Introduction

Nucala® is a drug that works with the immune system. It reduces a type of white blood cell known as an eosinophil. Too much of this type of blood cell is thought to contribute to the symptoms of asthma. Nucala is an add-on medication. This means it’s used with other asthma medications in people who have severe asthma even though they are using their prescribed medications. Nucala can help prevent severe asthma attacks, which are known as exacerbations. This policy describes when Nucala may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucala® (mepolizumab)</td>
<td>Nucala® (mepolizumab) may be considered medically necessary for the labeled indication of add-on maintenance treatment of patients with severe asthma aged 12 years and</td>
</tr>
</tbody>
</table>
Drug Medical Necessity

older, and with an eosinophilic phenotype, when the following conditions are met:

1. Patient has a history of 2 or more exacerbations in the previous year, requiring bursts of systemic steroids and commonly requiring urgent care visits,* ER visits and/or hospitalizations, despite regular use of high-dose inhaled corticosteroids (such as those listed in the table below), plus at least one additional controller (such as long-acting beta agonists (LABAs) salmeterol or formoterol.

AND

2. Patient has had AT LEAST ONE of the following 2 criteria in the previous 12 months:
   - Blood **eosinophil count greater than 150 cells/mcL at the time of treatment
   - OR
   - Sputum **eosinophil count greater than or equal to 3%

*Note: Urgent care visits are not always required, since some patients are given a standing prescription for a systemic steroid that they can fill when exacerbations occur, eliminating the need for an unnecessary urgent care visit that could actually delay initiation of the steroid burst.

**Note: Eosinophil count is a type of blood test that measures the quantity of a type of white blood cell called eosinophils. If the number in the blood or sputum is high (greater than 150 cells/mcL or 3%, respectively), this suggests that the patient is unresponsive to their regular maintenance (inhaled or oral) corticosteroid treatment, in which case Nucala can be considered medically necessary.

All other uses of mepolizumab, including for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus, are considered investigational.

Initial and all subsequent treatment requests may be approved for 12 months at a time.

Approval beyond the first authorization would require
Drug Medical Necessity
evidence (ie, chart notes) demonstrating continued clinical benefit.

### High Dose Regimens of Inhaled Corticosteroids

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Formulation</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beclomethasone HFA</strong></td>
<td><strong>Qvar</strong></td>
<td>80 to 160 mcg</td>
<td>&gt;160 to 320 mcg</td>
<td>&gt;320 mcg</td>
</tr>
<tr>
<td>40 mcg per puff</td>
<td></td>
<td>2 to 4 puffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mcg per puff</td>
<td></td>
<td>1 to 2 puffs</td>
<td>3 to 4 puffs</td>
<td>&gt;4 puffs</td>
</tr>
<tr>
<td><strong>Budesonide DPI</strong></td>
<td><strong>Pulmicort Flexhaler</strong></td>
<td>180 to 360 mcg</td>
<td>&gt;360 to 720 mcg</td>
<td>&gt;720 mcg</td>
</tr>
<tr>
<td>90 mcg per inhalation</td>
<td></td>
<td>2 to 4 inhalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 mcg per inhalation</td>
<td></td>
<td>1 to 2 inhalations</td>
<td>3 to 4 inhalations</td>
<td>&gt;4 inhalations</td>
</tr>
<tr>
<td><strong>Ciclesonide HFA</strong></td>
<td><strong>Alvesco</strong></td>
<td>80 to 160 mcg</td>
<td>&gt;160 to 320 mcg</td>
<td>&gt;320 mcg</td>
</tr>
<tr>
<td>80 mcg per puff</td>
<td></td>
<td>1 to 2 puffs</td>
<td>3 to 4 puffs</td>
<td></td>
</tr>
<tr>
<td>160 mcg per puff</td>
<td></td>
<td>1 puff</td>
<td>2 puffs</td>
<td>&gt;2 puffs</td>
</tr>
<tr>
<td><strong>Fluticasone propionate HFA</strong></td>
<td><strong>Flovent HFA</strong></td>
<td>88 to 220 mcg</td>
<td>&gt;220 to 440 mcg</td>
<td>&gt;440 mcg</td>
</tr>
<tr>
<td>44 mcg per puff</td>
<td></td>
<td>2 to 5 puffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>110 mcg per puff</td>
<td></td>
<td>1 to 2 puffs</td>
<td>3 to 4 puffs</td>
<td></td>
</tr>
<tr>
<td>220 mcg per puff</td>
<td></td>
<td>2 puffs</td>
<td></td>
<td>&gt;2 puffs</td>
</tr>
<tr>
<td><strong>Fluticasone propionate DPI</strong></td>
<td><strong>Flovent Diskus</strong></td>
<td>100 to 250 mcg</td>
<td>&gt;250 to 500 mcg</td>
<td>&gt;500 mcg</td>
</tr>
<tr>
<td>50 mcg per inhalation</td>
<td></td>
<td>2 to 5 inhalations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mcg per inhalation</td>
<td></td>
<td>1 to 2 inhalations</td>
<td>3 to 5 inhalations</td>
<td></td>
</tr>
<tr>
<td>250 mcg per inhalation</td>
<td></td>
<td>1 inhalation</td>
<td>2 inhalations</td>
<td>2 inhalations</td>
</tr>
<tr>
<td>500 mcg per inhalation</td>
<td><strong>strength not available in the U.S.</strong></td>
<td></td>
<td>1 inhalation</td>
<td>&gt;1 inhalation</td>
</tr>
<tr>
<td><strong>Fluticasone furoate DPI</strong></td>
<td><strong>Arnuity Ellipta</strong></td>
<td>Not available for low dose</td>
<td>100 mcg</td>
<td>200 mcg</td>
</tr>
</tbody>
</table>

