Department:	Utilization Management	**Original Approval:**	08/10/2018
Policy #:	PM149	**Last Approval:**	08/10/2018
Title:	Antiasthmatic Monoclonal Antibodies- IL-5 Antagonists		
Approved By:	UM Pharmacy Subcommittee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Mepolizumab (Nucala), Benralizumab (Fasenra), and Reslizumab (Cinqair) for subcutaneous use for asthma: History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Age -Prescribed by or in consultation with an allergist, immunologist, or pulmonologist -Labs/diagnostics - Medication list (current and past) to include start and end dates of previous trials for all asthma.
Documentation required to determine medical necessity for Mepolizumab (Nucala) for EGPA History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Age -Prescribed by or in consultation with a specialist in allergy, cardiology, hematology, pulmonology, or rheumatology -Labs/diagnostics - Medication list (current and past) to include start and end dates of previous trials for all EGPA.

BACKGROUND

Mepolizumab (Nucala), Benralizumab (Fasenra), and Reslizumab (Cinqair) are interleukin (IL)-5 antagonist immunoglobulin G (IgG)1κ monoclonal antibodies. They are indicated for add-on maintenance treatment of patients with severe asthma aged ≥ 12 years who have an eosinophilic phenotype, as well as the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).[1]

Limitation of use: Not for relief of acute bronchospasm or status asthmaticus.[1]

INDICATIONS/CRITERIA

Coverage of Mepolizumab (Nucala), Benralizumab (Fasenra), and Reslizumab (Cinqair) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Asthma in Patients with Severe Disease and an Eosinophilic Phenotype[1]

MediCAID Members	***Nucala is not considered for approval for IgE mediated moderate to severe persistent asthma unless member has tried and failed 2 different inhaled***

	corticosteroids. Document if member meets this criteria, which medications were tried, and deny if criteria is not met. Otherwise, continue to clinical criteria below.
MediCARE Members	***Step-utilization of Part D drugs not required.*** ***Continue to criteria for approval below.***

A) Initial Therapy with Mepolizumab (Nucala), Benralizumab (Fasenra), and Reslizumab (Cinqair). Approve for 12 months if the patient meets ALL of the following criteria:

1. Documentation of blood eosinophil count (in the absence of other potential causes of eosinophilia) of **ONE** of the following:
    a. Greater than or equal to (≥) 150 cells/µL in prior 6 weeks
    b. Greater than or equal to (≥) 300 cells/µL in prior 12 months
2. Uncontrolled or inadequately controlled severe asthma is defined by at least **ONE** of the following:
    a. FEV_1 less than (<) 80% predicted
    b. Two or more bursts of systemic corticosteroids in the previous 12 months
    c. Poor symptom control (e.g., ACQ score consistently greater than 1.5 or ACT score consistently less than 20)
3. History of failure (remains symptomatic after 6 weeks), contraindication or intolerance to high-dose inhaled corticosteroid in combination with additional controller(s)
4. Used in combination with additional asthma controller medications
5. NOT used in combination with other monoclonal antibodies for the treatment of asthma (e.g. mepolizumab, reslizumab, benralizumab, omalizumab)
6. Age limits:
    a. Benralizumab, mepolizumab: greater than or equal to (≥) 12 years of age
    b. Raslizumab: greater than or equal to (≥) 18 years of age
7. Prescribed by or in consultation with a specialist in allergy, pulmonology, or immunology

B) Patients Continuing Therapy. Approve for 12 months if there is clinical documentation of disease stability or improvement compared to baseline measures.

Dosage and Quantity Limits:

benralizumab (FASENRA®)	30mg (1 syringe) every 4 weeks x3 doses, then 30mg (1 syringe) every 8 weeks
mepolizumab (NUCALA®)	100mg every 4 weeks; 1 vial per 28-day supply
Reslizumab (CINQAIR®)	3mg/kg every 4 weeks

