Subject: Nucala (mepolizumab)	Original Effective Date: 9/21/2016
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Review Date(s):	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of **Nucala (mepolizumab)** for the treatment of the following indications when appropriate criteria are met:

- Severe asthma with an eosinophilic phenotype in adults and children 12 years and older, and
- Eosinophilic granulomatosis with polyangiitis (EGPA also referred to as Churg-Strauss syndrome)

The intent of the Nucala (mepolizumab) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies.

- Asthma is a common, chronic respiratory disease in which the lung's airways become inflamed and narrowed. While the majority of patients with asthma can be treated effectively with the proper use of maintenance medications, patients with severe asthma are refractory to current standards of treatment, including oral corticosteroids.
  - Generally, eosinophils circulate in the peripheral blood and are found in peripheral tissue and respiratory mucosa, and levels increase in the presence of acute inflammation. Eosinophils are recruited into the airway in allergic asthma by the action of cytokines and chemokines, such as interleukin-5 (IL-5), a potent eosinophil activator that facilitates recruitment into tissues. **IL-5 antagonists** block IL-5 from binding to eosinophils, resulting in the inhibition of eosinophil growth and differentiation, recruitment, activation, and survival.
  - **Eosinophilic asthma** is a subset of **severe asthma** that is characterized by increased eosinophil counts. Because increased eosinophilia correlates with worse disease, mediators of the eosinophil pathway, such as interleukin-5 (IL-5), are targets for preventing eosinophil-mediated inflammation.
  - **Cinqair (reslizumab), Nucala (mepolizumab), and Fasenra (benralizumab)** are indicated for the add-on maintenance treatment of severe eosinophilic asthma and are indicated for use in severe eosinophilic asthma. Used as maintenance therapy, these agents may benefit individuals with eosinophilic asthma.

- The anti-asthmatic monoclonal antibodies are subdivided into two subclasses: Anti-IgE antibodies and Anti-IL-5 antibodies.
  1) **Anti-IL-5 monoclonal antibodies: Cinqair (reslizumab), Nucala (mepolizumab), Fasenra (benralizumab)**
     - IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils (a cell type associated with inflammation and an important component of the pathogenesis of asthma).
     - Benralizumab, a humanized monoclonal antibody (IgG1, kappa), is an interleukin-5 antagonist. Benralizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of benralizumab action in asthma has not been definitively established.
     - Cinqair (reslizumab), Nucala (mepolizumab), and Fasenra (benralizumab) are indicated for the add-on maintenance treatment of severe eosinophilic asthma. **These agents have been evaluated in combination with other asthma treatments and are <u>not</u> utilized as monotherapy.**
     - Fasenra (benralizumab) and Nucala (mepolizumab) have been shown to be safe and effective for use in **children 12 years of age and older**. Cinqair (reslizumab) is indicated for **adults** ages 18 year and older. There are currently no generic products available for these agents.
     - Due to the associated risks of anaphylaxis and complicated administration, all three agents (benralizumab, mepolizumab, reslizumab) must be **administered by a healthcare professional**.
  2) **Anti-immunoglobulin E (IgE) monoclonal antibodies: Xolair (omalizumab)**
     - Xolair (omalizumab) is the only anti-IgE antibody currently available and is FDA-approved for the treatment of moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen in addition to chronic idiopathic urticaria.

- **Eosinophilic granulomatosis with polyangiitis (EGPA also referred to as Churg-Strauss syndrome)**
  - A chronic rare disease that is characterized by asthma, high levels of eosinophils and inflammation of small- to medium-sized blood vessels (vasculitis). The inflamed vessels can affect various organ systems, including the lungs, gastrointestinal tract, skin, heart and nervous system.
  - Can result in damage to lungs, sinuses, skin, heart, gastrointestinal tract, nerves and other organs
  - The most common symptoms include extreme fatigue, muscle and joint pain, weight loss, sinonasal symptoms, and breathlessness.
  - Current approach to disease management is primarily based on reduction of active inflammation and suppression of the immune response through the use of corticosteroids and concomitant immunosuppressive therapy (*e.g., methotrexate, azathioprine, mycophenolate mofetil*) and/or cytotoxic agents (*e.g. cyclophosphamide*). Although the use of these treatments can be effective for establishing remission, the long-term use of these therapies and the risk of relapse, particularly if the dose of corticosteroid is reduced is a significant limiting factor
  - Global incidence is estimated in the range of 1-4 per million, with an estimated prevalence of approximately 14-45 per million; approximately 5000 patients with EGPA in the US. The mean age of diagnosis is 48 years, and the disease can be life-threatening for some patients.
  - Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma and EGPA has not been definitively established.

- **Nucala (mepolizumab)**
  - **<u>Severe asthma, Add-on maintenance in patients with eosinophilic phenotype</u>**
    - The first FDA-approved biologic agent that targets IL-5, which regulates the function of eosinophils. Mepolizumab is a first-in-class interleukin-5 antagonist (immunoglobulin G1 [IgG1] kappa) monoclonal antibody for the treatment of severe eosinophilic asthma.
    - FDA approval for add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype the based upon three pivotal phase III trials: MENSA, SIRIUS, and DREAM. ****Refer to 'Summary of Clinical Evidence' section of policy for additional information***

- Nucala has been shown to decrease the incidence of asthma exacerbations in adult and adolescent patients 12 years of age and older with severe asthma whose symptoms are inadequately controlled with inhaled corticosteroids. Nucala is approved for patients who have a history of severe asthma attacks (exacerbations) despite receiving their current asthma medicines.

- **Eosinophilic Granulomatosis with polyangiitis (EPGA)**
  - FDA expanded approval to treat adult patients with EPGA, a rare autoimmune disease that causes vasculitis, an inflammation in the wall of blood vessels of the body
  - Nucala (mepolizumab) is the first targeted treatment for eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome
  - The FDA based its expanded approval on data from a 52-week clinical trial that compared mepolizumab with placebo. Patients received 300 mg of mepolizumab or placebo once every 4 weeks while continuing their stable daily oral corticosteroids therapy. Oral corticosteroids were tapered during the treatment period at week 4. The primary efficacy assessment in the trial measured mepolizumab's treatment impact on disease remission while on an oral corticosteroid dose of 4 mg or less of prednisone. ***Refer to 'Summary of Clinical Evidence' section of policy for additional information***
  - Patients receiving mepolizumab achieved a significantly greater accrued time in remission compared with those who received a placebo. A significantly higher proportion of patients receiving mepolizumab achieved remission at both week 36 and week 48 compared with placebo. In addition, significantly more patients who received mepolizumab achieved remission within the first 24 weeks, and remained in remission for the remainder of the 52-week study treatment period compared with patients who received the placebo.

