Respiratory Interleukins (IL)

Policy Number: 2017D0055A

Effective Date: January 1, 2017

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTRUCTIONS FOR USE</td>
<td>1</td>
</tr>
<tr>
<td>BENEFIT CONSIDERATIONS</td>
<td>1</td>
</tr>
<tr>
<td>COVERAGE RATIONALE</td>
<td>2</td>
</tr>
<tr>
<td>U.S. FOOD AND DRUG ADMINISTRATION</td>
<td>4</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>4</td>
</tr>
<tr>
<td>APPLICABLE CODES</td>
<td>4</td>
</tr>
<tr>
<td>CLINICAL EVIDENCE</td>
<td>4</td>
</tr>
<tr>
<td>CENTERS FOR MEDICARE AND MEDICAID SERVICES</td>
<td>8</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>8</td>
</tr>
<tr>
<td>POLICY HISTORY/REVISION INFORMATION</td>
<td>8</td>
</tr>
</tbody>
</table>

INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.
This policy provides information about the use of certain specialty pharmacy medications administered by either the subcutaneous (SC) or intravenous (IV) route for severe asthmatic conditions.

This policy refers to the following drug products, both of which are interleukin-5 (IL-5) antagonists:

1. **Nucala**® (mepolizumab)
2. **Cinqair**® (reslizumab)

**COVERAGE RATIONALE**

**Proven**

**Nucala** for subcutaneous use is **proven** for add-on therapy for:

1. Patients who meet **both** of the following criteria:¹
   
   A. Has an eosinophilic phenotype
   
   B. Will be used as add-on maintenance therapy in the treatment of severe asthma

**Additional information to support medical necessity review where applicable:**

**Nucala** is **medically necessary** when **all** of the following criteria are met:¹,³-⁶

A. Diagnosis of severe asthma

   **AND**

B. Classification of asthma as uncontrolled or inadequately controlled as defined by at least **one** of the following:

   1. Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20)
   
   **OR**

   2. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months
   
   **OR**

   3. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician’s office visit for nebulizer or other urgent treatment)
   
   **OR**

   4. Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second [FEV1] less than 80% predicted [in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal])

   **AND**

C. Asthma is an eosinophilic phenotype as defined by a baseline (pre-mepolizumab treatment) peripheral blood eosinophil level ≥ 150 cells/μL within the past 6 weeks

   **AND**

D. Used in combination with **one** of the following:

   1. **One** maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta₂-agonist (LABA) product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]
   
   **OR**

   2. Combination therapy including **both** of the following:

   a. **One** high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]
   
   **AND**

   b. **One** additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®); leukotriene receptor antagonist – montelukast (Singulair®); theophylline]

   **AND**

E. Patient is **not** receiving Nucala in combination with either of the following:

   1. Xolair (omalizumab)
   
   2. Cinqair (reslizumab)

   **AND**

F. Nucala dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 100mg subcutaneously once every 4 weeks

   **AND**

G. Prescribed by or in consultation with a pulmonologist or allergist/immunologist

**Cinqair** for intravenous use is **proven** for add-on therapy for:

1. Patients who meet **both** of the following criteria:²

   A. Have an eosinophilic phenotype
   
   B. Will be used as add-on maintenance therapy in the treatment of severe asthma
Additional information to support medical necessity review where applicable:
Cinqair is medically necessary when all of the following criteria are met:

A. Diagnosis of severe asthma
   AND
B. Classification of asthma as uncontrolled or inadequately controlled as defined by at least one of the following:
   1. Poor symptom control (e.g., ACQ score consistently greater than 1.5 or ACT score consistently less than 20)
   OR
   2. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months
   OR
   3. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician’s office visit for nebulizer or other urgent treatment)
   OR
   4. Airflow limitation (e.g., after appropriate bronchodilator withhold FEV1 less than 80% predicted [in the face of reduced FEV1/FVC defined as less than the lower limit of normal])
   AND
C. Asthma is an eosinophilic phenotype as defined by a baseline (pre-reslizumab) peripheral blood eosinophil level of ≥ 400 cells/μL within the past 4 weeks
   AND
D. Used in combination with one of the following:
   1. One maximally-dosed (appropriately adjusted for age) combination ICS/LABA product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]
   OR
   2. Combination therapy including both of the following:
      a. One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]
      AND
      b. One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®), leukotriene receptor antagonist – montelukast (Singulair®), theophylline]
   AND
E. Patient is not receiving Cinqair in combination with either of the following:
   1. Xolair (omalizumab)
   2. Nucala (mepolizumab)
   AND
F. Cinqair dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 3 mg/kg intravenously once every 4 weeks
   AND
G. Prescribed by or in consultation with a pulmonologist or allergist/immunologist

