LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.559

IL-5 Inhibitors

Effective Date:	**Jan. 3, 2025***	RELATED MEDICAL POLICIES:
Last Revised:	Sept. 10, 2024	5.01.513 Xolair (omalizumab)
Replaces:	N/A	
*Click here to view the current policy.		

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Introduction

Eosinophils are a type of white blood cell. Eosinophils promote inflammation to isolate germs and other substances harmful to the body. However, too much inflammation can lead to other medical issues, like asthma. IL-5 inhibitors are drugs that reduce the number of eosinophils. IL-5 inhibitors are add-on medications used to help prevent severe asthma attacks. This policy describes when IL-5 inhibitors may be considered medically necessary.

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

Policy Coverage Criteria

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home.

Drugs subject to site of service review addressed in this policy are:

- Cinqair (reslizumab)

Site of Service Administration	Medical Necessity
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* **Note:** *This does not include when standard dosing between infusions is 6 months or longer **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.**

Site of Service Administration	Medical Necessity
	This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following: • Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC less than or equal to 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion therapy • A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.**

Drug	Medical Necessity
Nucala (mepolizumab) SC Managed under pharmacy and medical benefit	**Nucala (mepolizumab) may be considered medically necessary for the labeled indication of add-on maintenance treatment of individuals with severe asthma with an eosinophilic phenotype, when the following conditions are met:** • Individual is aged 6 or older **AND** • Individual is using maximum doses of an inhaled corticosteroid **AND** • Individual is using an inhaled long-acting beta-agonist (LABA) **AND** • Individual meets one of the following:

Drug	Medical Necessity
	○ Two or more asthma exacerbations in the previous 12 months requiring use of oral corticosteroids **OR** ○ One or more asthma exacerbations requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous 12 months **OR** ○ Forced expiratory volume in 1 second (FEV_1) less than 80% predicted **AND** • Individual has had AT LEAST ONE of the following 3 criteria in the previous 12 months: ○ Blood *eosinophil count greater than 300 cells/mcL **OR** ○ Sputum *eosinophil count greater than or equal to 3% **OR** ○ Individual has oral corticosteroid dependent asthma and is not able to discontinue use of oral corticosteroids for blood eosinophil or sputum eosinophil tests **AND** • Nucala (mepolizumab) will not be used in combination with Cinqair (reslizumab), Dupixent (dupilumab), Fasenra (benralizumab), Tezspire (tezepelumab-ekko), or Xolair (omalizumab) when the medications are being used for the treatment of asthma **AND** • Nucala (mepolizumab) is prescribed by or in consultation with an allergist/immunologist or pulmonologist **AND** • The dose is limited to 100 mg every 4 weeks **Note:** ***Eosinophil count is a type of blood test that measures the quantity of a type of white blood cell called eosinophils. If the number in the blood or sputum is high (greater than 300 cells/mcL or 3%, respectively), this suggests that the individual is unresponsive to their regular maintenance (inhaled or oral) corticosteroid treatment.

Drug	Medical Necessity

	Nucala (mepolizumab) may be considered medically necessary for the labeled indication of treatment of adult individuals with eosinophilic granulomatosis with polyangiitis (EGPA) when all the following conditions are met:
	• Individual is aged 18 years and older
	AND
	• Individual has a history or presence of asthma
	AND
	• Individual has been taking a stable dose of prednisone or prednisolone between 7.5 mg and 50 mg with or without additional immunosuppressive therapy
	AND
	• A blood eosinophil level of greater than or equal to 10% OR absolute eosinophil count greater than or equal to 1500 cells/microL
	AND
	• Presence of AT LEAST ONE of the following criteria:
	  ○ Polyangiitis documented by one of the following:
	  ▪ Biopsy showing necrotizing vasculitis
	  ▪ Biopsy showing necrotizing or crescentic glomerulonephritis
	  ▪ Alveolar hemorrhage
	  ▪ Palpable purpura
	  ▪ Myocardial infarction due to proven coronary arteritis
	  ○ Vasculitis supported by one of the following:
	  ▪ Hematuria associated with red cell casts or greater than 10 percent dysmorphic erythrocytes
	  ▪ Hematuria with 2+ proteinuria
	  ▪ Leukocytoclastic vasculitis/eosinophilic infiltration of an arterial wall on biopsy
	  ○ Mononeuritis or mononeuritis multiplex
	  ○ ANCA and systemic manifestations (eg, myocarditis, pericarditis, peripheral neuropathy, other renal disease, abdominal pain)
	AND
	• Nucala (mepolizumab) is prescribed by or in consultation with an allergist/immunologist, pulmonologist, or rheumatologist

Drug	Medical Necessity
	AND • The dose is limited to 300 mg every 4 weeks **Nucala (mepolizumab) may be considered medically necessary for the labeled indication of treatment of adult and pediatric individuals with hypereosinophilic syndrome (HES) when all the following conditions are met:** • Individual is aged 12 or older **AND** • Documented history for greater than or equal to 6 months without an identifiable non-hematologic secondary cause (eg, drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy) **AND** • Without Fip1-like1-Platelet Derived Growth Factor Receptor α (FIP1L1-PDGFRA) kinase-positive HES as confirmed by FISH or RT-PCR genetic testing **AND** • A blood eosinophil level of greater than or equal to 1,000 cells/microL **AND** • Two or more HES flares that resulted in worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy in the past 12 months **AND** • Prior to initiating treatment with Nucala the individual is receiving background HES therapy for greater than or equal to 4 weeks **AND** • Nucala (mepolizumab) is prescribed by or in consultation with a hematologist **AND** • The dose is limited to 300 mg every 4 weeks **Nucala (mepolizumab) may be considered medically necessary for the labeled indication of treatment of adults with chronic**