*Not available for low dose*
### High Dose Regimens of Inhaled Corticosteroids

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mcg per inhalation</td>
<td></td>
<td>1 inhalation</td>
<td>2 inhalations</td>
</tr>
<tr>
<td>200 mcg per actuation</td>
<td></td>
<td></td>
<td>1 inhalation</td>
</tr>
<tr>
<td><strong>Mometasone DPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Asmanex DPI)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>110 mcg per inhalation</td>
<td>110 to 220 mcg</td>
<td>&gt;220 to 440 mcg</td>
<td>&gt;440 mcg</td>
</tr>
<tr>
<td>220 mcg per inhalation</td>
<td>1 to 2 inhalations</td>
<td>2 inhalations</td>
<td>&gt;2 inhalations</td>
</tr>
<tr>
<td><strong>Mometasone HFA</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>(Asmanex HFA)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mcg per actuation</td>
<td>100 to 200 mcg</td>
<td>&gt;200 to 400 mcg</td>
<td>&gt;400 mcg</td>
</tr>
<tr>
<td>200 mcg per actuation</td>
<td>1 to 2 inhalations</td>
<td>2 inhalations</td>
<td>&gt;2 inhalations</td>
</tr>
</tbody>
</table>

*Note:* Inhaled fluticasone furoate has a greater anti-inflammatory potency per microgram than fluticasone propionate inhalers. Thus, fluticasone furoate is administered at a lower daily dose and used only once daily.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2182</td>
<td>Injection, mepolizumab, 1 mg <em>(Nucala®)</em> <em>(new code effective 1/1/17)</em></td>
</tr>
</tbody>
</table>

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### Related Information

**Benefit Application**

The drugs included in this policy are covered under the medical benefit.
Evidence Review

Description

**Nucala® (mepolizumab)**

Mepolizumab, a humanized monoclonal antibody (IgG1 kappa), is the first of a novel class of medications capable of treating severe asthma in refractory patients. Unlike omalizumab, a monoclonal antibody that is effective in treating IgE related asthma, mepolizumab is designed to prevent exacerbations in patients with eosinophil mediated disease. Eosinophils have a variety of functions in inflammatory immune reactions. They can bind worms and parasites via IgE, present antigens, release pro-inflammatory mediators including IL-5 and leukotrienes, and kill microorganisms. Within their granules they contain peroxidase, major basic protein, and eosinophil-derived neurotoxin. IL-5 acts on eosinophils directly via the alpha chain of IL-5Ra, a type I IL-5 receptor. IL-5 also plays a role in other cytokine cellular mediators such as basophils and mast cells. Mepolizumab binds directly to IL-5 with high specificity and also high affinity, preventing the association of IL-5 with the eosinophil receptor IL-5Ra and thus preventing the inflammatory cascade.