- **Comparative Efficacy**

<u>Severe asthma, Add-on maintenance in patients with eosinophilic phenotype</u>

- No head-to-head trials comparing benralizumab with other anti-IL-5 antibodies benralizumab (Fasenra) and reslizumab (Cinqair) are available.
- Head-to-head trials comparing anti-IL-5 antibodies to omalizumab (Xolair) have not been conducted at this time also; therefore, the comparative efficacy and safety are unknown at this time.
- Concurrent use of mepolizumab (Nucala) with omalizumab (Xolair): The efficacy and safety of mepolizumab (Nucala) in combination with omalizumab (Xolair) have not been established.
  - *Xolair is a recombinant humanized immunoglobulin G (IgG) monoclonal antibody 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.*
- Nucala (mepolizumab) and Xolair (omalizumab) have different indications for use and the two drugs are not interchangeable. While there is a possibility that patients with severe asthma may meet criteria for treatment with both omalizumab (allergic asthma) and mepolizumab (eosinophilic asthma), there is currently no clinical trials evaluating combination therapy with two monoclonal antibodies. Therefore, such use is not recommended.
- **There are no comparative trials among the agents in this class to suggest preference of one agent over another for the treatment of severe asthma.**
- Mepolizumab (Nucala) and reslizumab (Cinqair) are humanized IL-5 antagonist monoclonal antibodies that reduce eosinophils, while benralizumab (Fasenra) targets IL-5 receptor alpha, resulting in nearly complete depletion of eosinophil**s. It is unknown if the difference in binding sites has a clinically significant impact on efficacy or safety among these 3 drugs.**

CLASSIFICATION: Interleukin-5 Receptor Antagonist; Monoclonal Antibody, Anti-Asthmatic

FDA INDICATIONS

⌘ **SEVERE ASTHMA WITH AN EOSINOPHILIC PHENOTYPE**
Add-on maintenance treatment of severe asthma in adults and pediatric patients ≥ **12 years of age** with an eosinophilic phenotype.

Limitations of use: Not indicated for the relief of acute bronchospasm or status asthmaticus

⌘ **EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS**
For the treatment of eosinophilic granulomatosis with polyangiitis in adults

Available as: Vial: 100 mg of lyophilized powder in a single-dose vial for reconstitution
FDA Approved

- Severe asthma with an eosinophilic phenotype: November 4, 2015
- Eosinophilic Granulomatosis with polyangiitis (EPGA): December 2017

Black Box Warning: None at the time of this writing
REMS: None at the time of this writing

RECOMMENDATIONS/COVERAGE CRITERIA

SEVERE ASTHMA, ADD-ON MAINTENANCE IN PATIENTS WITH EOSINOPHILIC PHENOTYPE

Nucala (mepolizumab) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

❒ Prescribed by, or in consultation with, a board-certified asthma specialist (allergist, immunologist, pulmonologist) or physician experienced in the management of asthma. Submit consultation notes if applicable.

NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]
Clinical **documented** diagnosis of (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*): [ALL]

❒ Diagnosis of **severe** asthma with an eosinophilic phenotype or predominantly eosinophil-driven disease also described as "airway eosinophilia"
- *Benralizumab is not approved for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.*

❒ **Blood eosinophil counts** within 6 weeks of request * in the absence of other potential causes associated with elevated peripheral eosinophil counts. Laboratory documentation required: [ONE]
**Clinically important pulmonary disease other than asthma (e.g. active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome)*

- ❍ 150 cells/microliter or greater (within the previous 6 weeks) at the initiation of therapy [1 microliter (µL) is equal to 1 cubic millimeter (mm^3)]
- ❍ 300 cells/microliter or greater (within the previous 12 months)
- ❍ Sputum eosinophilic count of at least 3% or greater (within the previous 12 months)

Informational Note

- *In 1 clinical trial, patients were required to have blood eosinophil count of 300 cells/mcL or greater or a sputum eosinophil count 3% or greater in the previous 12 months.*
- *In 2 clinical trials, patients were required to have blood eosinophil count of 150 cells/mcL or greater within 6 weeks of dosing or blood eosinophil count of 300 cells/mcL or greater within 12 months of enrollment.*

Appendix 4: Blood Eosinophil Counts

3. Age/Gender/Other restrictions [ALL]

- ❒ 12 years of age or older
  - *Safety and efficacy of mepolizumab have not been established in patients younger than 12 years of age*
- ❒ Member is a non-smoker OR smoking cessation has been at least 6 months
- ❒ Underlying conditions or triggers for asthma or pulmonary disease are being maximally managed

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ Exacerbation(s) or hospitalization(s) *within the past 12 months* documented by **ONE (1)** of the following: [ONE]
  - ❍ TWO (2) or more exacerbations requiring treatment with systemic corticosteroid (intramuscular, intravenous, or oral) despite the use of high-dose inhaled corticosteroids in the past 12 months
    OR
  - ❍ Two-fold increase or greater in the dose of systemic corticosteroid treatment for asthma exacerbations
    OR
  - ❍ Asthma worsens upon tapering of oral corticosteroid therapy
    OR
  - ❍ ONE (1) or more asthma-related urgent treatment (such as hospitalization, emergency room visit, unscheduled physician's office visit) within the previous 12 months
    OR
  - ❍ Mechanical ventilation in the past 12 months
    OR
  - ❍ Poor symptom control indicated by ACQ score consistently greater than 1.5 or ACT score consistently less than 20)
    OR
  - ❍ Forced expiratory volume in 1 second (FEV1) < 80% predicted **OR** FEV1/forced vital capacity (FVC) < 0.80

❒ Symptoms inadequately controlled (as documented in criteria above) after an **adherent** regimen of at **least 3 months** of the following COMBINATION THERAPY: **[A OR B]**

A. High-dose Inhaled Corticosteroid (appropriately adjusted for age) **AND** a second controller drug (i.e. long-acting beta agonist, leukotriene receptor antagonist) with or without oral corticosteroid **[ONE: 1 OR 2]**

1. **High-dose inhaled corticosteroid* (or maximally tolerated dose)** [*e.g. Aerospan (flunisolide), Alvesco (ciclesodine), Asmanex (mometasone furoate), Flovent HFA (fluticasone propionate), Pulmicort (budesonide), QVAR (beclomethasone dipropionate HFA)*]

   [Appendix 2: Estimated Comparative Daily Dosages for ICS in ≥ 12 years of age and Adults]

   AND

   ONE (1) ADDITIONAL ASTHMA CONTROLLER MEDICATION
   - ❍ Long-acting beta-agonists (LABA) [e.g., salmeterol products (Serevent)]
   - ❍ Leukotriene Receptor Antagonists (LTRAs) [e.g., montelukast tablets/granules (Singulair, generics), zafirlukast tablets (Accolate)]
   - ❍ Inhaled long-acting muscarinic antagonist (LAMA) [e.g. tiotropium bromide inhalation spray (Spiriva, Respimat)]
   - ❍ Theophylline (Theo-24, Uniphyl, TheoChron ER, generics)

OR

2. Combination inhaled corticosteroid/long-acting beta2-agonist product* at maximum recommended doses of ICS/LABA combinations (or maximally tolerated dose) [i.e. fluticasone propionate/salmeterol (Advair), mometasone/formoterol (Dulera), budesonide/formoterol (Symbicort)]
   **Maximum recommended doses of ICS/LABA combinations (not an all-inclusive list):*
   - ▪ *Fluticasone/salmeterol (Advair): Advair Diskus 500 mcg/50 mcg twice daily, or 2 inhalations of Advair HFA 230 mcg/21 mcg twice daily*
   - ▪ *Budesonide/formoterol (Symbicort): 160 mcg/4.5 mcg twice daily*
   - ▪ *Mometasone/formoterol (Dulera): 200 mcg/5 mcg twice daily*