Drug	Medical Necessity

	rhinosinusitis with nasal polyps (CRSwNP) when all the following conditions are met:
	• Individual is aged 18 years or older
	AND
	• Diagnosed with inadequately controlled bilateral CRSwNP
	AND
	• At least two the following symptoms are present:
	  ○ Facial pressure or pain
	  ○ Moderate to severe nasal congestion or obstruction
	  ○ Significant loss of smell
	AND
	• Had greater than or equal to 1 surgery to treat nasal polyps within the last 10 years
	AND
	• Had an adequate trial and failure of an intranasal corticosteroid as monotherapy
	AND
	• Nucala is prescribed in combination with an intranasal corticosteroid
	AND
	• The prescribed dose is 100 mg administered subcutaneously once every 4 weeks
	AND
	• Nucala (mepolizumab) will not be used in combination with Dupixent (dupilumab) or Xolair (omalizumab) when the medications are being used for the treatment of CRSwNP
	AND
	• Nucala is prescribed by or in consultation with an allergist/immunologist or otolaryngologist

Fasenra (benralizumab) SC **Managed under pharmacy and medical benefit**	**Fasenra (benralizumab) may be considered medically necessary for the labeled indication of add-on maintenance treatment of individuals with severe asthma and with an eosinophilic phenotype, when the following conditions are met:** • Individual is 6 years of age or older **AND** • Individual is using maximum doses of an inhaled corticosteroid

Drug	Medical Necessity

	AND
	• Individual is using an inhaled long-acting beta-agonist (LABA)
	AND
	• Individual meets one of the following:
	  ○ Two or more asthma exacerbations in the previous 12 months requiring use of oral corticosteroids
	  OR
	  ○ One or more asthma exacerbations requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous 12 months
	  OR
	  ○ Forced expiratory volume in 1 second (FEV_1) <80% predicted
	AND
	• Individual has had AT LEAST ONE of the following 3 criteria in the previous 12 months:
	  ○ Blood *eosinophil count greater than 300 cells/mcL
	  OR
	  ○ Sputum *eosinophil count greater than or equal to 3%
	  OR
	  ○ Individual has oral corticosteroid dependent asthma and is not able to discontinue use of oral corticosteroids for blood eosinophil or sputum eosinophil tests
	AND
	• Fasenra (benralizumab) will not be used in combination with Cinqair (reslizumab), Dupixent (dupilumab), Nucala (mepolizumab), Tezspire (tezepelumab-ekko), or Xolair (omalizumab) when the medications are being used for the treatment of asthma
	AND
	• Fasenra (benralizumab) is prescribed by or in consultation with an allergist/immunologist or pulmonologist
	AND
	• The maintenance dose is limited to 30 mg every 8 weeks
	
	***Note:** Eosinophil count is a type of blood test that measures the quantity of a type of white blood cell called eosinophils. If the number in the blood or

Drug	Medical Necessity
	sputum is high (greater than 300 cells/mcL or 3%, respectively), this suggests that the individual is unresponsive to their regular maintenance (inhaled or oral) corticosteroid treatment.
Cinqair (reslizumab) IV **Managed under medical benefit**	**Cinqair (reslizumab) IV is subject to review for site of service administration.** **Cinqair (reslizumab) may be considered medically necessary for the labeled indication of add-on maintenance treatment of individuals with severe asthma and with an eosinophilic phenotype, when the following conditions are met:** • Individual is aged 18 or older **AND** • Individual is using maximum doses of an inhaled corticosteroid **AND** • Individual is using an inhaled long-acting beta-agonist (LABA) **AND** • Individual meets one of the following: ○ Two or more asthma exacerbations in the previous 12 months requiring use of oral corticosteroids **OR** ○ One or more asthma exacerbations requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous 12 months **OR** ○ Forced expiratory volume in 1 second (FEV_1) <80% predicted **AND** • Individual has had AT LEAST ONE of the following 3 criteria in the previous 12 months: ○ Blood *eosinophil count greater than 300 cells/mcL **OR** ○ Sputum *eosinophil count greater than or equal to 3% **OR** ○ Individual has oral corticosteroid dependent asthma and is not able to discontinue use of oral corticosteroids for blood eosinophil or sputum eosinophil tests **AND**

Drug	Medical Necessity
	• Cinqair (reslizumab) will not be used in combination with Dupixent (dupilumab), Fasenra (benralizumab), Nucala (mepolizumab), Tezspire (tezepelumab-ekko) or Xolair (omalizumab) when the medications are being used for the treatment of asthma **AND** • Cinqair (reslizumab) is prescribed by or in consultation with an allergist/immunologist or pulmonologist **AND** • The dose is limited to 3 mg/kg every 4 weeks ***Note:** Eosinophil count is a type of blood test that measures the quantity of a type of white blood cell called eosinophils. If the number in the blood or sputum is high (greater than 300 cells/mcL or 3%, respectively), this suggests that the individual is unresponsive to their regular maintenance (inhaled or oral) corticosteroid treatment.

