# Medical Policy

**Utilization Management and Clinical Medical Policy**

| Policy Name: | Policy Number: | Scope: | Origination Date: | Effective Date: |
|---|---|---|---|---|
| **Monoclonal Antibodies to Interleukin-5 [Cinqair® (reslizumab), Fasenra® (benralizumab), Nucala® (mepolizumab)], Exdensur® (depemokimab-ulaa)** | **MP-RX-FP-58-23** | ☒ **MMM MA**<br>☒ **MMM MultiHealth** | **11/30/2023** | **5/6/2026** |
| | | | **Last Review Date:** **5/6/2026** | **Frequently Revision:** **Annual** |

**Service Category:**

- ☐ Anesthesia
- ☐ Surgery
- ☐ Radiology Procedures
- ☐ Pathology and Laboratory Procedures
- ☐ Medicine Services and Procedures
- ☐ Evaluation and Management Services
- ☐ DME/Prosthetics or Supplies
- ☒ Other: Part B Drugs

## Service Description:

This document addresses the use of Monoclonal Antibodies to Interleukin-5 (IL-5), approved by the Food and Drug Administration (FDA), for the treatment of eosinophilic conditions.

## Background Information:

This document addresses the use of monoclonal antibodies against interleukin-5 (IL-5) in the treatment of individuals with eosinophilic conditions, including severe uncontrolled eosinophilic asthma, chronic rhinosinusitis with nasal polyps, eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome. These drugs target IL-5, a cytokine primarily involved in the development, recruitment, and activation of eosinophils, which are key drivers in eosinophilic inflammation and associated diseases. The agents approved by the Food and Drug Administration (FDA) include:

A. Cinqair (reslizumab), a monoclonal anti-IL-5 antibody
B. Fasenra (benralizumab), a monoclonal anti-IL-5 receptor alpha antibody
C. Nucala (mepolizumab), a monoclonal anti-IL-5 antibody
D. Exdensur (depemokimab-ulaa), a monoclonal anti-IL-5 antibody

*Eosinophilic Asthma*

Researchers have discovered that eosinophils play a pivotal role in immune development and asthma. Eosinophils are a type of white blood cell whose natural role is to defend the body against disease and environmental substances. Eosinophils accumulate wherever allergic reactions take place, including those in allergic asthma. In individuals with eosinophilic asthma, white blood cells accumulate and release chemicals that may damage the lining of the lungs. Studies examining individuals with mild asthma have shown that airway inflammation due to eosinophils is a typical characteristic, and eosinophilic airway inflammation appears to be closely related to the risk of severe asthma exacerbations. Although the role eosinophils play in the pathophysiology of asthma is unclear, they represent a biomarker for predicting whether individuals will respond to corticosteroids, predicting which persons are at risk of exacerbation and for guiding steroid therapy in these events.

Cinqair, Exdensur, Fasenra and Nucala are approved by the FDA to treat severe eosinophilic asthma. In 2013, the European Respiratory Society/American Thoracic Society (ERS/ATS) released guidance for defining, evaluating and treating severe asthma. The guidelines recommend to start by confirming the asthma diagnosis, including a spirometry assessment, and then differentiating severe asthma from milder asthma. The guidelines define severe asthma as asthma which has required treatment with high dose inhaled corticosteroids and a long-acting beta agonist, leukotriene modifier or theophylline for the previous year in order to prevent asthma

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symptoms from becoming uncontrolled. Alternatively, severe asthma can be defined as asthma that has required systemic corticosteroid treatment for over 50% of the previous year.

ERS/ATS guidance defines uncontrolled asthma as meeting one of the following:

E. Poor symptom control: Asthma Control Questionnaire (ACQ) consistently >1.5, Asthma Control Test (ACT) <20
F. Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year
G. History of serious exacerbation: at least one hospitalization, intensive care unit stay or mechanical ventilation in the previous year
H. Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted

Cinqair is approved by the FDA for add-on maintenance treatment of individuals 18 years of age and older with severe asthma with an eosinophilic phenotype. Cinqair is administered monthly by intravenous infusion. The safety and efficacy of Cinqair was evaluated in two multicenter, randomized, double-blind, placebo-controlled trials in individuals with severe eosinophilic asthma confirmed by blood eosinophils ≥ 400 cells/microliter. Participants received background treatment consisting of medium-to-high dose inhaled corticosteroids +/- long-acting beta agonist (LABA) +/- oral corticosteroids. Study data confirms the efficacy of Cinqair in reducing asthma exacerbations and improving asthma control and quality of life measures.

Cinqair has a black box warning for anaphylaxis. Anaphylaxis occurred with Cinqair infusion in 0.3% of participants in placebo-controlled studies. Individuals should be observed after Cinqair administration for an appropriate period of time by a healthcare professional prepared to manage anaphylaxis that can be life-threatening. Discontinue Cinqair immediately if the patient experiences signs or symptoms of anaphylaxis.