NOTE: Use of a combination inhaler containing both an ICS and a LABA (#2) fulfills the requirement for both criteria (in #1)

MOLINA STAFF: Verify pharmacy claims data for **compliance** with the combination therapy above (member is currently receiving this regimen) AND **for rescue medication** use within the last 90 days. For new members to Molina Healthcare, confirm rescue medications use in medical chart history. **Non-compliance, which can be documented by review of the prescription fill history, would not constitute therapeutic failure.**

B. Labeled contraindication(s) or clinical intolerance(s) to the agent(s) in the above criterion [i.e. adverse effects from high-dose inhaled corticosteroid or long-term risks of adverse effects from high dose ICS or oral c Symptoms inadequately controlled (as documented in criteria above) after an **adherent** regimen of at **least 3 months** of the following COMBINATION THERAPY: **[A OR B]**

NOTE

- *Inhaled corticosteroids (ICS) are the preferred treatment option for all severities according to current clinical guidelines for the treatment of persistent asthma,*
- *The 2014 International European Respiratory Society (ERS)/American Thoracic Society (ATS) Guidelines on Definition, Evaluation, and Treatment of Severe Asthma define severe asthma as patients with a confirmed asthma diagnosis which requires treatments with ICS plus long-acting beta-2 agonist (LABA) or leukotriene modifier/theophylline therapy to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy.*
- *As with other severe forms of asthma, the International Guidelines treatment for severe asthma, including eosinophilic asthma, is high dose ICS plus a LABA, leukotriene modifier or theophylline and/or continuous systemic corticosteroids as background therapy.*

❒ Nucala (mepolizumab) is **not** being prescribed as: [ANY]

❍ Monotherapy for asthma [*Nucala (mepolizumab) must be prescribed as add-on maintenance to be used in combination with other medications for long-term control of asthma*]

❍ Concurrent therapy use with other monoclonal antibodies typically used to treat asthma: Xolair (omalizumab) **OR** other IL-5 inhibitors [Cinqair (reslizumab), Fasenra (benralizumab)]

- *Member with severe asthma may meet criteria for treatment with both omalizumab (allergic asthma) and benralizumab (eosinophilic asthma); however, there is currently no clinical trials evaluating combination therapy with two monoclonal antibodies and this combination has not been studied and no evidence or relevant clinical data supporting the concurrent use of both agents are available thus such use cannot be recommended and will not be authorized.*

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

❒ Non-FDA approved indications
❒ Non-FDA approved dosing regimen or route of administration (Subcutaneous injection on upper arm, thigh, or abdomen)
❒ Severe hypersensitivity reaction to Nucala (mepolizumab) or any of its excipients
- *Hypersensitivity reactions (e.g., angioedema, anaphylaxis, bronchospasm, hypotension, urticarial, rash) may occur, typically within hours of administration. Delayed hypersensitivity reactions, occurring days after administration, have also been reported. Discontinue use in patients who experience a hypersensitivity reaction.*

❑ Known or suspected infection
❍ Herpes zoster: Use may result in an opportunistic infection of herpes zoster. Herpes zoster vaccination prior to initiation of therapy with mepolizumab recommended.
❍ Helminth infections: Members with pre-existing helminth infections should undergo treatment prior to initiation of mepolizumab

❑ Exclusions [ANY]
❍ Concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma
❍ Nucala (mepolizumab) therapy initiated with samples AND member does not meet policy criteria for coverage prior to the start of therapy. Coverage will not be authorized upon completion of samples.
❍ Concurrent use with Xolair (omalizumab) [If currently treated with Xolair (omalizumab), then Xolair (omalizumab) must be discontinued when starting Fasenra (benralizumab)]
❍ Concurrent use with any other IL-5 inhibitor [Fasenra (benralizumab), Cinqair (reslizumab)]

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EPGA)

Nucala (mepolizumab) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a board-certified asthma specialist (allergist, immunologist, pulmonologist) rheumatologist, or physician experienced in the management of EPGA. Submit consultation notes if applicable.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]
Clinical **documented** diagnosis of (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*): [ALL]

- ❒ Diagnosis of EGPA (also referred to as Churg-Strauss Syndrome) as confirmed by ALL of the following: [ALL]
  - ❍ Past medical history or presence of asthma
    AND
  - ❍ ONE (1) of the following values at diagnosis: [ONE]
    - Blood eosinophil level of at least 10% of leucocytes
    - Absolute eosinophil count > 1,000 cells/µL

    AND
  - ❍ Presence of at least TWO (2) of the following characteristics typical of EGPA: [TWO]
    - Histopathological evidence of: Eosinophilic vasculitis, Perivascular eosinophilic infiltration, or Eosinophil-rich granulomatous inflammation
    - Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)
    - Pulmonary infiltrates, non-fixed
    - Sino-nasal abnormality
    - Cardiomyopathy (established by echocardiography or MRI)
    - Glomerulonephritis (hematuria, red cell casts, proteinuria)
    - Alveolar hemorrhage (by bronchoalveolar lavage)
    - Palpable purpura
    - Anti-neutrophil cytoplasmic antibody (ANCA) positive

- ❒ History of relapsing or refractory disease defined as ONE (1) of the following: [ONE]
  - ❍ Relapsing disease as defined as a past history (within the past 2 years) of at least one EGPA relapse (requiring additional or dose escalation of corticosteroids or immunosuppressant, or hospitalization)
  - ❍ Refractory disease as defined as failure to attain remission within the prior 6 months following induction treatment with standard therapy regimens

3. Age/Gender/Other restrictions [ALL]

- ❒ 18 years of age or older
  - *Safety and efficacy of mepolizumab for EGPA has not been established in patients younger than 18 years of age*

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ Concomitant oral corticosteroid therapy for at least 4 weeks and on stable dosage (i.e. prednisone or prednisolone at a dose of 7.5 mg/day). Documentation required.

  MOLINA STAFF: Verify pharmacy claims data for within the last 90 days. For new members to Molina Healthcare, confirm rescue medications use in medical chart history. Non-compliance, which can be documented by review of the prescription fill history, would not constitute therapeutic failure.

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Non-FDA approved dosing regimen or route of administration (Subcutaneous injection on upper arm, thigh, or abdomen)
- ❒ Severe hypersensitivity reaction to Nucala (mepolizumab) or any of its excipients
  - *Hypersensitivity reactions (e.g., angioedema, anaphylaxis, bronchospasm, hypotension, urticarial, rash) may occur, typically within hours of administration. Delayed hypersensitivity reactions, occurring days after administration, have also been reported. Discontinue use in patients who experience a hypersensitivity reaction.*
- ❑ Known or suspected infection
  - ❍ Herpes zoster: Use may result in an opportunistic infection of herpes zoster. Herpes zoster vaccination prior to initiation of therapy with mepolizumab recommended.
  - ❍ Helminth infections: Members with pre-existing helminth infections should undergo treatment prior to initiation of mepolizumab
- ❑ Exclusions [ANY]
  - ❍ Concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma
  - ❍ Nucala (mepolizumab) therapy initiated with samples AND member does not meet policy criteria for coverage prior to the start of therapy. Coverage will not be authorized upon completion of samples.
  - ❍ Concurrent use with Xolair (omalizumab) [If currently treated with Xolair (omalizumab), then Xolair (omalizumab) must be discontinued when starting Fasenra (benralizumab)]
  - ❍ Concurrent use with any other IL-5 inhibitor [Fasenra (benralizumab), Cinqair (reslizumab)]

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Nucala (mepolizumab) may be authorized for continuation of therapy if meet ALL of the following criteria are met: [ALL]

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria

- ❑ Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually. The prescribing physician should periodically reassess the need for continuation of therapy based on the member's disease severity and level of asthma control. Continuation of therapy requires submission of relevant medical records or chart notes documenting continued efficacy.

