available.<sup>28</sup>

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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**HISTORY**

Type of Revision	Summary of Changes	Approval Date
New Policy	--	09/26/2018
Early Annual Revision	Updated initial therapy criteria for “Asthma in Patients with Severe Disease and an Eosinophilic Phenotype” to more concisely state the previous therapies required. Added the following: NOTE: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-IL-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an ICS for at least 3 consecutive months.	02/20/2019
Selected Revision	<ul style="list-style-type: none"> <li>• Asthma: Approval indication was changed from “Asthma in Patients with Severe Disease and an Eosinophilic Phenotype” to “Asthma”. Age approval changed from <math>\geq 12</math> years of age to <math>\geq 6</math> years of age. Wording in reference to “according to the prescribing physician” was changed to “according to the prescriber”. Added Wixela Inhub, a generic to Advair Diskus, to list of examples of asthma controller/maintenance medications. Updated Dosing to include dosing for patients 6 to 11 years of age.</li> <li>• Eosinophilic Granulomatosis with Polyangiitis (EGPA): Wording in reference to “according to the prescribing physician” was changed to “according to the prescriber”.</li> </ul>	09/25/2019