Exdensur is approved by the FDA as add-on maintenance treatment of individuals 12 years of age and older with severe asthma with an eosinophilic phenotype. Exdensur is administered every 6 months by subcutaneous injection. The safety and effectiveness of Exdensur was established in two multicenter, double-blind, randomized, placebo-controlled trials (SWIFT-1, SWIFT-2) in individuals with severe eosinophilic asthma confirmed by blood eosinophils ≥ 150 cells/microliter at initiation of treatment or blood eosinophils ≥ 300 cells/microliter in the past 12 months. Participants received background treatment consisting of medium-to-high dose inhaled corticosteroids + controller therapy. Study data confirms the efficacy of Exdensur in reducing the annualized rate of exacerbations compared to placebo.

Fasenra is approved by the FDA for add-on maintenance treatment of individuals 6 years of age and older with severe asthma with an eosinophilic phenotype. Fasenra is administered every 8 weeks by subcutaneous injection. The safety and efficacy of Fasenra was evaluated in three multicenter, randomized, double-blind placebo-controlled trials (CALIMA, SIROCCO, ZONDA) in individuals with severe eosinophilic asthma confirmed by blood eosinophils ≥ 300 cells/microliter. The steroid-sparing study (ZONDA) enrolled participants with blood eosinophils ≥ 150 cells/microliter. Participants received background treatment consisting of medium-to-high dose inhaled corticosteroids + LABA +/- oral corticosteroids. Study data confirms the efficacy of Fasenra in reducing exacerbations that require hospitalization or emergency department visits, improving asthma control and providing a steroid-sparing benefit.

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Nucala is approved by the FDA as add-on maintenance treatment of individuals 6 years of age and older with severe asthma with an eosinophilic phenotype. Nucala is administered monthly by subcutaneous injection. The safety and effectiveness of Nucala was established in three multicenter, double-blind, randomized, placebo-controlled trials (DREAM, SIRIUS, MENSA) in individuals with severe eosinophilic asthma confirmed by blood eosinophils ≥ 150 cells/microliter at initiation of treatment or blood eosinophils ≥ 300 cells/microliter in the past 12 months. Participants received background treatment consisting of high dose inhaled corticosteroids + controller therapy +/- oral corticosteroids. Study data confirms the efficacy of Nucala in reducing exacerbations that require hospitalization or emergency department visits, improving asthma control and quality of life measures and providing a steroid-sparing benefit.

The 2024 Global Initiative for Asthma (GINA) guidelines include Cinqair, Fasenra and Nucala as treatment options in Step 5 of their asthma management algorithm. Add-on targeted biologic therapy should be considered for individuals with severe asthma experiencing exacerbations or poor symptom control despite taking at least high-dose inhaled corticosteroid/long acting beta2 –agonists and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroids. The 2020 European Respiratory Society/American Thoracic Society (ERS/ATS) guideline on management of severe asthma makes a similar recommendation, suggesting an anti-IL-5 agent as add-on therapy for adults with severe uncontrolled asthma with an eosinophilic phenotype. ERS/ATS suggests blood eosinophils ≥ 150 cells/microliter as a guide for anti-IL-5 therapy initiation.

**Comparative Doses for Inhaled Corticosteroids (Adults and Adolescents) (Wenzel 2021)**

| Drug | Low Daily Dose | Medium Daily Dose | High Daily Dose |
|---|---|---|---|
| **Beclomethasone**<br>40 or 80 mcg/actuation | 80-160 mcg | >160-320 mcg | >320-640 mcg |
| **Budesonide**<br>90 or 180 mcg/actuation | 180-360 mcg | >360–720 mcg | >720-1440 mcg |
| **Ciclesonide**<br>80 or 160 mcg/actuation | 160 mcg | 320 mcg | 640 mcg |
| **Fluticasone propionate**<br>MDI: 44, 110 or 220 mcg/actuation<br>DPI: 50, 100 or 250 mcg/dose | 176–220 mcg<br>100-250 mcg | >220–440 mcg<br>>250–500 mcg | >440-1760 mcg<br>>500-2000 mcg |
| **Fluticasone furoate**<br>50, 100 or 200 mcg/dose | 50 mcg | 100 mcg | 200 mcg |
| **Mometasone**<br>MDI: 50, 100 or 200 mcg/actuation<br>DPI: 110 or 220 mcg/actuation | 200 mcg<br>220 mcg | >200-400 mcg<br>>220-440 mcg | >400-800 mcg<br>>440-880 mcg |

*Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)*

Nucala is approved by the FDA as add-on maintenance treatment of adults with chronic rhinosinusitis with nasal polyps (CRSwNP). FDA approval was based on the results of a randomized, double-blind, placebo-controlled trial where nasal polyp score (NPS) and nasal obstruction visual analog scale (VAS) score were the principal outcome. The trial enrolled individuals with recurrent and symptomatic nasal polyps with an inadequate response to at least 8 weeks of nasal corticosteroids as well as at least one surgery for polyp removal within the previous 10 years. Participants received Nucala or placebo in addition to background nasal corticosteroid therapy. The

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Nucala group had a statistically significant greater improvement at week 52 in NPS and nasal obstruction VAS score compared to the placebo group.

