Nucala (mepolizumab injection for subcutaneous use)

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Nucala (mepolizumab) for the treatment of asthma in patients with severe disease and an eosinophilic phenotype, when it meets the following criteria.

When Policy Topic is covered
Coverage of Nucala is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Asthma in Patients with Severe Disease and an Eosinophilic Phenotype.
   A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv and v):
      i. Patient is ≥ 12 of age; AND
      ii. Nucala is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND
      iii. Patient has a peripheral blood eosinophil count of ≥ 150 cells per microliter within the previous 6 weeks (prior to treatment with Nucala); AND
      iv. 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., 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}, Aerospan™ {flunisolide HFA inhalation aerosol}, Alvesco® {ciclesonide inhalation aerosol}, Pulmicort Flexhaler® {budesonide inhalation powder}, QVAR® {beclomethasone HFA inhalation aerosol}]; AND
         b) 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 fulfill the requirement for both criteria a and b (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
      v. Patient’s asthma continues to be uncontrolled 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 (FEV₁) < 80% predicted; OR
d) Patient has an FEV₁/forced vital capacity (FVC) < 0.80; OR
e) The patient’s asthma worsens upon tapering of oral corticosteroid therapy.

B) Patients Continuing Nucala Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, iii and iv):

i. Patient is ≥ 12 years of age; AND

ii. Nucala is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND

iii. Patient continues to receive therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid (ICS) [e.g. Flovent® HFA {fluticasone inhalation aerosol}, Flovent® Diskus® {fluticasone inhalation powder}, Arnuity™ Ellipta® {fluticasone furoate inhalation powder}, Asmanex® Twinhaler® {mometasone furoate inhalation powder}, Asmanex® HFA {mometasone furoate inhalation aerosol}, Aersopan™ (flunisolide HFA inhalation aerosol), Alvesco® {ciclesonide inhalation aerosol}, Pulmicort Flexhaler® {budesonide inhalation powder}, QVAR® {beclomethasone HFA inhalation aerosol}]; AND

b) 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 fulfill the requirement for both criteria a and b (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, Uniphyl, TheoChron ER, generics); AND

iv. 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).

C) Asthma dosing: 100mg administered subcutaneously once every 4 weeks

Nucala is indicated for add-on maintenance treatment of patients with severe asthma aged ≥ 12 years who have an eosinophilic phenotype. According to the 2014 ERS/ATS guidelines, 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. Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control; frequent severe exacerbations (two or more requiring systemic corticosteroids per year); serious exacerbations (one hospitalization in the previous year); or airflow limitation (FEV₁ < 80% of predicted in the setting of reduced FEV₁/FVC). Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids (high-dose ICSs or systemic corticosteroids). Nucala has only been studied in patients who were also receiving treatment with high-dose ICSs alone or in combination with maintenance oral corticosteroids and an additional controller medication. Current guidelines confirm that ICS therapy remains the mainstay of therapy even in the setting of difficult-to-treat, severe asthma. For patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence to high-
dose ICS therapy and a second controller medication (e.g., a LABA), referring the patient to a specialist with expertise in the management of severe asthma to investigate and consider additional treatments is recommended. Finally, in pivotal trials of Nucala, all patients were required to demonstrate evidence of eosinophilic inflammation. In the DREAM study, exploratory subgroup analyses indicated that the efficacy of Nucala improved with larger elevations in blood eosinophil counts; however, elevated sputum eosinophil counts were not found to predict enhanced efficacy. Again in the MENSA study, a subgroup of patients with very elevated blood eosinophil counts at baseline demonstrated an enhanced response to Nucala. In patients who did not have a blood eosinophil level ≥ 150 cells/microliter at screening (n = 86), Nucala therapy did not result in a significant reduction in exacerbations compared with placebo. In studies including patients without evidence of eosinophilic inflammation, Nucala did not produce significant improvements in lung function compared with placebo. In the opinion of expert physicians reviewing the data we have adopted the eosinophil criteria and criteria for uncontrolled asthma.