Drug	Investigational
Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab)	**All other uses of Cinqair (reslizumab), Fasenra (benralizumab) and Nucala (mepolizumab) for conditions not outlined in this policy are considered investigational. This includes treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Cinqair (reslizumab), Fasenra (benralizumab) and Nucala (mepolizumab) may be approved up to 1 year.**
Re-authorization criteria	**Future re-authorization of Cinqair (reslizumab), Fasenra (benralizumab), and Nucala (mepolizumab) for asthma and EPGA may be approved up to 1 year if the medical necessity criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by any of the following parameters:**

Length of Approval	
Approval	**Criteria**
	• Decrease in requirement for oral steroids, exacerbation frequency, ER and urgent care visits, hospitalizations **OR** • Decrease in frequency and severity of asthma symptoms **OR** • Increase in quality-of-life measures and ability to perform activities of daily living **Future re-authorization of Nucala (mepolizumab) for the treatment of HES may be approved up to 1 year if the medical necessity criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by any of the following parameters:** • Decrease in number or severity of HES flares from baseline **Future re-authorization of Nucala (mepolizumab) for the treatment of CRSwNP may be approved up to 1 year if the medical necessity criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by both of the following parameters:** • Decrease from baseline of nasal polyp size **AND** • Improvement in nasal congestion score (NCS*) or documented decrease from baseline of nasal congestion ***Note**: NCS scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, laboratory values, physical evaluation, and medication history

High Dose Regimens of Inhaled Corticosteroids			
Drug Name	**Low Dose**	**Medium Dose**	**High Dose**
Beclomethasone HFA (Qvar) 40 mcg per puff 80 mcg per puff	80 to 160 mcg 2 to 4 puffs 1 to 2 puffs	>160 to 320 mcg 3 to 4 puffs	>320 mcg >4 puffs
Budesonide DPI (Pulmicort Flexhaler) 90 mcg per inhalation 180 mcg per inhalation	180 to 360 mcg 2 to 4 inhalations 1 to 2 inhalations	>360 to 720 mcg 3 to 4 inhalations	>720 mcg >4 inhalations
Ciclesonide HFA (Alvesco) 80 mcg per puff 160 mcg per puff	80 to 160 mcg 1 to 2 puffs 1 puff	>160 to 320 mcg 3 to 4 puffs 2 puffs	>320 mcg >2 puffs
Fluticasone propionate HFA (Flovent HFA) 44 mcg per puff 110 mcg per puff 220 mcg per puff	88 to 220 mcg 2 to 5 puffs 1 to 2 puffs	>220 to 440 mcg 3 to 4 puffs 2 puffs	>440 mcg >2 puffs
Fluticasone propionate DPI (Flovent Diskus) 50 mcg per inhalation 100 mcg per inhalation 250 mcg per inhalation 500 mcg per inhalation (strength not available in the U.S.)	100 to 250 mcg 2 to 5 inhalations 1 to 2 inhalations 1 inhalation	>250 to 500 mcg 3 to 5 inhalations 2 inhalations 1 inhalation	>500 mcg 2 inhalations >1 inhalation
Fluticasone furoate DPI (Arnuity Ellipta)* 50 mcg per inhalation 100 mcg per inhalation 200 mcg per actuation	50 mcg 1 inhalation	100 mcg 1 inhalation	200 mcg 2 inhalations 1 inhalation
Mometasone DPI	110 to 220 mcg	>220 to 440 mcg	>440 mcg

High Dose Regimens of Inhaled Corticosteroids			
Drug Name	**Low Dose**	**Medium Dose**	**High Dose**
(Asmanex DPI) 110 mcg per inhalation 220 mcg per inhalation	 1 to 2 inhalations 1 inhalation	 2 inhalations	 >2 inhalations
Mometasone HFA (Asmanex HFA) 100 mcg per actuation 200 mcg per actuation	100 to 200 mcg 1 to 2 inhalations 1 inhalation	>200 to 400 mcg 2 inhalations	>400 mcg >2 inhalations

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

Coding

Code	Description
Reviewed for Medical Necessity	
HCPCS	
J0517	Injection, benralizumab (Fasenra), 1 mg
J2182	Injection, mepolizumab (Nucala), 1 mg
J2786	Injection, reslizumab (Cinqair), 1 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

Nucala (mepolizumab) is managed under both pharmacy and medical benefits.

Fasenra (benralizumab) is managed under both the pharmacy and medical benefits.

Cinqair (reslizumab) is managed under the medical benefit only.

Consideration of Age

The ages noted in the policy statements are based on the FDA labeling for these agents.

For site of service for medical necessity the age described in this policy is 13 years of age or older. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. The age criterion for site of service for medical necessity is based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to individuals above the age of 13.

Evidence Review

Description

Asthma

Asthma is a chronic disease that causes the airways of the lungs to become narrow due to inflammation, which leads to difficulty breathing. During an asthma attack, breathing can become so difficult that the individual is unable to get enough oxygen. Severe attacks can make the individual seek medical attention, even hospitalization, and these attacks can be life-threatening. There are more than 400,000 asthma-related hospitalizations each year. Severe asthma is estimated to account for 5-10% of all cases, with only 3% being severe, refractory, eosinophilic disease.[8] Individuals with severe asthma are at risk for frequent exacerbations and hospitalizations. Development of therapies to control asthma in this subpopulation is an unmet need.

More than 22 million people in the U.S. have asthma, and it is the most common chronic childhood disease.[4] Asthma affects many people regardless of age, race, and sex. According to the CDC, as of 2013, 8.3% of children and 7% of adults struggle with asthma. African Americans have the highest prevalence at 9.9%, followed by Whites at 7.4% and Hispanics, 5.9%.

In asthmatics, certain internal or external triggers can set off an allergic or hypersensitivity reaction in the bronchial airways. In some individuals, this is associated with hypereosinophilia. IL-5 is a key player in the growth, development, and function of eosinophils to cause and sustain airway inflammation. Inflammation can lead to asthma attacks. Repeated attacks can lead to worse symptoms, sensitivity to further attacks, and bad outcomes including death.