In 2014, the Joint Task Force on Practice Parameters (JTFPP) representing the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI) and the Joint Council of Allergy, Asthma & Immunology published a practice parameter on the diagnosis and management of rhinosinusitis. In 2015, the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNS) published a clinical practice guideline on adult sinusitis. Both publications recommend confirming a clinical diagnosis of nasal polyps with imaging using anterior rhinoscopy, nasal endoscopy or computed tomography (CT). Intranasal corticosteroids are recommended for long-term treatment of nasal polyps. A short course of oral corticosteroids is included as a reasonable option to decrease polyp size and alleviate symptoms. Sinonasal surgery is another treatment option. The AAAAI/ACAAI guidance predates Nucala receiving FDA approval for nasal polyps but states Nucala has shown benefit in treatment of CRSwNP.

In 2022, the JTFPP published guidelines for the medical management of CRSwNP. The guidelines focus on select interventions for treatment of CRSwNP including intranasal corticosteroids, biologics and aspirin therapy after desensitization. The guidelines recommend intranasal corticosteroids over no intranasal corticosteroids in individuals with CRSwNP. The guidelines also recommend biologics over no biologics but note it is a conditional recommendation as other treatment options should be considered or used together with biologics (including inhaled corticosteroids and surgery.

*Eosinophilic Granulomatosis with Polyangiitis*

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a multisystem disorder characterized by chronic rhinosinusitis, asthma and prominent peripheral blood eosinophilia. EGPA is classified as a vasculitis of the small to medium-sized arteries although the vasculitis is often not apparent in the initial phases of the disease. This blood vessel inflammation affects organ systems including the lungs, gastrointestinal tract, skin, heart and nervous system. Nucala and Fasenra are approved by the FDA for the treatment of adults with EGPA.

The safety and efficacy of Nucala for the treatment of EGPA was evaluated in a multicenter, parallel-group, double-blind, phase 3 trial of 136 adults with a diagnosis of relapsing or refractory EGPA for at least six months who had received at least 4 weeks of a stable prednisolone or prednisone therapy. The clinical trial inclusion criteria defined EGPA as a history or presence of asthma, a blood eosinophil level of greater than 10% of leukocytes or an absolute eosinophil count of greater than 1000 cells per microliter and the presence of two or more features associated with EGPA. Participants were randomized to receive Nucala or placebo in addition to standard care (glucocorticoid treatment with or without immunosuppressive therapy).

The two primary endpoints in the clinical trial were the accrued weeks of disease remission over a 52-week period and the proportion of participants in remission at both week 36 and week 48 of treatment. Remission was defined as Birmingham Vasculitis Activity Score (BVAS) = 0 [no active vasculitis] and the receipt of prednisolone or prednisone at a dose of 4 mg or less per day. Participants receiving Nucala achieved a significantly greater accrued time in remission compared to placebo (28% vs. 3% of participants had ≥ 24 weeks of accrued remission; odds ratio, 5.91; 95% CI, 2.68 to 13.03; $p<0.001$) and a significantly higher proportion of participants in remission

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at both week 36 and week 48 compared to placebo (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; p<0.001).

The safety and efficacy of Fasenra for the treatment of EGPA was evaluated in a multicenter, double-blind, phase 3, randomized, active-controlled noninferiority trial comparing Fasenra to Nucala. The trial included 140 adults with a diagnosis of relapsing or refractory EGPA for at least six months who had received at least 4 weeks of stable prednisolone therapy or equivalent. The clinical trial inclusion criteria defined EGPA as a history or presence of asthma, a blood eosinophil level of greater than 10% of leukocytes or an absolute eosinophil count of greater than 1000 cells per microliter and the presence of two or more features associated with EGPA. Participants were randomized to receive Fasenra or Nucala in addition to standard care (glucocorticoid treatment with or without immunosuppressive therapy). The primary end point in the clinical trial was the proportion of participants in remission at weeks 36 and 48 of treatment. Remission was defined as Birmingham Vasculitis Activity Score (BVAS) = 0 [no active vasculitis] and the receipt of prednisolone or prednisone at a dose of 4 mg or less per day. Fasenra demonstrated noninferiority but not superiority compared to Nucala.

In 2021, the American College of Rheumatology/Vasculitis Foundation (ACR/VF) published guidelines for the management of vasculitis. The guidelines discuss the role of Nucala in non-severe relapsing disease. For individuals with active, non-severe EGPA, ACR/VF conditionally recommends initiating treatment with Nucala and glucocorticoids over methotrexate, azathioprine or mycophenolate mofetil and glucocorticoids. For individuals with EGPA who have experienced relapse with non-severe disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine or mycophenolate mofetil, ACR/VF conditionally recommends adding Nucala over switching to another agent. For patients with EGPA who have experienced relapse with non-severe disease manifestations (asthma and/or sinonasal disease) while receiving low-dose glucocorticoids and no other therapy, ACR/VF conditionally recommends adding Nucala over adding methotrexate, azathioprine or mycophenolate mofetil. The ACR/VF guidelines predate the approval of Fasenra for EGPA.