2. Eosinophilic Granulomatosis with Polyangiitis (EGPA) [formerly known as Churg-Strauss Syndrome]. (FDA approved indication Dec 12, 2017)
   A) The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)

Estimated to affect about 5,000 Americans, EGPA damages internal organs, nerves and skin by causing inflammation in the walls of smaller blood vessels. Nucala is the first drug specifically approved to treat EGPA. Previously, patients used corticosteroids and immunosuppressants that relieve inflammation or decrease immune response. In a clinical study, participants using Nucala in addition to their usual medications had fewer disease flares, went into remission more often, stayed symptom-free longer and decreased dependence on steroids to manage symptoms as compared to patients using standard treatment plus a placebo.

   B) EGPA Dosing: 300mg as 3 separate 100mg-injections administered subcutaneously once every 4 weeks.

When Policy Topic is not covered
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.)

Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.

1. Atopic Dermatitis (AD). There are no studies evaluating the use of SC Nucala in patients with atopic dermatitis. 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 Physician’s Global Assessment of Improvement scores compared with placebo (P = 0.115). 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.

2. Chronic Obstructive Pulmonary Disease (COPD). 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)1κ monoclonal indicated for use in adults and adolescents (aged ≥ 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.11 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.1 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).12 Mean esophageal eosinophil counts decreased from 46 cells/high-power field (hpf) to 6 cells/hpf and maximal esophageal eosinophil counts decreased from 153 cells/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 (≥ one 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].13 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).14 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.15 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 (JCAA) 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.16 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. Hypereosinophilic Syndrome (HES), Idiopathic. Nucala is not indicated for the treatment of eosinophilic conditions other than asthma.1 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.20 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-PDGFRA fusion gene).21 Mepolizumab 750 mg IV for 36 months resulted in significantly more patients reducing their prednisone dose ≤ 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 ≥ 12 weeks.22 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.23
6. **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.

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

**Considerations**

Prior authorization is recommended for prescription benefit coverage of Nucala. 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, approval requires Nucala to be prescribed by or in consultation with a physician who specializes in the condition being treated. Refer to criteria below for approval durations.

Nucala is a medical benefit.

**Description of Procedure or Service**

Nucala, an interleukin (IL-5) antagonist immunoglobulin G (IgG)1κ monoclonal antibody, 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.

**Rationale**

**Summary of Nucala Pivotal Trial Data in Patients with Asthma**

There were three pivotal studies that evaluated the efficacy of Nucala in patients ≥ 12 years of age with refractory eosinophilic asthma. The DREAM (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma) study (n = 616) [published] found that 52 weeks of therapy with mepolizumab 75 mg IV, 250 mg IV, or 750 mg IV every 4 weeks significantly decreased the number of clinically significant asthma exacerbations per patient per year. Reductions of 48%, 39%, and 52% vs. placebo were observed with the 75 mg, 250 mg, and 750 mg mepolizumab IV doses, respectively. Of note, Nucala is not Food and Drug Administration (FDA)-approved for IV use; in later studies, mepolizumab 75 mg IV and Nucala 100 mg SC demonstrated similar efficacy. The MENSA (MEpolizumab as adjunctive therapy iN patients with Severe Asthma) trial (n = 576) [published] found that following 32 weeks of therapy, the estimated annual exacerbation rate per patient was significantly lower with mepolizumab 75 mg IV and Nucala 100 mg SC than with placebo; reductions of 47% and 53% were observed, respectively (P < 0.001 for both comparisons). The SIRIUS (SteroId Reduction with mepolIzUmab Study) trial (n = 135) [published] assessed the efficacy of Nucala 100 mg SC to reduce the need for maintenance oral glucocorticoid therapy in patients ≥ 12 years of age with severe eosinophilic asthma. At Week 24, significantly more patients in the Nucala group were able to reduce their oral glucocorticoid dose vs. the placebo group (odds ratio [OR] 2.39; P = 0.008). The annualized exacerbation rate was 1.44 per year with Nucala therapy vs. 2.12 with placebo (rate ratio 0.68; 95% CI: 0.47, 0.99; P = 0.04).
Guidelines
The 2015 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention addresses asthma treatment using a step-wise approach.\textsuperscript{5} For patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence to high-dose ICS therapy and a second controller medication, referring the patient to a specialist with expertise in the management of severe asthma to investigate and consider additional treatments is recommended. It is noted that very few patients are completely resistant to corticosteroids; ICSs remain the mainstay of therapy even in the setting of difficult-to-treat, severe asthma. Optimizing the ICS/LABA dose is also important, as some patients may respond to doses of ICSs that are higher than doses routinely recommended for general use. If this strategy is utilized, the risk of systemic AEs increases and dose reduction should be considered at 3 to 6 month intervals. Some patients with severe asthma may also require low-dose oral corticosteroid maintenance treatment; however, long-term AEs need to be considered and patients should be monitored for osteoporosis. Other add-on therapies may be considered, including theophylline and leukotriene receptor antagonists (LTRAs), although data to support their use is limited and the benefits demonstrated were minimal in patients with severe asthma. The addition of Spiriva\textsuperscript{R} Respimat\textsuperscript{R} (tiotropium bromide inhalation spray), a long-acting muscarinic antagonist (LAMA), to moderate to high dose ICS/LABA has also demonstrated improved lung function and reduced time to first exacerbation.

