# mepolizumab (Nucala®)

**Policy #** 00501
Original Effective Date: 02/17/2016
Current Effective Date: 02/21/2018

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), 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.*

Based on review of available data, the Company may consider mepolizumab (Nucala®)‡ for add-on maintenance treatment of severe asthma (eosinophilic phenotype) OR for the treatment of patients with eosinophilic granulomatosis with polyangitis (EGPA) 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 12 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™])‡; AND
IV. Nucala is dosed at 100 mg every 4 weeks; AND
V. 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 ≥ 300 cells per microliter within the previous 12 months; AND
VI. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
*(Note that the 3 month timeframe is an additional company requirement and will be denied as not medically necessary if not met)*;
    a) An inhaled corticosteroid (ICS), (e.g., fluticasone products [Flovent® HFA, Flovent® Diskus®, Arnuity™ Ellipta®]‡, 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]‡); 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]‡, 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®]‡); 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) 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.

**Re-Authorization**

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

I. Nucala is being used for the treatment of severe asthma (eosinophilic phenotype); AND
II. Nucala is NOT being used in combination with other monoclonal antibodies typically used to treat asthma [e.g., reslizumab (Cinqair), omalizumab (Xolair), benralizumab (Fasenra); AND
III. Patient is greater than or equal to 12 years of age; AND
IV. Nucala is dosed at 100 mg every 4 weeks; 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.)
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary if not met)*;

**<u>Eosinophilic Granulomatosis with Polyangitis</u>**

<u>Patient Selection Criteria</u>

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
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary if not met)*;
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 5 therapy (e.g., Nucala, Cinqair, Fasenra); AND
V. Nucala is dosed at 300 mg every 4 weeks.

**Re-Authorization**
Coverage continuation for mepolizumab (Nucala) will be considered for the treatment of EGPA when the following criteria are met:
I. Patient has a diagnosis of EGPA; AND
II. Patient is 18 years of age or older; 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).
*(Note that this criterion is an additional company requirement and will be denied as not medically necessary if not met)*;

**When Services Are Considered Not Medically Necessary**
Based on review on available data, the Company 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 on available data, the Company 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 Company 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 Company 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 to be **investigational.***

mepolizumab (Nucala®)

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## 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 12 years and older, with an eosinophilic phenotype as well as for the treatment of adults with EGPA. 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 and EGPA. 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 and EGPA has not been definitively established. Nucala is provided in 100 mg lyophilized powder in a single-dose vial for reconstitution. Nucala should be reconstituted and administered by a healthcare professional. The dosing of Nucala is 100 mg administered subcutaneously (SC) once every 4 weeks in severe asthma and 300 mg administered SC 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 Polyangitis**

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.

## 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.

## Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

**Asthma**

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 SC in the subsequent trials. Nucala is not indicated for IV use and should only be administered by the SC 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 SC (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 SC 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 SC (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 FEV1 was measured in all 3 trials. Compared with placebo, Nucala did not provide consistent improvements in mean change from baseline in FEV1.

**Eosinophilic Granulomatosis with Polyangitis**
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.

## References

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## Policy History

Original Effective Date: 02/17/2016
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02/04/2016 Medical Policy Committee review
02/17/2016 Medical Policy Implementation Committee approval. New Policy.

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|---|---|
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes and HCPCS code update |
| 02/02/2017 | Medical Policy Committee review |
| 02/15/2017 | Medical Policy Implementation Committee approval. Clarified that Nucala should not be used along with other monoclonal antibodies used to treat asthma. |
| 02/01/2018 | Medical Policy Committee review |
| 02/21/2018 | Medical Policy Implementation Committee approval. Added a new indication and criteria: eosinophilic granulomatosis with polyangitis. Updated background info and rationale to reflect the new indication. |
| 06/01/2018 | In Asthma Patient Selection Criteria under Initial Authorization IV, the open bullets points were corrected to read “a)” and “b)”. Coverage eligibility unchanged. |

Next Scheduled Review Date: 02/2019

## Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 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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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, J3490, J3590 |
| ICD-10 Diagnosis | J45.20 J45.21 J45.22 J45.30 J45.31 J45.32 J45.40 J45.41 J45.42 J45.50 J45.51 J45.52 J45.901 J45.902 J45.909 J45.991 J45.998 L92.2 |

*****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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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