Reauthorization/Continuation of Care Criteria
For patients currently on Nucala or Cinqair for the treatment of severe eosinophilic asthma, authorization for continued use will be approved based on all of the following criteria:
A. Documentation of positive clinical response (e.g., reduction in exacerbations)
   AND
B. Used in combination with an ICS-containing controller medication
   AND
C. One of the following:
   1. Patient is not receiving Nucala in combination with either of the following:
      a. Xolair (omalizumab)
      b. Cinqair (reslizumab)
   OR
   2. Patient is not receiving Cinqair in combination with either of the following:
      a. Xolair (omalizumab)
      b. Nucala (mepolizumab)
   AND
D. One of the following:
   1. Nucala dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 100mg subcutaneously once every 4 weeks
   OR
   2. Cinqair dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 3 mg/kg intravenously once every 4 weeks
   AND
E. Prescribed by or in consultation with a pulmonologist or allergist/immunologist
Unproven
Nucala and Cinqair are **unproven and not medically necessary** in the following:1,2,8
1. Other eosinophilic conditions
2. Acute bronchospasm
3. Status asthmaticus
4. Chronic obstructive pulmonary disease (COPD)

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

**Nucala (mepolizumab)**
Nucala is approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, who have an eosinophilic phenotype. Nucala is not indicated for the treatment of other eosinophilic conditions or for acute bronchospasm or status asthmaticus.1

**Cinqair (reslizumab)**
Cinqair is approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of patients with severe asthma aged 18 years and older, who have an eosinophilic phenotype. Cinqair is not indicated for the treatment of other eosinophilic conditions or for acute bronchospasm or status asthmaticus. Because of the risk of anaphylaxis, healthcare providers administering Cinqair should observe patients closely for an appropriate period of time and be prepared to manage anaphylaxis that can be life-threatening.2

BACKGROUND

Asthma is a common chronic inflammatory disease of the airways that affects an estimated 24 million adults and children. Although the disease is well controlled with inhaled therapy in most patients, approximately 1.2-2.4 million people have severe asthma (i.e., 5-10% of the asthma population) that is associated with substantial morbidity, mortality, and economic effects. Asthma has been divided into subtypes, some of which are associated with airway inflammation with eosinophils. It is estimated that about half of individuals with severe asthma exhibit the eosinophilic phenotype with elevated eosinophil levels (a marker of inflammation) in both the blood and airways. Activated eosinophils can increase airway smooth muscle contraction and mucus secretion, which are hallmarks of asthma. Interleukin-5 (IL-5) is an important cellular signal in eosinophilic inflammation. Therapies that decrease IL-5 levels, such as Nucala (mepolizumab) and Cinqair (reslizumab), may decrease eosinophils in lung tissue.4,7,9,10

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2182</td>
<td>Injection, mepolizumab, 1 mg</td>
</tr>
<tr>
<td>J2786</td>
<td>Injection, reslizumab, 1 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J45.50</td>
<td>Severe persistent asthma, uncomplicated</td>
</tr>
<tr>
<td>J45.51</td>
<td>Severe persistent asthma with (acute) exacerbation</td>
</tr>
<tr>
<td>J45.52</td>
<td>Severe persistent asthma with status asthmatic</td>
</tr>
<tr>
<td>J82</td>
<td>Pulmonary eosinophilia, not elsewhere classified</td>
</tr>
</tbody>
</table>

CLINICAL EVIDENCE

**Proven**
**Severe Eosinophilic Asthma**

Mepolizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.1
Reslizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.\textsuperscript{2}

**Professional Societies**

**Severe Eosinophilic Asthma**

The Global Initiative for Asthma (GINA, 2016) recommends that for Step 5 treatment, adults and adolescents, aged \( \geq \) 12 years old may be treated with **mepolizumab** as follows (Evidence B: Randomized controlled trials and meta-analyses. Limited body of evidence):\textsuperscript{6}

- **Step 5:** Higher level care and/or add-on treatment. Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in management of severe asthma (Evidence D: Panel consensus judgment).
- Treatment options that may be considered at Step 5 (in not already tried) include: add-on **mepolizumab** (anti-interleukin-5 treatment) for patients \( \geq \) 12 years old with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (Evidence B).