**Asthma**

Asthma is a chronic disease that causes airways of the lungs to become narrow due to inflammation, which leads to difficulty breathing. During an asthma attack, breathing can become so difficult that the patient is unable to get enough oxygen. Severe attacks can make the patient seek medical attention, even hospitalization, and these attacks can be life-threatening. There are more than 400,000 asthma-related hospitalizations each year. Severe asthma is estimated to account for 5-10% of all cases, with only 3% being severe, refractory, eosinophilic disease. Patients with severe asthma are at risk for frequent exacerbations and hospitalizations. Development of therapies to control asthma in this subpopulation is an unmet need.

More than 22 million people in the U.S. have asthma, and it is the most common chronic childhood disease. Asthma affects many people regardless of age, race, and sex. According to the CDC, as of 2013, 8.3% of children and 7% of adults struggle with asthma. African Americans have the highest prevalence at 9.9%, followed by Whites at 7.4% and Hispanics, 5.9%.
In asthmatics, certain internal or external triggers can set off an allergic or hypersensitity reaction in the bronchial airways. In some patients, this is associated with hypereosinophilia. IL-5 is a key player in the growth, development and function of eosinophils to cause and sustain airway inflammation. Inflammation can lead to asthma attacks. Repeated attacks can lead to worse symptoms, sensitivity to further attacks, and bad outcomes including death.

Alternative treatments for asthma include inhaled corticosteroids (ICS), inhaled long-acting beta-adrenergic agents (LABAs), leukotriene modifying drugs, methylxanthines, and the monoclonal antibody to IgE omalizumab (Xolair). Inhaled corticosteroids have become the cornerstone of maintenance therapy for patients with persistent asthma. In spite of these available therapies, there are patients who remain poorly controlled on maximum therapy (including oral corticosteroids) and there are patients with severe persistent asthma who are resistant to corticosteroids.

**Nucala® (mepolizumab)**

**Efficacy**

Mepolizumab is a recently-approved new alternative for treating severe eosinophilic asthma. The key studies supporting efficacy of mepolizumab in severe eosinophilic asthma are the DREAM and MENSA trials. In DREAM, 621 refractory asthma patients were randomized on a 1:1:1:1 ratio to placebo, 75mg mepolizumab IV, 250mg IV, and 750mg IV. Standard background treatment included ≥ 880 mcg/day fluticasone equivalent +/− oral corticosteroids (OCS) and other controllers. Eosinophilic asthma was defined as having an eosinophil count ≥ 300 cells/mcL, sputum eosinophils 3%, exhaled NO ≥ 50 ppb, or deterioration of control in the last 12 months following < 26% reduction in inhaled corticosteroid (ICS). Patients received 13 infusions at 4 week intervals. The primary outcome was the rate of significant exacerbations from start through 4 weeks after the last visit (approximately 12 months). The 3 mepolizumab groups experienced reduction in exacerbation rates per year of 48% (95% CI 31–61%; p<0.0001), 39% (19–54%; p=0.0005), and 52% (36–64%; p<0.0001) vs placebo, respectively. A post hoc analysis examined differences in exacerbation rates in OCS dependent patients (3.12 P; 1.54 M) and non-OCS dependent (1.9 P; 1.07 M). Both groups benefited from the addition of mepolizumab.

In MENSA, 576 patients with recurrent exacerbations on high-dose ICS and with eosinophil counts of ≥ 300 cells/mcL in the last 12 months or those 150 cells/mcL were randomized to mepolizumab 75mg IV, 100mg SQ, or placebo for 32 weeks. The primary endpoint was exacerbation rate. The 100mg SQ dose showed a 53% reduction (47% for 75mg IV) over placebo.
at 32 weeks. Unlike in the DREAM trial where FEV1 improvement was <82 mL for all groups and not statistically significant, in MENSA, FEV1 in the SQ treatment group improved 98mL from baseline over placebo.