2. Compliance

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including:
  - ❍ Adherent to the prescribed medication regimen
  - ❍ Tolerance to therapy
  - ❍ No severe adverse reactions or drug toxicity

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

  NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY

3. Labs/Reports/Documentation required [ALL]

Documentation of significant reduction in corticosteroid dosage or asthma exacerbations as demonstrated by ONE (1) of the following: **[ONE: A** (Severe Asthma, Eosinophilic) **OR B** (EPGA)**]**

A. Severe asthma, Add-on maintenance in patients with eosinophilic phenotype

Nucala (mepolizumab) therapy has resulted in clinical improvement as documented by ONE (1) or more of the following from baseline. Documentation required. [ONE]

- ❒ Improvement in lung function (increase in percent predicted FEV1 or PEF) from pre-treatment baseline
- ❒ Decreased utilization of rescue medications
- ❒ Decreased frequency of exacerbations (*defined as worsening of asthma that requires increase in inhaled corticosteroid dose or treatment with systemic corticosteroids)*
- ❒ Decreased frequency of unscheduled clinic, urgent care or emergency department visits
- ❒ Reduction in reported symptoms: chest tightness, coughing, shortness of breath, nocturnal wakening wheezing, sustained improvement in Asthma Control Test (ACT) scores
- ❒ Reduction use of ICS, leukotriene or beta agonist therapy
- ❒ Reduction in reported symptoms (decrease in asthma symptom score), as evidenced by decreases in frequency or magnitude of one or more of the following symptoms:
  - ❍ Asthma attacks
  - ❍ Chest tightness or heaviness

- ❍ Coughing or clearing throat
- ❍ Difficulty taking deep breath or difficulty breathing out
- ❍ Shortness of breath
- ❍ Sleep disturbance, night wakening, or symptoms upon awakening
- ❍ Tiredness
- ❍ Wheezing/heavy breathing

B. <u>Eosinophilic Granulomatosis with polyangiitis (EPGA)</u>

Nucala (mepolizumab) therapy has resulted in clinical improvement of signs and symptoms compared to baseline as evidenced by ONE (1) or more of the following from baseline. Documentation required. [ONE]

- ❒ Improvement in asthma symptoms or asthma exacerbations
- ❒ Improvement in duration of remission or decrease in the rate of relapses
- ❒ Decrease in severity or frequency of EGPA-related symptoms
- ❒ Decrease in the frequency and/or severity of relapses
- ❒ Reduction or discontinuation of maintenance doses of systemic corticosteroids and/or immunosuppressant
- ❒ Decreased blood eosinophil count or inflammatory markers
- ❒ Improvement in Birmingham Vasculitis Activity Score (BVAS) score compared to baseline
- ❒ Member is in remission as defined by BVAS score = 0 and a prednisone/prednisolone daily dose of ≤ 7.5 mg

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or absence of unacceptable toxicity from the drug
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
  - ❍ Non-FDA approved indications
  - ❍ Non-FDA approved dosing regimen
  - ❍ Non-FDA approved route of administration (subcutaneous injection only)
  - ❍ Severe hypersensitivity reaction to mepolizumab or any component of the formulation OR previous anaphylactic reaction to Nucala (mepolizumab)
- ❑ Known or suspected infection
  - ❍ Herpes zoster: Use may result in an opportunistic infection of herpes zoster. Herpes zoster vaccination prior to initiation of therapy with mepolizumab recommended.
  - ❍ Helminth infections: If an infection occurs while being treated with mepolizumab and does not respond to anti-helminth therapy, discontinue mepolizumab until infection resolves.
- ❑ <u>Exclusions</u> [ANY]
  - ❍ Concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma.
  - ❍ Nucala (mepolizumab) therapy initiated with samples AND member does not meet policy criteria for coverage prior to the start of therapy. Coverage will <u>not</u> be authorized upon completion of samples.
  - ❍ Concurrent use with omalizumab (Xolair)
  - ❍ Concurrent use with any other IL-5 inhibitor (Cinqair)

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. **Recommended Dosage [ALL]**

   - ❒ **Severe asthma (eosinophilic phenotype) for add-on maintenance treatment of patients (12 years and older)**: 100 mg subcutaneous once every 4 weeks injected into the upper arm, thigh or abdomen
     - *Pediatrics (younger than 12 years of age): Safety and efficacy have not been established.*

   - ❒ **Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome):** 300 mg subcutaneous (given as 3 separate 100mg injections at least 5 cm apart in the upper arm, thigh, or abdomen) once every 4 weeks

2. **Authorization Limit [ALL]**

   - ❒ Quantity limit: [AS APPLICABLE PER INDICATION]
     - ❍ Severe asthma (eosinophilic phenotype) for add-on maintenance treatment of patients (12 years and older): One vial per 28 days
     - ❍ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome): 100 mg single dose vial for injection: 3 vials every 28 days
   - ❒ Duration of initial authorization: **3 months**
   - ❒ Continuation of treatment: Re-authorization is required every **6 months** to determine effectiveness of therapy and continued need based on documented positive clinical response. *Refer to 'Continuation of Therapy' section.*
     - Goal should be the objective improvement in selected markers of asthma control, such as symptoms severity, frequency of rescue treatments, oral steroid requirements, and frequency of urgent outpatient visits and/or hospitalization.
   - ❒ Duration of continuation of treatment: May be authorized up to **6 months** at a time

3. **Route of Administration [ALL]**

   - ❒ Nucala (mepolizumab) is considered a **provider-administered** medication
   - ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

COVERAGE EXCLUSIONS

All other uses of Nucala (mepolizumab) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- Non-FDA approved indication [i.e. urticaria and other eosinophilic conditions; severe allergic asthma without documentation of severe eosinophilia]
- Younger than 12 years of age
  - *Nucala (mepolizumab) is not indicated for use in children younger than 12 years of age. Safety and efficacy of benralizumab have not been established in this age group.*
- Non-FDA approved dosing regimen(s)
- Individuals who have had previous anaphylactic reaction to Nucala (mepolizumab)
- Nucala (mepolizumab) therapy initiated with samples and the member does not meet policy criteria for coverage (as outlined above) prior to the start of therapy. Coverage will not be authorized upon completion of samples.
- Concurrent use with omalizumab (Xolair)
  - *In the clinical trials, patients who had previously received omalizumab were eligible for inclusion into the study if they had not received omalizumab for at least 6 months. The washout period was to avoid any potential carry over from omalizumab which has a long half-life. There are no recommendations in the labeling requiring a waiting period before starting reslizumab; however, providers should be aware of any potential adverse drug events.*
- Concurrent use with other IL-5 inhibitors [*Cinqair (reslizumab), Fasenra (benralizumab)*]
- Administration in any manner other that which is FDA-approved (for subcutaneous injection) will not be authorized

SEVERE ASTHMA, ADD-ON MAINTENANCE IN PATIENTS WITH EOSINOPHILIC PHENOTYPE

Severe asthma is defined as Global Initiative for Asthma (GINA) steps 4-5 asthma requiring treatment with guideline-suggested medications (such as high-dose inhaled corticosteroids and long-acting beta agonists, a leukotriene modifier, or theophylline for the preceding year, or systemic corticosteroids for ≥ 50% of the previous year) to prevent it from becoming uncontrolled, or which remains uncontrolled despite therapy.[Dynamed 2018]

Prevalence of asthma in the United States (U.S.) continues to rise. An estimated 7.8% (24.6 million) Americans have asthma with approximately 10% to 20% in poor control (CDC: Asthma Data, Statistics, and Surveillance; Wakford HH et al.)