*Hypereosinophilic Syndrome*

Hypereosinophilic syndromes (HES) are a group of rare disorders marked by increased levels of eosinophils in blood and tissues. Eosinophils can infiltrate many organ systems and lead to dermatological, pulmonary, gastrointestinal, neurologic and cardiovascular manifestations. HES diagnosis can be confirmed by blood eosinophil counts greater than or equal to 1,500 cells/microliter on two or more occasions and/or tissue eosinophilia. The goal of treatment is to reduce eosinophil levels and prevent organ damage. Systemic corticosteroids are the backbone of HES therapy. Immunosuppressive and cytotoxic agents are also utilized in treatment of HES. Nucala is approved by the FDA for the treatment of individuals aged 12 years and older with HES for ≥6 months without an identifiable non-hematologic secondary cause.

The safety and efficacy of Nucala for the treatment of HES was evaluated in a randomized, double-blind, placebo-controlled, multicenter, 32-week trial in 108 individuals aged 12 and older with HES for at least six months. Participants in the trial had experienced at least two HES flares within the past 12 months and had a blood eosinophil count greater than or equal to 1,000 cells/microliter at screening. Individuals with non-hematologic secondary HES (including drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic

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malignancy) or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Participants were randomized to receive Nucala or placebo in addition to background HES therapy consisting of chronic or episodic oral corticosteroids, immunosuppressive and/or cytotoxic therapy.

The primary endpoint in the clinical trial was the number of HES flares. HES flare was defined as worsening of clinical signs and symptoms of HES or increasing eosinophils resulting in the need to escalate background HES therapy by increasing the oral corticosteroid dose or increasing/adding cytotoxic or immunosuppressive therapy. Over the 32-week treatment period, the incidence of HES flares was 28% for the Nucala group compared to 56% for the placebo group.

*Chronic Obstructive Pulmonary Disease (COPD)*

Nucala is approved by the FDA as add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype.

The clinical efficacy of Nucala was demonstrated in two phase 3, multicenter, randomized, double-blind, placebo-controlled trials in 1,266 individuals with COPD with an eosinophilic phenotype. Participants were required to have a post-bronchodilator FEV1 20–80% of predicted normal and FEV1/FVC less than 0.7. Participants had a documented history of two moderate COPD exacerbations or one severe COPD exacerbation in the previous 12 months while receiving triple inhaled therapy for COPD. The blood eosinophil requirements differed between the two trials, but the efficacy population included individuals with an eosinophil count greater than or equal to 300 cells/microliter at screening or in the previous 12 months. In both trials, Nucala demonstrated a lower annualized rate of moderate or severe exacerbations when compared to placebo.

## Approved Indications

A. Cinqair®
   a. Eosinophilic Asthma
B. Fasenra®
   a. Eosinophilic Asthma
   b. Eosinophilic granulomatosis with polyangiitis (EGPA)
C. Nucala®
   a. Eosinophilic Asthma
   b. Eosinophilic granulomatosis with polyangiitis (EGPA)
   c. Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
   d. Hypereosinophilic Syndrome (HES)
   e. COPD
D. Exdensur®
   a. Eosinophilic Asthma

## Other Uses

A. N/A

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## Medical Necessity Guidelines:

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.*

**B vs D Criteria:** All drugs included in this PA are subject to B vs D evaluation. Medication must be furnished "incident to" physician service provided and usually not self-administered to be covered by Medicare and to be eligible to be evaluated through part B. If not, medication must be evaluated through part D.

*Reslizumab (Cinqair®)*

### A. Criteria For Initial Approval

Initial requests for Cinqair (reslizumab) for severe eosinophilic asthma may be approved if the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Individual has a diagnosis of severe eosinophilic asthma; **AND**
III. Evidence of asthma is demonstrated by the following (NAEPP, 2008):
  A. A pretreatment forced expiratory volume in 1 second (FEV1) less than 80% predicted; **AND**
  B. FEV1 reversibility of at least 12% and 200 ml after albuterol administration; **AND**
IV. Documentation is provided that individual has had a 3 month trial and inadequate response or intolerance to combination controller therapy (high dose inhaled corticosteroids plus long acting beta2 –agonists, leukotriene modifiers, long-acting muscarinic antagonists or oral corticosteroids) (GINA 2024); **AND**
V. Individual has experienced two or more asthma exacerbations in the prior 12 months requiring use of a systemic corticosteroid **or** temporary increase in the individual's usual maintenance dosage of oral corticosteroids (ERS/ATS, 2013); **AND**
VI. Documentation is provided that individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection) greater than or equal to 400 cells/microliter (400 cells/$mm^3$) at initiation of therapy.