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

Nucala (mepolizumab)

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

Efficacy

Mepolizumab was approved in July 2021 for treatment of chronic rhinosinusitis with nasal polyps. The key study supporting efficacy of mepolizumab in chronic rhinosinusitis was the SYNAPSE trial. In SYNAPSE, 407 adult individuals with CRSwNP were randomized to receive NUCALA 100 mg or placebo administered subcutaneously once every 4 weeks while continuing nasal corticosteroid therapy. Individuals must have received background nasal corticosteroid for greater than or equal to8 weeks pre-screening. Individuals had recurrent and symptomatic CRSwNP, and had at least 1 surgery for the removal of nasal polyps within the previous 10 years. Individuals were required to have nasal obstruction symptoms with a visual analog scale (VAS) score of >5 out of a maximum score of 10. Individuals were also required to have an endoscopic bilateral nasal polyp score (NPS) of greater than or equal to5 out of 8 with NPS greater than or equal to2 in each nasal cavity. Individuals reported nasal obstruction VAS scores daily by placing a single mark on a continuous line labeled from 0 (none) to 100 (as bad as you can imagine). The distance along the line was converted to a 0-to-10-point scale for scoring. For NPS, polyps on each side of the nose were graded on a categorical scale (0 = no polyps, 1 = small polyps in the middle meatus not reaching below the inferior border of the middle concha, 2 = polyps reaching below the lower border of the middle turbinate, 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha, 4 = large polyps causing almost complete congestion/obstruction of the inferior meatus) for a total score of 0 to 8.

Individuals who received NUCALA 100 mg had a statistically significant improvement (decrease) in bilateral NPS at Week 52 and nasal obstruction VAS score from Weeks 49 to 52 at the end of the 52-week treatment period. The proportion of individuals who had surgery was significantly reduced by 57% (hazard ratio: 0.43, 95% CI: 0.25, 0.76) in the group treated with NUCALA 100 mg compared with the placebo group.

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

p<0.0001) vs placebo, respectively. A post hoc analysis examined differences in exacerbation rates in OCS dependent individuals (3.12 P; 1.54 M) and non-OCS dependent (1.9 P; 1.07 M). Both groups benefited from the addition of mepolizumab.

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

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

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

Safety

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

(total): herpes zoster 13.6 (13.6), atrial flutter 3.3 (6.8), and hypersensitivity 3.3 (6.8). There were 3 new malignancies in the placebo group (N=412) and 0 in the mepolizumab group (N=263).

No imbalance in withdrawals occurred across the three key studies supporting efficacy. Four deaths were reported across the treatment groups (N=916) but only three were caused by respiratory problems. Due to the severity of asthma in the individual populations, no deaths have been attributed directly related to mepolizumab treatment.

A year-long follow-up study (mepolizumab N=29) conducted over a 12-month period monitored the rebound effect of taking individuals off anti-IL-5 treatment. While no appreciable increase in exacerbation rate was found in the placebo-treated group, the mepolizumab group increased in exacerbations from 0.56 per individual in the first three months to 1.2 in months 3-6 ($P < 0.007$). However, the rates of exacerbations never went over pre-treatment baselines.

Fasenra (benralizumab)

Fasenra (benralizumab) is a monoclonal antibody to the IL-5 receptor. It binds to the receptor's alpha subunit on the cell surface of eosinophils and basophils, leading to cell death and accompanied by a rapid and nearly complete elimination of eosinophils in blood and airway sputum.[29] Also, a reduction in cytotoxic granules (eg, ECP, EDN) was seen following benralizumab administration.[30] Note that the site of action of the other two IL-5 antagonists for severe eosinophilic asthma, mepolizumab (Nucala) and reslizumab (Cinqair), is different from that of benralizumab. Mepolizumab and reslizumab act by binding to circulating IL-5.

Efficacy

The CALIMA (n=1306) and SIROCCO (n=1205) trials were double blind, placebo controlled, multicenter phase 3 pivotal trials that enrolled adults with asthma uncontrolled by inhaled corticosteroids and long-acting beta agonists.21,22 Subjects received BEN 30mg given by subcutaneous injection every four weeks for 3 doses, then every four or eight weeks for 48-56 weeks, along with stable doses of background therapy. The primary outcome for both trials was the asthma exacerbation rate in subjects with baseline eosinophil counts of at least 300 cells per microliter. Key secondary outcomes were the exacerbation rates in subjects with eosinophil counts under 300 cells per microliter, lung function, and asthma symptom scores.

The table below shows results for subjects broken down by those with higher eosinophil levels at baseline (>300 cells/µL), which is the primary analysis group, and results for the lower eosinophil group (<300 cells/µL), a secondary analysis group.