Phenotyping of asthma is also addressed in the GINA guidelines.\textsuperscript{5} Patients with severe asthma may benefit from phenotyping into disease categories such as severe allergic, aspirin-exacerbated, or eosinophilic asthma. Overall it is noted that more research is needed to fully understand the clinical utility of phenotypic classification. Anti-immunoglobulin E (IgE) therapy (Xolair\textsuperscript{R} [omalizumab injection for subcutaneous use]) may be beneficial in patients with severe allergic asthma with elevated IgE levels. LTRAs may be useful in patients found to be aspirin-sensitive. Sputum-guided treatment may allow corticosteroid dose and/or exacerbation frequency to be reduced as treatment can be adjusted on the basis of sputum eosinophils; however, this requires a center with expertise in inducing and analyzing sputum. The GINA guidelines state that in rare cases of steroid-resistant asthma with eosinophilia, an anti-IL-5 antibody can reduce asthma exacerbations, although Nucala is not referenced specifically. Non-pharmacological interventions are discussed as well with the consensus that more studies are needed to determine the value of these treatments.

The 2014 International European Respiratory Society (ERS)/American Thoracic Society (ATS) Guidelines on Definition, Evaluation, and Treatment of Severe Asthma are generally in-line with the GINA recommendations.\textsuperscript{5,6} The ERS/ATS guidelines state that no specific asthma phenotypes have been broadly agreed upon, although several have been identified.\textsuperscript{6} Identification of eosinophilic inflammation may be helpful when considering both non-specific (corticosteroids) and targeted therapies. It is noted that in adult patients with severe asthma, treatment should be guided by clinical criteria as well as sputum eosinophil counts performed in centers that are experienced with this technique, rather than clinical criteria alone. The ERS/ATS guidelines do not specifically address the use of blood eosinophil levels to guide therapy; however, they do note that blood eosinophils are biomarkers of T-helper cell inflammation. The clinical utility of blood eosinophils, as well as more specific biomarkers, requires confirmation. Blood and sputum eosinophils are often elevated in patients with severe allergic asthma, eosinophilic asthma, and patients experiencing recurrent exacerbations. The ERS/ATS guidelines also recommend a trial of Xolair in patients with severe allergic asthma ≥ 6 years old with an elevated IgE level despite optimal pharmacological and non-pharmacological management. Nucala is mentioned as a possible new targeted severe asthma therapy that was not found to be beneficial in unselected adult patients with moderate asthma, but decreased exacerbations and reduced oral corticosteroid requirements in patients with severe asthma and persistent sputum eosinophilia.

**Billing Coding/Physician Documentation Information**

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<th>Code</th>
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<td>J2182</td>
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Policy Implementation/Update Information

02/2016  New policy
02/2017  No changes to policy statement; replaced J3490 with J2182
01/2018  Annual review: added FDA approved indication treatment of adults with eosinophilic granulomatosis with polyangiitis (EGPA)
01/2019  Reviewed – no changes made

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