### B. Criteria For Continuation of Therapy

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Continuation requests for Cinqair (reslizumab) for severe eosinophilic asthma may be approved if the following criteria are met:

i. Treatment with Cinqair has resulted in clinical improvement in one or more of the following:
   A. Decreased utilization of rescue medications;
   **OR**
   B. Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids);
   **OR**
   C. Increase in percent predicted FEV1 from pretreatment baseline;
   **OR**
   D. Reduction in reported asthma-related symptoms, such as asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing;
   **AND**
ii. Individual continues to use Cinqair in combination with inhaled corticosteroid-based controller therapy.

**C. Authorization Duration**

i. Initial Approval Duration: 6 months
ii. Reauthorization Approval Duration: 12 months

**D. Conditions Not Covered**

*Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):*

i. Cinqair (reslizumab) may not be approved for the following:
   A. In combination with Dupixent, Exdensur, Fasenra, Nucala, Tezspire or Xolair;
   **OR**
   B. May not be approved when the above criteria are not met and for all other indications.

## *Depemokimab-ulaa (Exdensur®)*

**A. Criteria For Initial Approval**

Initial requests for Exdensur (depemokimab-ulaa) for severe eosinophilic asthma may be approved if the following criteria are met:

i. Individual is 12 years of age or older; **AND**
ii. Individual has a diagnosis of severe eosinophilic asthma; **AND**
iii. Evidence of asthma is demonstrated by the following (NAEPP 2008):
   A. A pretreatment forced expiratory volume in 1 second (FEV1) less than 80% predicted;
   **AND**

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B. FEV1 reversibility of at least 12% and 200 milliliters after albuterol administration; **AND**

iv. Documentation is provided that individual has had a 3 month trial and inadequate response or intolerance to combination controller therapy (high dose inhaled corticosteroids plus long acting beta2–agonists, leukotriene modifiers, long-acting muscarinic antagonists or oral corticosteroids) (GINA 2024); **AND**

v. Individual has experienced two or more asthma exacerbations in the prior 12 months requiring use of a systemic corticosteroid or temporary increase in the individual's usual maintenance dosage of oral corticosteroids (ERS/ATS 2013); **AND**

vi. Documentation is provided that individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease and known or suspected parasitic infection) greater than or equal to 150 cells/microliter (150 cells/mm3) at initiation of therapy.

**B. Criteria For Continuation of Therapy**

Continuation requests for Exdensur (depemokimab-ulaa) for severe eosinophilic asthma may be approved if the following criteria are met:

i. Treatment with Exdensur (depemokimab-ulaa) has resulted in clinical improvement in one or more of the following:
   A. Decreased utilization of reliever medications; **OR**
   B. Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids); **OR**
   C. Increase in percent predicted FEV1 from pretreatment baseline; **OR**
   D. Reduction in reported asthma-related symptoms, including asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance or wheezing; **AND**

ii. Individual continues to use Exdensur (depemokimab-ulaa) in combination with inhaled corticosteroid-based controller therapy.

**C. Authorization Duration**

i. Initial Requests: 6 months
ii. Continuation Requests: 12 months

**D. Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Exdensur (depemokimab-ulaa) may not be approved for the following:
   A. In combination with Cinqair, Dupixent, Fasenra, Nucala, Tezspire or Xolair; **OR**
   B. May not be approved when the above criteria are not met and for all other indications.

*Benralizumab (Fasenra®)*

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## A. Criteria For Initial Approval

I. Initial requests for Fasenra (benralizumab) for *severe eosinophilic asthma* may be approved if the following criteria are met:
   i. Individual is 6 years of age or older; **AND**
   ii. Individual has a diagnosis of severe eosinophilic asthma; **AND**
   iii. Evidence of asthma is demonstrated by the following (NAEPP, 2008):
      A. A pretreatment forced expiratory volume in 1 second (FEV1) less than 80% predicted; **AND**
      B. FEV1 reversibility of at least 12% and 200 milliliters after albuterol administration; **AND**
   iv. Documentation is provided that individual has had a 3 month trial and inadequate response or intolerance to combination controller therapy (high dose inhaled corticosteroids plus long acting beta2 –agonists, leukotriene modifiers, long-acting muscarinic antagonists or oral corticosteroids) (GINA 2024); **AND**
   v. Individual has experienced two or more asthma exacerbations in the prior 12 months requiring use of a systemic corticosteroid or temporary increase in the individual's usual maintenance dosage of oral corticosteroids (ERS/ATS, 2013); **AND**
   vi. Documentation is provided that individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection) greater than or equal to 150 cells/microliter (150 cells/mm3) at initiation of therapy.