CALIMA: Placebo adjusted changes in exacerbation rates, lung function, and asthma symptom scores by baseline eosinophil level and treatment regimen

	Baseline eosinophils ≥ 300 cells/µL (primary analysis group)		**Baseline eosinophils < 300 cells/µL (secondary analysis group)**	
Mean (95%CI)	BEN Q 4 wks (n=241)	BEN Q 8 wks (n=239)	BEN Q 4 wks (n=116)	BEN Q 8 wks (n=125)
Exacerbation rate	-0.33 (-0.54, -0.12)*	-0.26 (-0.48, 0.04)*	-0.43 (-0.7, -0.08)*	-0.48 (-0.82, -0.14)*
FEV_1 (in liters)	0.125 (0.037, 0.213)*	0.116 (0.028, 0.204)*	0.064 (0.049, 0.176)	0.15 (0.127, 0.096)
Asthma symptom score	-0.19 (0.38, -0.01)*	-0.25 (-0.44, -0.07)*	-0.24 (-0.51, 0.03)	-0.10 (-0.37, 0.16)

* Indicates a statistically significant difference vs. placebo, CI= confidence interval, RR= rate reduction, Q= every, wks=weeks

SIROCCO: Placebo adjusted changes in exacerbation rates, lung function, and asthma symptom scores by baseline eosinophil level and treatment regimen

	Baseline eosinophils ≥ 300 cells/µL (primary analysis group)		**Baseline eosinophils < 300 cells/µL (secondary analysis group)**	
Mean (95%CI)	BEN Q 4 wks (n=275)	BEN Q 8 wks (n=267)	BEN Q 4 wks (n=124)	BEN Q 8 wks (n=131)
Exacerbation rate	-0.60 (-0.87, -0.33)*	-0.68 (-0.95, -0.42)*	-0.36 (-0.71, 0.00)*	-0.21 (-0.58, 0.16)
FEV_1 (in liters)	0.106 (0.016, 0.196)*	0.159 (0.068, 0.249)*	-0.025 (-0.134, 0.083)	0.102 (0.003, 0.208)
Asthma symptom score	-0.15 (-034, 0.4)	-0.29 (-0.48, -.10)*	0.00 (-0.27, 0.27)	-0.22 (-0.48, 0.05)

* Indicates a statistically significant difference vs. placebo, CI= confidence interval, Q= every, wks=weeks

A published, post-hoc, subgroup analysis of CALIMA and SIROCCO focused on results in the BEN 30mg every 8-week cohorts, excluding data from every 4-week cohorts.[35] The goal was to ascertain the effect of BEN using a different cutoff for subgroup analyses of 150 cells/μL, instead of the pre-defined 300 cells/μL cutoff. Details of these subgroup analyses are shown below and demonstrate that most key outcome results were statistically significant in the cohorts with baseline eosinophil counts of at least 150 cells/μL compared to placebo, but not in those with lower counts.

Placebo-adjusted outcomes by baseline eosinophil count (BEN 30mg Q8 week cohorts only)

	Baseline blood eosinophils ≥150 cells/μL		Baseline blood eosinophils <150 cells/μL	
mean (95% CI)	SIROCCO (n=325)	CALIMA (n=300)	SIROCCO (n=48)	CALIMA (n=48)
All exacerbations	-0.63 (-0.91, -0.345)*	-0.40 (-0.61, -0.19)*	-0.33 (-0.91, 0.25)	-0.54 (-1.23, 0.14)
ED visit/hosp	-0.10 (-0.19, -0.002)*	Not calculable	0.15 (-0.10, 0.40)	Not calculable
FEV_1 in liters	0.163 (0.087, 0.239)*	0.116 (0.41, 0.191)*	0.140 (-0.45, 0.325)	-0.131 (-0.306, 0.045)
Asthma sx score	-0.23 (-0.41, -0.06)*	-0.16 (-0.33, 0.01)	-0.40 (-0.78, -0.03)*	0.04 (-0.37, 0.45)

* Indicates a statistically significant difference vs. placebo, sx=symptom

A second published, post-hoc, subgroup analysis of pooled data from CALIMA and SIROCCO showed that trial subjects with baseline blood eosinophils of 150 cells/μL or more had significantly better reductions in the annual rate of asthma exacerbations compared to placebo.[36] The table below shows the relationship between baseline eosinophil levels and change in asthma exacerbation rates for this post hoc analysis.

Placebo-adjusted asthma exacerbation rate by baseline blood eosinophil count and dosing regimen[39]

Eosinophil cells/μL	Benralizumab 30mg every four weeks	Benralizumab 30mg every eight weeks
<150	-0.29 (95% CI -0.71, 0.13) n=101	-0.35 (95% CI -0.76, 0.06) n=105

Eosinophil cells/µL	Benralizumab 30mg every four weeks	Benralizumab 30mg every eight weeks
150-299	-0.43 (95% CI -0.79, -0.08)* n=136	-0.27 (95% CI -0.65, 0.10) n=147
300-449	-0.41 (95% CI -0.66, -0.17)* n=216	-0.32 (95% CI -0.58, -0.05)* n=201
≥450	-0.47 (95% CI -0.69, -0.25)* n=295	-0.59 (95% CI -0.8, -0.37)* n=298

* Indicates a statistically significant difference vs. placebo, CI= confidence interval

ZONA[23] (n=220) was a 28 week, randomized, double blind, placebo-controlled phase 3 trial that compared the ability of BEN to reduce oral corticosteroid use in asthmatic adults with a minimum blood eosinophil count of 150 cells per microliter taking 7.5mg to 40mg of prednisone daily and stable doses of background therapy prior to enrollment. The dosing regimens of BEN were the same as those used in CALIMA and SIROCCO. The graphs below show a marked and statistically significant reduction in oral prednisone requirements in both BEN groups vs. placebo, while concurrently reducing asthma exacerbation rates. Also, a greater proportion of subjects in the BEN groups were able to reduce their oral prednisone to physiologic levels (≤5mg/day) compared to placebo.