Nucala is indicated for add-on maintenance treatment of patients with severe asthma aged ≥ 12 years who have an eosinophilic phenotype.[1] According to the 2014 ERS/ATS guidelines, severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.3 Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control; frequent severe exacerbations (two or more

requiring systemic corticosteroids per year); serious exacerbations (one hospitalization in the previous year); or airflow limitation (FEV1 < 80% of predicted in the setting of reduced FEV1/FVC). Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids (high-dose ICSs or systemic corticosteroids). Nucala has only been studied in patients who were also receiving treatment with high-dose ICSs alone or in combination with maintenance oral corticosteroids and an additional controller medication.[4-6] Current guidelines from the Global Initiative for Asthma (GINA) [2016] confirm that ICSs remain the mainstay of therapy even in the setting of difficult-to-treat, severe asthma.[2] For patients with persistent symptoms or exacerbations despite two or more controller medications plus an as needed r eliever medication, the GINA guidelines recommend referral of the patient to a specialist with expertise in the management of severe asthma to investigate and consider additional treatments. Options for add-on therapy in this patient population include Nucala in patients ≥ 12 years of age with severe eosinophilic asthma. Finally, in pivotal trials of Nucala, all patients were required to demonstrate evidence of eosinophilic inflammation.[4-6] In the DREAM study, exploratory subgroup analyses indicated that the efficacy of Nucala improved with larger elevations in blood eosinophil counts; however, elevated sputum eosinophil counts were not found to predict enhanced efficacy. Again in the MENSA study, a subgroup of patients with very elevated blood eosinophil counts at baseline demonstrated an enhanced response to Nucala. In patients who did not have a blood eosinophil level ≥ 150 cells/microliter at screening (n = 86), Nucala therapy did not result in a significant reduction in exacerbations compared with placebo.[1,7] In studies including patients without evidence of eosinophilic inflammation, Nucala did not produce significant improvements in lung function compared with placebo.8 A post-hoc analysis of data from the DREAM and MENSA studies assessed the relationship between baseline blood eosinophil counts and Nucala efficacy.[9] Clinically significant reductions in asthma exacerbations were observed with Nucala vs. placebo in patients with a blood eosinophil count ≥ 150 cells per microliter at baseline. In the opinion of expert physicians reviewing the data we have adopted the eosinophil criteria and criteria for uncontrolled asthma.

2. Eosinophilic Granulomatosis with Polyangiitis[1, 20, 21, 22]

MediCAID Members	***Nucala is not considered for approval for* Eosinophilic Granulomatosis with Polyangiitis *unless member has tried and failed systemic glucocorticoids***. *Document if member meets this criteria, which medications were tried, and deny if criteria is not met. Otherwise, continue to clinical criteria below*.
MediCARE Members	***Continue to criteria for approval below.***

A) Initial Therapy with mepolizumab (NUCALA®) only. Approve for 12 months if the patient meets all of the following criteria (i, ii, iii, iv and v):

Diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA)

1. Symptoms that include **TWO** of the following
    a. Documentation of blood eosinophil count (in the absence of other potential causes of eosinophilia) of **ONE** of the following:
        i. Greater than or equal to (≥) 150 cells/µL in prior 6 weeks

   ii. Greater than or equal to (≥) 300 cells/µL in prior 12 months
   b. White blood cells present outside blood vessels (extravascular eosinophils)
   c. Migratory spots or lesions on a chest X-ray (pulmonary infiltrates)
   d. Sinus problems (acute or chronic sinusitis)
   e. Damage to one or more nerve groups (mononeuropathy or polyneuropathy)
2. History of failure, contraindication or intolerance to **ONE** of the following:
   a. Oral corticosteroids
   b. Inhaled corticosteroids
   c. Immunosuppressants (e.g. cyclophosphamide, azathioprine, methotrexate)
3. Less than or equal to (≤) 300mg every 4 weeks
4. Prescribed by or in consultation with a specialist in allergy, cardiology, hematology, pulmonology, or rheumatology
5. Greater than or equal to (≥) 12 years of age
6. **NOT** to be used in combination with other antiasthmatic – monoclonal antibodies (e.g. benralizumab, omalizumab, reslizumab)

B) Patients Continuing Nucala Therapy. Approve for 12 months if there is clinical documentation of disease stability or improvement compared to baseline measures.

Dosage and Quantity Limits:

mepolizumab (NUCALA®)	300mg every 4 weeks; 3 vials per 28-day supply

Conditions Not Recommended for Approval

Nucala has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Atopic Dermatitis (AD). There are no studies evaluating the use of SC Nucala in patients with atopic dermatitis. In one small (n = 40) randomized, placebo-controlled, parallel group study, mepolizumab 750 mg IV once weekly for 2 weeks significantly reduced peripheral blood eosinophil counts in patients with moderate to severe atopic dermatitis.10 However, mepolizumab IV therapy did not result in clinical success as assessed by Physician's Global Assessment of Improvement scores compared with placebo (P = 0.115). Clinical outcomes (as measured by Scoring Atopic Dermatitis [SCORAD] index), pruritus scoring, and serum thymus and activation-regulated chemokine (TARC) values were also not significantly improved with mepolizumab IV vs. placebo. In the same patient population, mepolizumab IV also did not significantly reduce the macroscopic outcome of the atopy patch test, an in vivo model that is used to study the induction of eczema by inhalant allergens in patients with atopic dermatitis.[11]
2. Chronic Obstructive Pulmonary Disease (COPD). The safety and efficacy of Nucala have not been established in patients with COPD. There are currently two Phase III studies underway evaluating SC Nucala as an adjunct treatment in COPD management and in patients with severe COPD and recurrent