II. Initial requests for Fasenra (benralizumab) for *eosinophilic granulomatosis with polyangiitis (EGPA)* may be approved if the following criteria are met:
   i. Individual is 18 years of age or older; **AND**
   ii. Individual has been diagnosed with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) defined as (Wechsler, 2024):
      A. A history or presence of asthma; **AND**
      B. A blood eosinophil level of greater than or equal to 10% of leukocytes or an absolute eosinophil count of greater than 1000 cells per mm3 (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease and known or suspected parasitic infection), and documentation is provided; AND
      C. The presence of two or more features of eosinophilic granulomatosis with polyangiitis (such as, a biopsy showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatosis inflammation; neuropathy, mono or poly [motor deficit or nerve conduction abnormality]; pulmonary infiltrates, non-fixed; sinonasal abnormality; cardiomyopathy; glomerulonephritis; alveolar hemorrhage; palpable purpura; antineutrophil cytoplasmic antibody [ANCA] positive status; MPO or PR3 antibody positive status); **AND**
III. Individual is using in combination with oral corticosteroid therapy (Wechsler, 2024).

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**B. Criteria for Continuation Therapy**

I. Continuation requests for Fasenra (benralizumab) for *severe eosinophilic asthma* may be approved if the following criteria are met:

i. Treatment with Fasenra has resulted in clinical improvement in one or more of the following:
   A. Decreased utilization of rescue medications;
   **OR**
   B. Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids);
   **OR**
   C. Increase in percent predicted FEV1 from pretreatment baseline;
   **OR**
   D. Reduction in reported asthma-related symptoms, such as asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing;
   **AND**

ii. Individual continues to use Fasenra in combination with inhaled corticosteroid-based controller therapy.

II. Continuation requests for Fasenra (benralizumab) for *eosinophilic granulomatosis with polyangiitis (EGPA)* may be approved if the following criteria are met:

i. Treatment with Fasenra has resulted in the achievement of remission at some point during treatment, defined as (Wechsler, 2024):
   A. Birmingham Vasculitis Activity Score (BVAS), version 3, of 0 (on a scale from 0 to 63), and documentation is provided; **AND**
   B. Receipt of prednisolone or prednisone at a dose of 4 mg or less per day.

**C. Authorization Duration**

iii. Initial Requests: 6 months
iv. Continuation Requests: 12 months

**D. Conditions not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Fasenra (benralizumab) may not be approved for the following:
   A. In combination with Cinqair, Dupixent, Exdensur, Nucala, Tezspire or Xolair;
   **OR**
   B. May not be approved when the above criteria are not met and for all other indications.

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*Mepolizumab (Nucala®)*

**A. Criteria for Initial Approval**

I. Initial requests for Nucala (mepolizumab) for *severe eosinophilic asthma* may be approved if the following criteria are met:

i. Individual is 6 years of age or older; **AND**
ii. Individual has a diagnosis of severe eosinophilic asthma; **AND**
iii. Evidence of asthma is demonstrated by the following (NAEPP, 2008):
   A. A pretreatment forced expiratory volume in 1 second ($FEV_1$) less than 80% predicted;
   **AND**
   B. $FEV_1$ reversibility of at least 12% and 200 milliliters after albuterol administration; **AND**
iv. Documentation is provided that individual has had a 3 month trial and inadequate response or intolerance to combination controller therapy (high dose inhaled corticosteroids plus long acting $beta_2$ –agonists, leukotriene modifiers, long-acting muscarinic antagonists or oral corticosteroids) (GINA 2024); **AND**
v. Individual has experienced two or more asthma exacerbations in the prior 12 months requiring use of a systemic corticosteroid or temporary increase in the individual's usual maintenance dosage of oral corticosteroids (ERS/ATS, 2013); **AND**
vi. Documentation is provided that individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease and known or suspected parasitic infection) greater than or equal to 150 cells/microliter (150 cells/$mm^3$) at initiation of therapy.

II. Initial requests for Nucala (mepolizumab) for *eosinophilic granulomatosis with polyangiitis (EGPA)* may be approved if the following criteria are met:

i. Individual is 18 years of age or older; **AND**
ii. Individual has been diagnosed with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) defined as (Wechsler, 2017):
   A. A history or presence of asthma; **AND**
   B. A blood eosinophil level of greater than or equal to 10% of leukocytes or an absolute eosinophil count of greater than 1000 cells per mm3 (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease and known or suspected parasitic infection), and documentation is provided; **AND**
   C. The presence of two or more features of eosinophilic granulomatosis with polyangiitis (such as, a biopsy showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatosis inflammation;

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neuropathy, mono or poly [motor deficit or nerve conduction abnormality]; pulmonary infiltrates, non-fixed; sinonasal abnormality; cardiomyopathy; glomerulonephritis; alveolar hemorrhage; palpable purpura; antineutrophil cytoplasmic antibody [ANCA] positive status); **AND**

iii. Individual is using in combination with oral corticosteroid therapy (Wechsler, 2017).

III. Initial requests for Nucala (mepolizumab) for *hypereosinophilic syndrome (HES)* may be approved if the following criteria are met:

i. Individual is 12 years of age or older; **AND**
ii. Individual has been diagnosed with hypereosinophilic syndrome (HES) for at least six months; **AND**
iii. Individual has had a trial and inadequate response to oral corticosteroids (WHO 2022); **AND**
iv. Documentation is provided that individual has experienced two or more HES flares within the past 12 months requiring escalation in therapy (increase in oral corticosteroid dose or increase/addition of immunosuppressive or cytotoxic therapy); **AND**
v. Documentation is provided that individual has a blood eosinophil count greater than or equal to 1,000 cells/microliter.