Safety

The available safety evidence for BEN in severe asthma includes four yearlong trials (N=2125/3220)[21,22] and two trials of 3-6 months duration (N=217/330)[25,26]. The range of doses studied was from 2mg to 100mg, given by subcutaneous injection every 4 or 8 weeks, or by a one-time IV infusion. An overview of safety information from the pivotal trials is given here. These data represent the largest number of subjects receiving BEN for up to a year (N=1,664). Long-term safety data are being collected in the extension trial, BORA (NCT02258542), which is not yet completed.[34] The information presented here focuses on AEs of a more serious nature. There were nine deaths reported, seven with BEN and two with placebo, over the course of the yearlong pivotal trials (N=2511).[21,22] Deaths are not unexpected in this individual population. Serious adverse events (SAEs) occurred less frequently with BEN vs. placebo in the CALIMA trial (9-10% vs. 14%), the most common being worsening of asthma (4-5% vs. 5%). Ten subjects (<1%) withdrew from the trial due to an SAE, seven in the BEN groups and three in the placebo group. In the SIROCCO trial, SAEs occurred less frequently with BEN vs. placebo (12% vs. 14%), the most common being worsening of asthma (5-6% vs. 8%). Other SAEs were reported at less than 1%. Between 13%-15% of subjects developed an antibody response to BEN, but this did not affect efficacy and was not associated with hypersensitivity reactions. Overall, the AE profile

of BEN is like that of placebo across these pivotal trials, including the rate of injection site reactions.

Cinqair (reslizumab)

Cinqair (reslizumab) is a biologic that inhibits interleukin-5 (IL-5), a key cytokine in the regulation of eosinophil production. Specifically, reslizumab is a humanized monoclonal antibody that binds to IL-5, preventing IL-5 from binding to cell surface receptors and thereby interrupting cell signaling pathways leading to eosinophilia and airway inflammation. IL-5 receptors are present on several cells involved in the inflammatory processes of asthma, including eosinophils, basophils, mast cells, and airway smooth muscle cells.

Efficacy

Published data from the two, 52-week, placebo-controlled, pivotal trials (studies 3082/3083) in 953 subjects with eosinophilic asthma demonstrate superiority of reslizumab 3mg/kg in reducing exacerbation rate by approximately half (rate ratio 0.46, 95% CI 0.37,0.58, $p<0.0001$) compared to placebo. Exacerbations are considered a clinically meaningful endpoint. Results of these trials are appropriately pooled because of similarities in design, individual population, and consistency of results. Secondary endpoints: improvements in lung function were significantly greater in the reslizumab treatment groups (FEV1 +110ml, 95% CI 67,150, $p<0.0001$), but the placebo-adjusted change in quality of life (AQLQ) observed with reslizumab was not clinically meaningful (0.23 units, 95% CI 0.16,0.39, $p<0.0001$). Reslizumab had a profound effect on lowering eosinophil count (cells per microliter) compared to placebo (-576 vs. -101, 95% CI -501,-450, $p<0.0001$).

Subgroup analyses of exacerbation rate results by region of these two pivotal trials revealed no benefit to reslizumab over placebo for subjects in the United States. This was a pre-planned analysis appropriately incorporated into the stratified randomization scheme. Post-hoc analyses of exacerbation data conducted by the FDA showed no meaningful benefit to treatment in adolescents and blacks worldwide, as well as U.S. residents. Similarly, there was no meaningful improvement in lung function with reslizumab in adolescents, elderly, blacks, and Asians. However, these results were deemed an anomaly and the advisory panel agreed 13 (yes) to 1 (no) on the efficacy of reslizumab in adults. All 14 panel members agreed efficacy in adolescents (age 12-17) had not been established. Subgroup analyses for exacerbations and lung function results are illustrated in the figures below.

In addition to the two exacerbation trials noted above, there were two, Phase 3, lung function trials (studies 3081 and 3084) and one Phase 2 trial (study 5-0010) critiqued for this monograph.

Study 3081 was a 16-week trial involving 315 subjects with eosinophilic asthma treated with reslizumab 0.3mg/kg, reslizumab 3 mg/kg or placebo. The placebo-adjusted increase in FEV_1 was significant for both reslizumab treatment groups ($\geq$100ml and $p<0.05$) at week 16. Secondary endpoints: there were mixed results for the quality-of-life outcomes Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ). Neither reslizumab group was superior to placebo in ACQ. The proportion of responders (AQLQ $\geq$ 0.5 units) was significantly greater with reslizumab 3mg/kg vs. placebo (64% vs. 48%, $p=0.02$), but the reslizumab 0.3 mg/kg dosage was not superior to placebo. It should be noted that the responder analysis, for both ACQ and AQLQ results, was not the pre-planned method for analyzing these results, so may be prone to bias.

Study 3084 enrolled 496 subjects with moderate-to-severe asthma (with or without eosinophilia) in a placebo-controlled, 16-week trial of reslizumab 3mg/kg. Changes in FEV_1 and Asthma Control Questionnaire (ACQ) were analyzed according to baseline eosinophil levels (<150, 150-300, 300-500, > 500 cells/microliter). The greatest placebo-adjusted increase in FEV_1 was seen in the group with >500 cells/microliter, but this was not statistically significant. Similarly, there was no significant change from baseline in quality of life (ACQ) in any eosinophil subgroup.

The phase 2 study of reslizumab 3mg/kg vs. placebo in 106 subjects with eosinophilic asthma (study 5-0010) lasted 15 weeks. The investigators planned to look at results in two subgroups: those with nasal polyps and those without. Subjects with nasal polyps had a better improvement in quality of life compared to those without polyps, but lung function was improved more in the subjects without nasal polyps. Specifically, there was no significant improvement in quality of life (ACQ) seen with reslizumab in the all-treated analysis, but there was a significant placebo-adjusted benefit seen in the nasal polyp subgroup (-0.94, 95% CI -1.65, -0.22, $p=0.0119$). Overall results for lung function (change in FEV_1) were significantly better for reslizumab subjects, but this was mainly driven by the placebo-adjusted benefit seen in the subjects without nasal polyps (+249 ml, 95% CI 31,466, $p=0.0257$).