Severe asthma is reported to account for about 5%-10% of the total asthma population, but the exact prevalence is unknown due to heterogeneity in presentation of severe asthma and prior lack of a standardized definition.

PIVOTAL TRIALS

The safety and efficacy of Nucala (mepolizumab) were established in three randomized, double-blind, placebo-controlled clinical trials [DREAM; MENSA and SIRIUS (MEA115575)] in patients with severe asthma on currently available therapies (GSK, 2015; Ortega, et al., 2014; Bel, et al., 2014; Pavord, et al., 2012).
There were other randomized controlled trials; however most of these trials were small, or utilized dosing or included asthma phenotypes that are outside the product labeling. These studies will not be discuss below and will only address the three primary pivotal phase III trials.

The FDA approval of Nucala (mepolizumab) was based on three double-blind, randomized, placebo-controlled trials: one dose-ranging and exacerbation trial and two confirmatory trials.

Efficacy. A total of 1,327 subjects with asthma were evaluated in three randomized, placebo-controlled multicenter trials of 24 to 52 weeks duration. Of these, 1,192 subjects had a history of two or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control. All subjects had markers of eosinophilic airway inflammation and blood eosinophils of at least 150 cells/microliter at initiation of treatment or blood eosinophils of at least 300 cells/microliter in the last 12 months. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every four weeks; 263 subjects received mepolizumab by subcutaneous route for at least 24 weeks. Compared with placebo, individuals with severe asthma receiving mepolizumab had fewer exacerbations requiring hospitalization and/or emergency department visits, and a longer time to the first exacerbation. In addition, individuals with severe asthma receiving mepolizumab experienced greater reductions in their daily maintenance oral corticosteroid dose, while maintaining asthma control, compared with individuals receiving placebo.

Safety. In clinical trials, common adverse effects of mepolizumab (reported in ≥5% of patients and more frequently than with placebo) included injection-site reactions, headache, back pain, and fatigue. Hypersensitivity reactions have occurred. Herpes zoster infections have occurred rarely.

Study 1 (DREAM): Dose-Ranging and Exacerbation Trial

Dose-Ranging Efficacy and Safety with Mepolizumab (DREAM) Trial

Pavord and colleagues (2012) evaluated the efficacy and safety of mepolizumab on rates of exacerbation in individuals with recurrent severe asthma.

Mepolizumab decreases exacerbation risk in patients with severe eosinophilic asthma

- Based on randomized trial: International, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging dose selection trial
- Randomly assigned to receive intravenous mepolizumab at 75 mg, 250 mg, or 750 mg or placebo at 4-week intervals to week 48 for a treatment period of 52 weeks (13 infusions)
- 621 patients aged 12 to 74 years with recurrent severe asthma exacerbations and evidence of eosinophilic inflammation (i.e. sputum eosinophils, peripheral blood eosinophilia, or elevated exhaled nitric oxide) randomized to IV mepolizumab (75 mg vs. 250 mg vs. 750 mg) vs. matched placebo (13 total infusions at 4-week intervals over 1 year)
    - Background maintenance therapy with a high-dose ICS for the prior 12 months (with or without oral corticosteroids) plus an additional controller (LABA, leukotriene inhibitor, or theophylline) medication required
    - At least 1 of the following 4 pre-specified criteria in the previous 12 months: blood eosinophil count greater than or equal to 300 cells/mcL, sputum eosinophil count greater than or equal to 3%, exhaled nitric oxide concentration greater than or equal to 50 ppb, or deterioration of asthma control after less than or equal to 25% reduction in regular maintenance inhaled corticosteroids/oral corticosteroids
- All patients had history of ≥ 2 exacerbations requiring steroids in previous year
- Clinically significant asthma exacerbation defined as validated episode of worsening asthma symptoms requiring oral corticosteroid treatment for ≥ 3 days, hospital admission, or emergency department visit
- Primary outcome: **An annualized rate of clinically significant asthma exacerbations, was decreased in all mepolizumab groups compared with placebo with the greatest reduction in the 750 mg group** (52% reduction; 95% Confidence Interval [CI], 36%-64%; p<0.0001)
- 84% completed trial and 99% included in modified intention-to-treat analyses
- Clinically significant exacerbations at 1 year
    - 1.24 per patient per year with mepolizumab 75 mg ($p < 0.0001$ vs. placebo)
    - 1.46 per patient per year with mepolizumab 250 mg ($p = 0.0005$ vs. placebo)
    - 1.15 per patient per year with mepolizumab 750 mg ($p < 0.0001$ vs. placebo)
    - 2.4 per patient per year with placebo
- Mepolizumab associated with decreased serum eosinophil counts ($p < 0.0001$ for each)
- No significant differences in symptom scores, quality of life, FEV_1, or adverse events
    - It was reported that the effects of mepolizumab on traditional markers of asthma control (that is, symptoms and quality of life) and pulmonary function (FEV1) did not differ significantly from those reported with placebo.
    - The frequency of serious adverse events was similar across treatment groups, reported as headache and nasopharyngitis. There were no reports of serious life-threatening anaphylactic reactions.

Reference: DREAM trial (Lancet 2012 Aug 18;380(9842):651), editorial: Lancet 2012 Aug 18;380(9842):626

Study 2 (MENSA): Confirmatory Trial

MEpolizumab as adjunctive therapy iN patients with Severe Asthma (MENSA) Trial

The MENSA study, a 32-week clinical trial, included patients with asthma who had a history of ≥2 exacerbations in the previous year, despite regular treatment with high-dose inhaled corticosteroids plus an additional controller, with or without oral corticosteroids.[3] The MENSA trial was a double-blind randomized controlled trial (RCT) of 576 patients ages 12 years and older (mean age 50 years, 57% female, 25% chronic use of oral corticosteroids) with severe eosinophilic asthma and at least two asthma exacerbations in the past year (Ortega and colleagues, 2014[3]).