IV. Initial requests for Nucala (mepolizumab) for *chronic rhinosinusitis with nasal polyps (CRSwNP)* may be if approved if the following criteria are met:

i. Individual is 18 years of age or older; **AND**
ii. Individual has a diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP); A**ND**
iii. Documentation is provided that there is presence of nasal polyps demonstrated on one of the following (AAOHNS 2015):
   A. Anterior rhinoscopy;
   **OR**
   B. Nasal endoscopy;
   **OR**
   C. Computed tomography (CT); **AND**
iv. Individual has had a trial and inadequate response to maintenance intranasal corticosteroids; **AND**
v. Individual is refractory to or is ineligible or intolerant to the following (AAAAI/ACAAI 2014, JTFPP 2022):
   A. Systemic corticosteroids;
   **OR**
   B. Sinonasal surgery; **AND**
vi. Individual is requesting Nucala as add-on therapy to maintenance intranasal corticosteroids.

V. Initial requests for Nucala (mepolizumab) for *chronic obstructive pulmonary disease* may be approved if the following criteria are met:

i. Individual is 18 years of age or older; **AND**

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ii. Individual has a diagnosis of chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype; **AND**
iii. COPD diagnosis is demonstrated by post-bronchodilator FEV1/FVC <0.7; **AND**
iv. Individual has moderate to severe airflow obstruction demonstrated by post-bronchodilator FEV1 20% - 80% predicted; **AND**
v. Documentation is provided that individual is currently on long-acting muscarinic antagonist (LAMA) in combination with long-acting beta-2 agonist (LABA) and inhaled corticosteroid (ICS); **AND**
vi. Individual meets one of the following:
  A. Two or more moderate COPD exacerbations in the prior 12 months requiring use of a systemic corticosteroid or antibiotic; **OR**
  B. One or more severe COPD exacerbation in the prior 12 months requiring more than 24 hours hospitalization; **AND**
vii. Documentation is provided that individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease and known or suspected parasitic infection) greater than or equal to 300 cells/microliter (300 cells/mm3).

**B. Criteria for Continuation Requests**

I. Continuation requests for Nucala (mepolizumab) for *severe eosinophilic asthma* may be approved if the following criteria are met:

i. Treatment with Nucala has resulted in clinical improvement in one or more of the following:
  A. Decreased utilization of rescue medications;
  **OR**
  B. Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids);
  **OR**
  C. Increase in percent predicted FEV1 from pretreatment baseline;
  **OR**
  D. Reduction in reported asthma-related symptoms, such as asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing.
ii. Individual continues to use Nucala in combination with inhaled corticosteroid-based controller therapy.

II. Continuation requests for Nucala (mepolizumab) for *eosinophilic granulomatosis with polyangitis* may be approved if the following criteria are met:

i. Treatment with Nucala has resulted in the achievement of remission at some point during

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treatment defined as (Wechsler, 2017):

A. Birmingham Vasculitis Activity Score (BVAS), version 3, of 0 (on a scale from 0 to 63), and documentation is provided; **AND**
B. Receipt of prednisolone or prednisone at a dose of 4 mg or less per day.

III. Continuation requests for Nucala (mepolizumab) for *hypereosinophilic syndrome (HES)* may be approved if the following criteria are met:

i. Treatment with Nucala has resulted in clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to decrease or absence of HES flares, improvement in fatigue).

IV. Continuation requests for Nucala (mepolizumab) for *chronic rhinosinusitis with nasal polyps (CRSwNP)* may be if approved if the following criteria are met:

i. Treatment with Nucala has resulted in clinically significant improvement in clinical signs and symptoms of disease (including but not limited to improvement in nasal congestion or reduced nasal polyp size); **AND**
ii. Individual continues to use Nucala in combination with maintenance intranasal corticosteroids.

V. Continuation requests for Nucala (mepolizumab) for *chronic obstructive pulmonary disease* may be approved if the following criteria are met:

i. Treatment with Nucala (mepolizumab) has resulted in clinical improvement in one or more of the following:
ii. Decreased utilization of reliever medication; **OR**
iii. Decreased frequency or severity of exacerbations; **OR**
iv. Increase in percent predicted FEV1 from pretreatment baseline; OR
v. Reduction in reported COPD-related symptoms, including shortness of breath, cough, fatigue or sleep disturbance; **AND**
vi. Individual continues to use Nucala in combination with ICS/LAMA/LABA therapy.