Safety

Two serious safety signals, anaphylaxis and muscle toxicity, were identified in the pooled safety data from the placebo-controlled asthma studies. Three (of five) cases of anaphylaxis reported in the reslizumab group were deemed related to treatment. Potentially life-threatening creatine phosphokinase (CPK) elevations (ten times the upper limit of normal) were reported in 0.8% of

reslizumab subjects versus 0.4% of subjects in the placebo group. The most common adverse reaction (incidence greater than or equal to 2%) includes oropharyngeal pain.

Some subjects from the controlled trials (n=1052) elected to enroll in a two-year open-label extension study designed to further evaluate safety (study 3085). Three deaths were reported, but none were considered related to reslizumab. Serious adverse events (SAEs) were reported in 7% of subjects; 3 cases of skin basal cell carcinomas and ten other malignancies, which were characterized as typical for this individual population.

Most advisory panel members (11/14) agreed the safety profile of reslizumab in adults was acceptable for approval.

Practice Guidelines and Position Statements

IL-5 inhibitors are recommended as add-on treatment in step 5 of the GINA 2017 guidelines for asthma treatment[41].

2017 Update

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

2019 Update

Updated indicated age for Nucala (mepolizumab) from 12 years old to 6 years old per package insert. Also defined criteria for Nucala coverage for eosinophilic granulomatosis with polyangiitis (EGPA), used Lanham criteria for EGPA (like criteria used by clinical trial by Wechsler ME, Akuthota A, Jayne D, et al., doi10.1056/NEJMoa1702079). A literature search was conducted from August 1, 2017, to November 20, 2019. No other studies were found that would require further changes to this policy.

2020 Update

Reviewed prescribing information for Cinqair (reslizumab), Fasenra (benralizumab), and Nucala (mepolizumab). No new information was identified from the prescribing information. A literature search was conducted regarding combination use of the IL-5 inhibitors with Dupixent

(dupilumab) or Xolair (omalizumab). Only a few case studies were identified with limited evidence to support combination therapy. Updated criteria regarding combination therapy of the IL-5 inhibitors with Dupixent (dupilumab) or Xolair (omalizumab) based on limited evidence available regarding efficacy and safety of combined use. Updated the table on High Dose Regimens of Inhaled Corticosteroids and references.

2021 Update

Added a new indication to Nucala (mepolizumab) for adults with chronic rhinosinusitis with nasal polyps and defined criteria for medical necessity. Inclusion criteria from the SYNAPSE trial and policy criteria for Xolair and Dupixent were evaluated to guide analysis and criteria development.

2022 Update

Reviewed prescribing information for all drugs in policy. A literature search was conducted from November 1, 2021, through October 17, 2022. No new information was identified that required a change to the policy.

2023 Update

Reviewed prescribing information for all drugs in the policy. No new information was identified that required a change to the policy.

2024 Update

Reviewed prescribing information for all drugs in the policy. Updated Fasenra (benralizumab) age requirement from 12 years or older to 6 years or older. Updated Cinqair (reslizumab), Nucala (mepolizumab), and Fasenra (benralizumab) criteria requiring that Xolair (omalizumab), Dupixent (dupilumab), Cinqair (reslizumab), Fasenra (benralizumab), Tezspire (tezepelumab-ekko) and Nucala (mepolizumab) are not to be used as combination therapy with each other for the treatment of asthma. Added quantity limits per the prescribing information to Cinqair (reslizumab), Nucala (mepolizumab) and Fasenra (benralizumab). Updated Nucala (mepolizumab) coverage criteria to require that it is not used in combination with Dupixent

(dupilumab) or Xolair (omalizumab) for the treatment of nasal polyps. The following updates are effective January 3, 2025. Updated Nucala (mepolizumab), Fasenra (benralizumab), and Cinqair (reslizumab) asthma criteria eosinophil count from 150 cells/mcL within the last 12 months to 300 cells/mcL within the last 12 months. Updated Nucala asthma and eosinophilic granulomatosis with polyangiitis (EGPA) criteria to include a prescriber requirement. Updated Fasenra and Cinqair asthma criteria to include a prescriber requirement. Updated Nucala, Fasenra, and Cinqair asthma diagnostic criteria to the following: Individual has two or more asthma exacerbations in the previous 12 months requiring use of oral corticosteroids, one or more asthma exacerbations requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous 12 months, or forced expiratory volume in 1 second (FEV_1) <80% predicted.