IV and subcutaneous mepolizumab each reduce exacerbation rates and improve quality of life in patients with severe eosinophilic asthma

- Based on randomized, double-blind placebo study
- 576 patients aged 12-82 years with refractory eosinophilic asthma and history of recurrent severe exacerbations were randomized to receive mepolizumab 75mg intravenously, mepolizumab 100mg subcutaneously or placebo every 4 weeks for 32 weeks
    - 576 patients were evaluated with recurrent asthma exacerbations
    - History of 2 or more exacerbations in the previous year), despite high-dose regular use of inhaled (with or without systemic) glucocorticoids plus an additional controller in the previous year
    - Presence of eosinophilic inflammation is required, defined as blood eosinophil count 150/mcL at screening or 300/mcL at some point in the previous year
- Annualized rates of clinically significant exacerbations
    - Mepolizumab was **associated with a 53% reduction in asthma exacerbations** compared with placebo (95% confidence interval [CI]: 36%, 65%; p<0.001).
        - Rate of exacerbations was reduced by 47% in the intravenous mepolizumab group, 53% in the subcutaneous mepolizumab group, as compared with those receiving placebo (p <0.001 for both comparisons)
        - Exacerbations necessitating an emergency department visit or hospitalization were reduced by 32% in the intravenous mepolizumab group by 61% in the subcutaneous mepolizumab group
- Both formulations, subcutaneous and IV mepolizumab, decreased the rate of all exacerbations relative to placebo; however, only the 100mg SC formulation reduced the risk of hospitalization/ED visits and hospitalization alone compared to placebo.
- The MENSA trial measured quality of life with the ACQ and the SGRQ
    - Asthma control as assessed by 5-item Asthma Control Questionnaire (p < 0.001 for each vs. placebo)
        - The improvement in the Asthma Control Questionnaire (ACQ-5) score was 0.42 points and 0.44 points greater in the two study group than placebo (p< 0.001), respectively
    - Quality of life as assessed by St. George's Respiratory Questionnaire (p < 0.001 for each vs. placebo)
        - The improvement from baseline St. George's Respiratory Questionnaire (SGRQ) was 6.4 points and 7.0 points greater in the intravenous and subcutaneous mepolizumab groups, respectively, than in the placebo group (p< 0.001)
    - FEV_1 (p ≤ 0.03 for each vs. placebo)
        - Significant improvement from baseline FEV1 was noted, 100 mL greater in the intravenous mepolizumab group (p= 0.02), and 98mL improvement in the subcutaneous mepolizumab group (p= 0.03) in comparison to placebo, respectively.
- Adverse event rates were similar among groups (no p values reported)

Reference: MENSA trial (N Engl J Med 2014 Sep 25;371(13):1198), correction can be found in N Engl J Med 2015 Apr 30;372(18):1777, editorial can be found in N Engl J Med 2014 Sep 25;371(13):1249

Study 3 (SIRIUS): Confirmatory Trial

SteroId ReductIon with mepolizUmab Study (SIRIUS) Trial

The SIRIUS trial was a double-blind RCT of 135 patients ages 12 years and older (mean age 50 years, 55% female, 100% use of oral corticosteroids) with severe eosinophilic asthma who required 5 to 35 mg of prednisone daily for at least the prior six months. (Bel 2014[4]). SIRIUS, a 24-week clinical trial, evaluated the effect of mepolizumab on reducing the use of maintenance oral corticosteroids; the primary efficacy outcome was the percent reduction of the oral corticosteroid dose in weeks 20 to 24 compared with the baseline dose, while maintaining asthma control.[4]

Subcutaneous mepolizumab reduces requirement for oral glucocorticoids in patients with severe eosinophilic asthma

- Based on randomized, double-blind study
- 135 patients were enrolled with severe eosinophilic asthma (300 blood eosinophils/mcL during the 12 months prior to the study entry or 150 eosinophils/mcL during the optimization phase), despite daily oral glucocorticoid treatment in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s)
- Patients were randomized to receive mepolizumab 100mg or placebo subcutaneously every 4 weeks for 20 weeks
  - The trial subjects received mepolizumab (n=69) or placebo (n=66) once every 4 weeks for 24 weeks
  - The baseline mean oral corticosteroid use was similar between the Nucala and placebo group
- All patients received systemic glucocorticoids (5-35 mg/day of prednisone or equivalent) for ≥ 6 months
  - Glucocorticoid dose was maintained at optimization level for 4 weeks, then reduced by 1.25-10 mg/day to week 20
  - Mepolizumab discontinued at 20 weeks and glucocorticoid dose maintained to week 24
- Primary outcome in the SIRIUS trial was **the percentage reduction in daily oral glucocorticoid dose use.** This is not of direct clinical benefit but should reduce the long-term harms of OCS use (e.g., osteoporosis, muscle weakness, diabetes).
  - Overall, mepolizumab achieved greater reduction in oral corticosteroid use while maintaining asthma control when compared to placebo. However, the difference between the mepolizumab and placebo groups was not statistically significant.
    - ≥ 50% reduction in glucocorticoid dose in 54% vs. 33% (p = 0.03, NNT 5)
    - Reduction in glucocorticoid dose to ≤ 5 mg/day in 54% vs. 32% (p = 0.02, NNT 5)
    - Median reduction from optimized glucocorticoid dose at 24 weeks 50% vs. 0% (p = 0.007)
      The median percent reduction in OCS dose was 50% in the mepolizumab group and 0% in the placebo group (p=0.007).
      - The likelihood of a reduction in the glucocorticoid dose was 2.39 times greater in the mepolizumab group (95% CI, 1.25-4.56; p=0.008). The median percentage reduction from baseline in the daily oral glucocorticoid dose was 50% in the mepolizumab group compared with no reduction in the placebo group (p=0.007).
    - Glucocorticoids discontinued in 14% vs. 8% (not significant): The proportion of patients able to completely stop OCS was 14% in the mepolizumab group and 8% in the placebo group, but this did not differ statistically
    - Asthma exacerbation rates reported as secondary outcomes: Mepolizumab reduced total exacerbations by 32% (95% CI: 1%, 53%; p=0.04)
      - Annualized rate of exacerbations 1.44 per year vs. 2.12 per year (1.44 per year in the mepolizumab group vs. 2.12 per year in the placebo group; rate ratio, 0.68; 95% CI, 0.47 to 0.99; p=0.04) and improved control of asthma symptoms
    - Serious adverse events in 1% vs. 18% (no p value reported)

Reference: SIRIUS trial (N Engl J Med 2014 Sep 25;371(13):1189), editorial: N Engl J Med 2014 Sep 25;371(13):1249

CLINICAL PRACTICE GUIDELINES

Global Initiative for Asthma (GINA, 2018)

- Provides a stepwise approach to asthma management, adjusting treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects
- Step 5 treatment: Benralizumab (monoclonal anti-IL5 receptor) has been added to the existing Type 2-targeted biologics for severe eosinophilic asthma. The age ranges approved for Type 2-targeted biologics have also been clarified since GINA 2017
- Phenotype-guided add-on treatment:
    - Patients with severe asthma, uncontrolled on Step 4 treatment, may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma
    - Patients ≥ 6 years with severe allergic asthma with elevated IgE levels may benefit from omalizumab (anti-IgE) therapy (Evidence A)
    - Those with severe eosinophilic asthma may benefit from anti-IL5 therapy (subcutaneous mepolizumab (Nucala) ≥ 12 years; intravenous reslizumab (Cinqair) > 18 years) or anti-IL receptor therapy (subcutaneous benralizumab (Fasenra) ≥ 12 years) (Evidence A)
    - LTRAs may be helpful of patients found to be aspirin sensitive (Evidence A)

European Respiratory Society (ERS)/American Thoracic Society (ATS)