### C. Conditions not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Nucala (mepolizumab) for *hypereosinophilic syndrome (HES)* may not be approved for the following:

A. Individuals with non-hematologic secondary HES (including but not limited to drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy);

**OR**

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B. Individuals with FIP1L1-PDGFRα kinase-positive HES.

ii. Nucala (mepolizumab) may not be approved for the following:

A. In combination with Cinqair, Dupixent, Exdensur, Fasenra, Tezspire or Xolair;

**OR**

B. May not be approved when the above criteria are not met and for all other indications.

**D. Approval Duration**

i. Initial Approval Duration: 6 months

ii. Reauthorization Approval Duration: 12 months

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## Limits or Restrictions:

A. Therapeutic Alternatives

*The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.*

i. N/A

B. Quantity Limitations

*Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.*

***Selected Monoclonal Antibodies to Interleukin-5 Quantity Limits***

| Drug | Limit |
|---|---|
| Cinqair (reslizumab) 100 mg vial | • 3 mg/kg every 4 weeks |
| Exdensur (depemokimab-ulaa) 100 mg/mL prefilled pen/syringe | • 100 mg (1 pen/syringe) every 6 months |
| Fasenra (benralizumab) 10/0.5 mL mg prefilled syringe | • 10 mg (1 syringe/autoinjector) every 8 weeks |
| Fasenra (benralizumab) 30 mg prefilled syringe/autoinjector | • 30 mg (1 syringe/autoinjector) every 8 weeks |
| Nucala (mepolizumab) 40 mg/0.4 mL prefilled Syringe | • 40 mg (1 syringe) every 4 weeks |
| Nucala (mepolizumab) 100 mg vial, 100 mg/ml prefilled syringe/autoinjector | • 100 mg (1 vial/syringe/autoinjector) every 4 weeks |
| **Exceptions** | |
| For Fasenra, may approve 1 additional 30 mg/mL prefilled syringe/autoinjector or 10 mg/mL prefilled syringe at week 4. The total allowed quantity for initiation of therapy is 30 mg once every 4 weeks for the first 3 doses for individuals age 12 and older or age 6 – 11 weighing greater than or equal to 35 kg. The total allowed quantity for initiation of therapy is 10 mg once every 4 weeks for the first 3 doses for individuals age 6 – 11 weighing less than 35 kg.<br><br>For Fasenra, may approve 30 mg/mL prefilled syringe/autoinjector every 4 weeks if individual is using for eosinophilic granulomatosis with polyangiitis (EGPA).<br><br>For Nucala, may approve up to 300 mg (3 vials/syringes/autoinjectors) every 4 weeks if individual is using for eosinophilic granulomatosis with polyangiitis (EGPA) or hypereosinophilic syndrome (HES). | |

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## Codes Information:

*The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. 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 Guidelines may apply.*

**ICD-10 Diagnostic Codes:**

| Codes | Description |
|---|---|
| D72.110-D72.119 | Hypereosinophilic syndrome |
| J32.0-J32.9 | Chronic sinusitis |
| J33.0 – J33.9 | Nasal Polyp |
| J45.20-J45.998 | Asthma |
| J82.81-J82.89 | Pulmonary eosinophilia, not elsewhere classified |
| M30.1 | Allergic granulomatosis (Churg-Strauss) [Nucala and Fasenra] |
| J44.0-J44.9 | Other chronic obstructive pulmonary disease |

**HCPCS Codes:**

| Codes | Description |
|---|---|
| J0517 | Injection, benralizumab, 1 mg [Fasenra] |
| J2182 | Injection, mepolizumab, 1 mg [Nucala] |
| J2786 | Injection, reslizumab, 1 mg [Cinqair] |
| J3590 | Unclassified biologics [when specified as Exdensur (depemokimab-ulaa)] |

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Federal and state laws or requirements, contract language, and Plan utilization management programs or policies may take precedence over the application of this clinical criteria.

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## Policy History:

| Type of Review | Summary of Changes | P&T Approval Date | UM/CMPC Approval Date |
|---|---|---|---|
| **Focus Review** | Added clinical criteria and quantity limit for Exdensur. Updated may not approve in combination criteria for Cinqair, Fasenra and Nucala to include Exdensur. Updated reference to GINA Guideline 2024. Coding Reviewed: Added HCPCS J3590 for Exdensur. Added ICD-10-CM D72.110-D72.119 and expanded J33.0-J33.9. Administrative update to add documentation and incorporate new template. | 5/1/2026 | 5/6/2026 |
| **Annual Review** | Addition of COPD clinical criteria for Nucala. Addition of ICD10 code J44.0-J44.9 for COPD. Word formatting changes. | 9/5/2025 | 9/16/2025 |
| **Focus Review** | Added sections: Approved Indications, other uses, and Therapeutic Alternatives. Update Background information, Approved indications and Medical Necessity Guidelines (Clinical Criteria for initial and continuation requests) for the new indication for Fasenra for the treatment of EGPA. Update Fasenra age criteria. Add quantity limit to new strength. Wording and formatting changes. Coding Reviewed: No changes. | 2/24/2025 | 3/6/2025 |
| **Policy Inception** | 9/17/2023: Elevance Health's Medical Policy adoption. | N/A | 11/30/2023 |