In a smaller study, 135 patients with severe eosinophilic asthma were randomized to placebo or mepolizumab 100mg SQ in addition to baseline maintenance therapy. After a 3-8 week optimization phase, a 16 week steroid reduction phase followed. At the end of this phase, the placebo group was not able to reduce the OCS dose, while the treatment group achieved a median OCS dose reduction of 50%. One-quarter of the study group had no decrease in steroid dosage or withdrew, and 16% were able to achieve complete or near complete steroid reduction.

Another study used an investigational anti IL-5 monoclonal antibody during asthma exacerbations in the emergency department for patients with high eosinophil counts. Patients in the treatment group had fewer exacerbations at 12 weeks than those given placebo (3.59 vs 1.82; P = .01) and fewer exacerbations leading to hospitalization (1.62 vs 0.65; P = .02). Providers may assume these results apply to mepolizumab as well.

**Safety**

Mepolizumab is generally well tolerated compared to placebo. Common adverse events included headache, chest pain, flushing, erectile dysfunction, rash, conjunctivitis, fatigue, upper respiratory tract infection, rhinitis, bronchitis, sinusitis, viral infection, injury, nausea, and pharyngitis. Urinary tract infections and muscle spasms have also been reported in more than 3% of treated patients. A review of exposure-adjusted nonfatal serious adverse events using the three main efficacy trials as well as open label follow-up data (n=1299) was performed by the FDA. Placebo-subtracted SAEs per 1000 subject-years were (total): infections 5 (54.2), cardiac disease 3 (6.8), musculoskeletal and connective tissue disease 6 (13.6), immune system disorders 3 (6.8), metabolic and nutrition related 6.8 (6.8), skin and subcutaneous disorders 6.8 (6.8), and hepatobiliary disorders 6.8 (6.8). Within this data, the notable conditions above placebo are (total): herpes zoster 13.6 (13.6), atrial flutter 3.3 (6.8), and hypersensitivity 3.3 (6.8). There were 3 new malignancies in the placebo group (N=412) and 0 in the mepolizumab group (N=263).

No imbalance in withdrawals occurred across the three key studies supporting efficacy. Four deaths were reported across the treatment groups (N=916) but only three were caused by respiratory problems. Due to the severity of asthma in the patient populations, no deaths have been attributed directly related to mepolizumab treatment.
A year-long followup study (mepolizumab N=29) conducted over a 12-month period monitored the rebound effect of taking patients off of anti IL-5 treatment. While no appreciable increase in exacerbation rate was found in the placebo-treated group, the mepolizumab group increased in exacerbations from 0.56 per patient in the first three months to 1.2 in months 3-6 (P < 0.007). However, the rates of exacerbations never went over pre-treatment baselines.

2017 Update

Recent data do not indicate a need for change to the above medical necessity criteria.

References


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/12/16</td>
<td>New policy, add to Medical subsection. Considered medically necessary for labeled indications when criteria are met.</td>
</tr>
<tr>
<td>02/09/16</td>
<td>Interim Update. Medical necessity criteria liberalized; deterioration of asthma control criterion removed.</td>
</tr>
<tr>
<td>02/18/16</td>
<td>Minor typographical and formatting errors fixed.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Coding update; added new HCPCS code J2182 effective 1/1/17. Moved coding table to Policy Guidelines section.</td>
</tr>
<tr>
<td>07/07/17</td>
<td>Policy moved into new format, no changes to policy statement.</td>
</tr>
<tr>
<td>09/01/17</td>
<td>Annual review approved August 22, 2017. No changes to policy statement A literature search was conducted from 1/1/16 to 8/15/17. No new studies were found that would require changes to this policy. Removed HCPCS code J3490. Title changed from Mepolizumab (Nucala®) to Nucala® (mepolizumab).</td>
</tr>
</tbody>
</table>

**Disclaimer**: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and
local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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Deutsche (German):

Iollo (Illoco):
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Italiano (Italian):

037338 (07-2016)