- The guidelines recommend "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."
- Asthma is classified as severe when it requires treatment with high-dose inhaled corticosteroids plus a second asthma controller therapy (e.g., long-acting β2-agonist), and/or systemic corticosteroids to prevent asthma from becoming or remaining uncontrolled despite this therapy.
    - Although there are no widely accepted definitions for specific asthma phenotypes, an eosinophilic phenotype (i.e., eosinophilic asthma) is generally characterized by blood and sputum eosinophilia and eosinophilic inflammation, recurrent exacerbations, and, frequently, responsiveness to corticosteroids.
    - Sputum eosinophil counts are used as a reliable biomarker for eosinophilic lung inflammation; ATS and ERS currently recommend treatment of severe asthma guided by sputum eosinophil counts in addition to clinical criteria in adults, and treatment guided by clinical criteria alone in pediatric patients. However, sputum eosinophil counts are difficult to use in routine practice because testing must be performed in specialized centers experienced in using the technique.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

Mepolizumab is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)

In a multicenter, double-blind, parallel-group, phase 3 trial, Wechsler et al, evaluated the efficacy and safety mepolizumab versus placebo for eosinophilic granulomatosis with polyangiitis (EGPA) [Wechsler ME, et al. 2017]

- Patients with relapsing or refractory EGPA were randomly assigned to receive 300 mg of mepolizumab (n=68) or placebo (n=68) subcutaneously every 4 weeks, plus standard care, for 52 weeks.
- Patients had to have received treatment for at least 4 weeks and were taking stable corticosteroid dosing for at least 4 weeks.
- The two primary end points were the accrued weeks of remission over the 52 week period, and the proportion of participants in remission at both week 36 and week 48.
- Secondary endpoints included: time to first relapse and average daily glucocorticoid use at weeks 48 through 52).
- Results
    - Patients receiving mepolizumab had significantly more accrued weeks of remission than placebo (28% vs. 3% had 24 weeks of accrued remission; odds ratio, 5.91; 95% confidence interval [CI], 2.68 to 13.03; P<0.001) and a higher percentage of patients were in remission at both week 36 and week 48 (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; P<0.001).
    - Remission did not occur in 47% of the patients in the mepolizumab group versus 81% of those in the placebo group.
    - The annualized relapse rate was 1.14 in the mepolizumab group, as compared with 2.27 in the placebo group (rate ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001).
    - A total of 44% of the patients in the mepolizumab group, as compared with 7% of those in the placebo group, had an average daily dose of prednisolone or prednisone of 4.0 mg or less per day during weeks 48 through 52 (odds ratio, 0.20; 95% CI, 0.09 to 0.41; P<0.001).
- Summary: The authors concluded that in patients with EGPA, mepolizumab resulted in significantly more weeks in remission and a higher proportion of patients in remission than placebo, although only half of the patients treated with mepolizumab had protocol-defined remission.
    - Patients receiving mepolizumab achieved a significantly greater accrued time in remission compared with those who received a placebo.
        - A significantly higher proportion of patients receiving mepolizumab achieved remission at both week 36 and week 48 compared with placebo.
        - In addition, significantly more patients who received mepolizumab achieved remission within the first 24 weeks, and remained in remission for the remainder of the 52-week study treatment period compared with patients who received the placebo.

DEFINITIONS

- Controller medications: suppress the inflammatory causes of asthma to provide clinical control over the long term, whereas reliever medications relieve bronchoconstriction quickly.

  Controller medications include inhaled glucocorticoids (Flovent, Pulmicort, Qvar, Asmanex), long-acting beta-agonists (LABAs) such as salmeterol, formoterol, or vilanterol, and antileukotriene agents [montelukast (Singulair®), zafirlukast (Accolate®) or Zyflo® (zileuton)]. Theophylline is also a controller agent, however, it is not as efficacious as LABAs.

- Inhaled corticosteroid(s) (ICS or ICSs): A class of medications also referred to as inhaled steroids; used for the treatment of asthma and COPD. A potent anti-inflammatory medication that improves asthma control more effectively than any other agent used as a single treatment; helps to prevent chronic asthma symptoms such as wheezing, chest tightness, shortness of breath, and chronic cough.

- Long-acting beta-agonist(s) (LABA or LABAs): Also referred to as long-acting $beta_2$-adrenergic agonists. A type of bronchodilator whose effects last for 12 hours or more when used as adjunctive treatment for the prevention of asthma symptoms such as wheezing, chest tightness, shortness of breath, and cough; improves asthma symptoms by increasing airflow through the lungs.

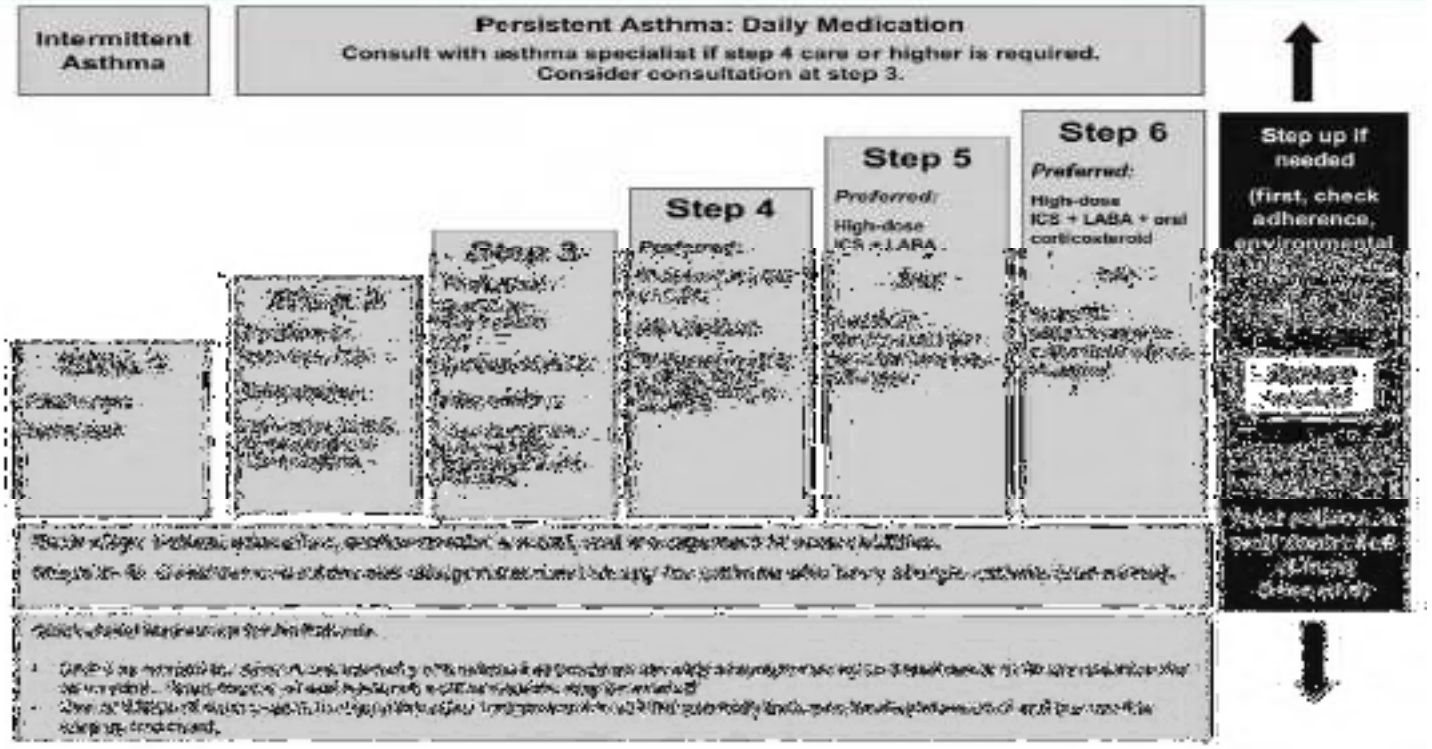
- Hypereosinophilia (HE): An absolute eosinophil count (AEC) in the peripheral blood of greater than 1.5×10^9/L (or greater than 1500 cells/microL) on 2 examinations separated in time by at least 1 month and/or pathologic confirmation of tissue HE.