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Appendix

Drug Class	Drug Names
Inhaled corticosteroids	Alvesco (ciclesonide), Arnuity Ellipta (fluticasone furoate), Asmanex HFA (mometasone), Asmanex Twisthaler (mometasone), Flovent Diskus (fluticasone propionate), Flovent HFA (fluticasone propionate), Pulmicort Flexhaler (budesonide), and QVAR Redihaler (beclomethasone)
Long-Acting Bronchodilators	Severent Diskus (salmeterol xinafoate)
Combination Long-acting Bronchodilator and Corticosteroid	Advair (fluticasone/salmeterol), Breo Ellipta (fluticasone/vilanterol), Dulera (mometasone/formoterol), Symbicort (budesonide/fomoterol fumarate)
Oral Corticosteroids	methylprednisolone, prednisone, prednisolone
Leukotriene Modifiers	Singulair (montelukast sodium), Accolate (zafirlukast)

History

Date	Comments
01/12/16	New policy, add to Medical subsection. Considered medically necessary for labeled indications when criteria are met.
02/09/16	Interim Update. Medical necessity criteria liberalized; deterioration of asthma control criterion removed.
02/18/16	Minor typographical and formatting errors fixed.
01/01/17	Coding update; added new HCPCS code J2182 effective 1/1/17. Moved coding table to Policy Guidelines section.
07/07/17	Policy moved into new format, no changes to policy statement.
09/01/17	Annual Review, approved August 22, 2017. No changes to policy statement. A literature search was conducted from 1/1/16 to 8/15/17. No new studies were found that would require changes to this policy. Removed HCPCS code J3490. Title changed from Mepolizumab (Nucala) to Nucala (mepolizumab).
02/01/18	Interim Review, approved January 16, 2018. Policy title was changed from "Nucala (mepolizumab)" to "IL-5 Inhibitors" to include Fasenra™ in policy. Added HCPCS codes J3490 and J3590.
03/01/18	Interim Review, approved February 27, 2018. Criteria for Nucala updated to include FDA label update. Reference was updated.
08/01/18	Annual Review, approved July 13, 2018. No changes made to policy.
09/21/18	Minor update. Added Consideration of Age statement.
01/01/19	Coding update, added HCPCS code J0517 (new code effective 1/1/19).

Date	Comments
01/01/20	Annual Review, approved December 17, 2019. Updated indicated age criteria, effective January 1, 2020, and defined EGPA coverage criteria for Nucala (mepolizumab), effective for dates of service on or after April 3, 2020, following provider notification. Removed HCPCS codes J3490 and J3590.
05/01/20	Interim Review, approved April 14, 2020. Added coverage criteria for Cinqair (reslizumab), which may be considered medically necessary as add-on maintenance treatment of patients with severe asthma when criteria are met. Coverage criteria for Cinqair (reslizumab) (HCPCS code J2786) becomes effective for dates of service on or after August 7, 2020, following provider notification.
08/01/20	Interim Review, approved July 23, 2020, and effective August 7, 2020. Updated criteria for Nucala (mepolizumab), Fasenra (benralizumab) and Cinqair (reslizumab) removing reference to "at the time of treatment" from blood eosinophil count.
10/01/20	Annual Review, approved September 17, 2020. Updated criteria for Cinqair (reslizumab), Fasenra (benralizumab), and Nucala (mepolizumab) that the medications are not to be used as combination therapy with Dupixent (dupilumab) or Xolair (omalizumab) for the treatment of asthma.
12/01/20	Interim Review, approved November 10, 2020. Added coverage criteria to Nucala (mepolizumab) for the treatment of hypereosinophilic syndrome (HES). Updated asthma criteria for Nucala (mepolizumab), Fasenra (benralizumab), and Cinqair (reslizumab) for patients with oral corticosteroid dependent asthma not able to discontinue use of oral corticosteroids for blood eosinophil or sputum eosinophil tests.
10/01/21	Annual Review, approved September 14, 2021. Added a new indication to Nucala for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP).
11/01/21	Interim Review, approved October 12, 2021. Updated Nucala (mepolizumab) criteria for the treatment of EGPA to include requirement patient is taking a stable dose of prednisone or prednisolone. Updated Nucala criteria for the treatment of HES to document patient is without FIP1L1-PDGFRA kinase-positive HES and that patient is receiving stable background HES therapy. Updated Nucala criteria are effective for dates of service on or after February 4, 2022. Added site of service review for Cinqair (reslizumab) for dates of service on or after February 4, 2022.
12/01/22	Annual Review, approved November 7, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
10/01/23	Annual Review, approved September 11, 2023. No changes to the policy statements.
06/01/24	Annual Review, approved May 24, 2024. Updated Fasenra (benralizumab) age requirement from 12 years or older to 6 years or older.
07/01/24	Interim Review, approved June 24, 2024. Updated Cinqair (reslizumab), Nucala (mepolizumab), and Fasenra (benralizumab) criteria requiring that Xolair (omalizumab), Dupixent (dupilumab), Cinqair (reslizumab), Fasenra (benralizumab), Tezspire (tezepelumab-ekko) and Nucala (mepolizumab) are not to be used as combination

Date	Comments
	therapy with each other for the treatment of asthma. Added quantity limits per the prescribing information to Cinqair (reslizumab), Nucala (mepolizumab) and Fasenra (benralizumab). Updated Nucala (mepolizumab) coverage criteria to require that it is not used in combination with Dupixent (dupilumab) or Xolair (omalizumab) for the treatment of nasal polyps.
10/01/24	Interim Review, approved September 10, 2024. The following policy changes are effective January 3, 2025, following a 90-day provider notification. Updated Nucala (mepolizumab), Fasenra (benralizumab), and Cinqair (reslizumab) asthma criteria eosinophil count from 150 cells/mcL within the last 12 months to 300 cells/mcL within the last 12 months. Updated Nucala asthma and eosinophilic granulomatosis with polyangiitis (EGPA) criteria to include a prescriber requirement. Updated Fasenra and Cinqair asthma criteria to include a prescriber requirement. Updated Nucala, Fasenra, and Cinqair asthma diagnostic criteria to the following: Individual has two or more asthma exacerbations in the previous 12 months requiring use of oral corticosteroids, one or more asthma exacerbations requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous 12 months, or forced expiratory volume in 1 second (FEV_1) <80% predicted.

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