On March 14, 2016, the Institute for Clinical and Economic Review (ICER) released a clinical report entitled, "Mepolizumab (Nucala\textsuperscript{®}, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks." ICER recommendations are as follows:\textsuperscript{4}

- ICER judges the current body of evidence on **mepolizumab** to be "comparable or better."
- For adult patients with severe eosinophilic asthma, ICER judges there to be moderate certainty of a comparable or better net benefit for **mepolizumab** 100mg SC every four weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and additional controller medications. There is moderate certainty because both the MENS A trial, which demonstrated a significant reduction in asthma exacerbations, and the SIRIUS trial, which demonstrated a significant reduction in oral corticosteroids dosage, were relatively small studies of short duration. There remains uncertainty about the long-term durability of the benefits of the therapy and about the potential harms from modulation of the immune system. Ongoing post-marketing trials and extension studies evaluating **mepolizumab** may demonstrate a wide variety of outcomes, from substantial net health benefit to a comparable net benefit given the potential harms associated with the monoclonal antibody (opportunistic infection, anaphylaxis).

The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines define severe asthma as that which requires treatment with high-dose ICSs plus a second controller (or systemic corticosteroids) to prevent progression to uncontrolled disease status or continuing uncontrolled disease status despite this therapy.\textsuperscript{3} The guidelines recommend that, "While the anti-IL5 antibody, mepolizumab, was not beneficial in unselected adult patients with moderate asthma, when studied in severe asthma patients with persistent sputum eosinophilia, two anti-IL-5 antibodies, mepolizumab and reslizumab, have been shown to decrease exacerbations and oral corticosteroid use, as well as improve symptoms and lung function to varying degrees."

The National Asthma Education and Prevention Program (NAEPP) published guidelines in 2007 entitled, "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma."\textsuperscript{5} The NAEPP guidelines provide information on classifying asthma severity in section 3, component 1: Measures of Asthma Assessment and Monitoring. The Expert Panel also states that the beneficial effects of long-acting beta-agonist (LABAs) in combination therapy for the great majority of patients who require more therapy than low-dose inhaled corticosteroid alone to control asthma (i.e., require step 3 care or higher) should be weighed against the increased risk of severe exacerbations, although uncommon, associated with the daily use of LABAs. Figure 1 shows how to establish asthma severity in children \( \geq \) 12 years of age and adults and also recommends a step for initiating therapy. Figure 2 shows how to classify asthma control and how to adjust therapy for children \( \geq \) 12 years of age and adults.
**Figure 4-6. Classifying Asthma Severity and Initiating Treatment in Youths ≥12 Years of Age and Adults**

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications.

### Components of Severity

<table>
<thead>
<tr>
<th>Classification of Asthma Severity</th>
<th>≥12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>≤1/year (see note)</td>
</tr>
</tbody>
</table>

**Key:** FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

**Notes:**
- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient/caregiver’s recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

Unproven

Nucala and Cinqair have additional uses listed in the FDA-label:1-2

- Other eosinophilic conditions
- Acute bronchospasm
- Status asthmaticus
- Chronic obstructive pulmonary disease (COPD)

Statistically robust randomized controlled trials are necessary to establish the safety and efficacy of Nucala and Cinqair to treat these conditions.1-2,8
CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Nucala® (mepolizumab). Local Coverage Determinations (LCDs) do not exist at this time.

Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf. (Accessed April 27, 2016)

Medicare does not have a National Coverage Determination (NCD) for Cinqair® (reslizumab). Local Coverage Determinations (LCDs) do not exist at this time.

Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf. (Accessed April 27, 2016)

REFERENCES

1. Nucala® [prescribing information]. Research Triangle Park, NC; GlaxoSmithKline, LLC; November 2015.
2. Cinqair® [prescribing information]. Frazer, PA; Teva Respiratory, LLC; March 2016.

POLICY HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1/2017</td>
<td>New policy 2016D0055A. Approved by the National Pharmacy &amp; Therapeutics Committee on 7/27/2016.</td>
</tr>
</tbody>
</table>