- FEV_1 (forced expiratory volume in 1 second): A measure of airway obstruction determined using spirometry. Individual FEV_1 values are compared to predicted values based on age, height, sex and race.

- PEF (peak expiratory flow): PEF is often described as a percent of personal best measurement. Personal best PEF is the highest PEF value attained after 2 to 3 weeks of testing when asthma is in good control.

APPENDIX

APPENDIX 1: NAEPP Expert Panel Guidelines: Managing Asthma in Youths ≥ 12 years of age and Adults



NOTE: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting beta2-agonist; Leukotriene Receptor Antagonists (LTRAs), SABA, inhaled short-acting beta2-agonist

Reference: *NIH, National Heart Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3 2007)* http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf

National Asthma Education and Prevention Program (NAEPP). Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication Number 08-5846. October 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf.

APPENDIX 2: ESTIMATED COMPARATIVE DAILY DOSAGES for INHALED CORTICOSTEROIDS (ICS) in YOUTH ≥12 YEARS of AGE and ADULTS

Estimated Comparative Daily Dosages for Inhaled Corticosteroids (ICS) in Youths ≥ 12 years of age and Adults
The values listed below were obtained from the National Institutes of Health.

Drug	Low Daily Dose Adult	Medium Daily Dose Adult	High Daily Dose Adult
Beclomethasone HFA 40 or 80 mcg/puff	80–240 mcg	>240–480 mcg	>480 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	180–600 mcg	>600–1,200 mcg	>1,200 mcg
Flunisolide 250 mcg/puff	500–1,000 mcg	>1,000–2,000 mcg	>2,000 mcg
Flunisolide HFA 80 mcg/puff	320 mcg	>320–640 mcg	>640 mcg
Fluticasone			
HFA/MDI: 44, 110, or 220 mcg/puff	88–264 mcg	>264–440 mcg	>440 mcg
DPI: 50, 100, or 250 mcg/inhalation	100–300 mcg	>300–500 mcg	>500 mcg
Mometasone DPI 200 mcg/inhalation	200 mcg	400 mcg	>400 mcg
Triamcinolone acetonide 75 mcg/puff	300–750 mcg	>750–1,500 mcg	>1,500 mcg

Key: DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler

Reference: Section 4, Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults
Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug.

APPENDIX 3: Clinically Relevant Outcomes for Severe Asthma

- Clinically relevant outcomes for severe asthma include reduction in asthma exacerbations that result in:
  - Decreased emergency department (ED) visits or hospitalizations;
  - Decreased chronic use of OCS;
  - Improved quality of life; and
  - Improved symptom management.

- These tests are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma and is self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users.
  1) **Asthma Control Questionnaire-7 (ACQ-7):** A 7-item questionnaire (1 week recall for items on symptoms and rescue inhaler use) that measures the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. The ACQ-7 assesses symptoms (5 items, self-administered), rescue in-bronchodilator use (1 item, self-administered), and FEV1% (1 item) completed by a healthcare professional. The 7-point scale reports symptoms as: 0 = no impairment; 6 = maximum impairment for symptoms and rescue use; and, 7 categories for FEV1%. The ACQ is 7-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.5 Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 the minimally clinical important difference.[1]
  2) **Asthma Quality of Life Questionnaire (AQLQ):** A 32-item disease-specific questionnaire assesses both physical and emotional impact of disease and used to reflect areas of function important to individuals with asthma; available in both interviewer- and self-administered forms. The 4 domains measured by the AQLQ include activity limitations, emotional function, exposure to environmental stimuli, and symptoms.[2] Scores range from 1 (severely impaired) to 7 (not impaired at all), with higher scores indicating better quality of life.[2] A difference of 0.5 overall and for each item is the minimally clinical important difference for this instrument.[2]
  3) **St. George's Respiratory Questionnaire (SGRQ):** A 50-item quality-of-life tool for patients with obstructive airway disease is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. The questionnaire is composed of 2 parts. Part 1 assesses symptoms and part 2 assesses limitation of activities and its social and psychological impact.[3] Scores range from 0 to 100, with lower scores indicate better functioning and higher scores indicating more limitations. A change of 4 units is considered to be clinically meaningful, 8 points for moderately efficacious treatment, and 12 points for very efficacious treatment.[3]
  4) **Asthma Control Test (ACT):** A score is a tool used to identify patients with poorly controlled asthma.[4] The test contains 5 items that assess the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. 8 Scores range from 5 (poor control of asthma) to 25 (complete control of asthma).[4] An ACT score greater than 19 indicates well-controlled asthma, with a change of 3 points the minimally clinical important difference over time.[4]
  5) **Asthma Symptom Utility Index (ASUI)** is an 11 item questionnaire with scores range from 0 (worst possible symptoms) to 1 (no symptoms). This instrument assesses frequency and severity of cough, wheezing, dyspenia, and nighttime awakening, and medication side effects.

References:

1) *American Thoracic Society - Asthma Control Questionnaire (ACQ). http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/acq.php#. Accessed April 2018.*
2) *American Thoracic Society - Asthma Quality of Life Questionnaire (AQLQ). http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/aqlq.php. Accessed April 2018.*
3) *American Thoracic Society - St. George's Respiratory Questionnaire (SGRQ). https://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/sgrq.php. Accessed April 2018.*
4) *American Thoracic Society - Asthma Control Test (ACT). http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/act.php. Accessed April 2018.*

APPENDIX 4: Blood Eosinophil Levels

Earlier studies with reslizumab indicate that eosinophilic asthma can be characterized by a sputum eosinophil count of ≥3% and that reslizumab is expected to benefit patients with asthma with sputum eosinophil count of ≥3%. The sponsor chose blood eosinophil as a surrogate of sputum eosinophilia because of the ease of obtaining in clinical practice. The sponsor selected ≥400 cells/μL as the threshold based on a secondary analysis of datasets from asthma patients that indicated blood eosinophil count of ≥400 cells/μL had a high positive predictive value for the presence of sputum eosinophils of ≥3%, and a count of <400 cells/μL identified the majority of patients without sputum eosinophilia. It should be noted that a definitive threshold value of eosinophilia has not been defined.

CODING INFORMATION

The codes listed in the policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

HCPCS	Description
J2182	Injection, mepolizumab, 1 mg

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Policy History	MCPC
Policy Developed	12/14/2016
Policy Revised *Peer Review: AMR Peer Review Network. MM/DD/2018. Practicing Physician. Board certified Board certified in Allergy & Immunology, Pediatrics*	7/10/2018

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