exacerbations; a third Phase III study is evaluating IV Nucala in patients with COPD with eosinophilic bronchitis.[12]

3. Concurrent use of Nucala with another interleukin (IL)-5 antagonist monoclonal antibody. Cinqair is another IL-5 antagonist IgG4κ monoclonal antibody indicated for add-on maintenance treatment of patients with severe asthma aged ≥ 18 years who have an eosinophilic phenotype.[13] The efficacy and safety of Nucala in combination with Cinqair or any other IL-5 antagonist have not been established.

4. Concurrent use of Nucala with Xolair® (omalizumab injection for subcutaneous use). Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody indicated for use in adults and adolescents (aged ≥ 6 years) with moderate to severe persistent asthma and who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.[14] The efficacy and safety of Nucala in combination with Xolair have not been established.

5. Eosinophilic Esophagitis (EoE), Eosinophilic Gastroenteritis, or Eosinophilic Colitis. In an open-label, Phase I/II study of mepolizumab IV in four adult patients with EoE, dysphagia, and esophageal strictures, three IV infusions of mepolizumab were found to decrease peripheral blood eosinophil counts (by 6.4-fold from baseline) and percent of CCR3+ cells (by 7.9-fold).[15] Mean esophageal eosinophil counts decreased from 46 cells/high-power field (hpf) to 6 cells/hpf and maximal esophageal eosinophil counts decreased from 153 cells/hpf to 28 cells/hpf following mepolizumab IV therapy. One small (n = 11), Phase II, randomized, double-blind, placebo-controlled study that assessed the efficacy of mepolizumab 750 mg IV (administered once weekly for 2 weeks) compared with placebo in patients with EoE experiencing frequent episodes of dysphagia (≥ one episode per week). At 4 weeks, mepolizumab therapy resulted in a significant reduction in esophageal eosinophilia (54% reduction) compared with placebo (5% reduction) [P = 0.03].[16] Another study evaluated three infusions of either 0.55 mg/kg, 2.5 mg/kg, or 10 mg/kg mepolizumab IV administered every 4 weeks in pediatric patients with EoE (n = 59).[17] No placebo comparator was used. Peak eosinophil counts were reduced to < 5 cells/hpf in 8.8% of the patients; no differences between the three doses of mepolizumab IV were observed. In total, 31.6% of patients experienced reduced peak eosinophil counts of < 20 cells/hpf and in 89.5% of patients, mepolizumab IV reduced mean eosinophil counts to < 20 per hpf. The American College of Gastroenterology clinical guideline for the diagnosis and management of esophageal eosinophilia and EoE state that further studies utilizing anti-IL-5 therapies are needed to define their role in EoE.[18] They note two trials of mepolizumab IV, but highlight that while eosinophil counts declined, the majority of patients did not achieve complete histologic resolution and in adults symptoms did not improve. A 2014 updated food allergy practice parameter from the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology (JCAAI) Joint Task Force addressed the treatment of EoE, but also noted that biologic therapies, including anti-IL-5 therapy, have had varying success and are not recommended for routine use in patients with EoE.[19] There are no data to support the use of Nucala in patients with eosinophilic gastroenteritis or eosinophilic colitis. Further research is warranted to determine if Nucala has a place in therapy in the treatment of these conditions.

6. Hypereosinophilic Syndrome (HES), Idiopathic. One small (n = 4) open-label trial of three IV doses of mepolizumab (10 mg/kg; maximum dose of 750 mg) every 4 weeks in patients with HES found mepolizumab IV significantly lowered peripheral blood eosinophil counts, even in the setting of continued systemic glucocorticoid therapy.[23] This effect was sustained for up to 12 weeks following the last dose of mepolizumab IV. Another randomized, double-blind, placebo-controlled, multicenter, Phase II trial (published) [n = 85] evaluated mepolizumab IV therapy in patients with HES (negative for the

FIP1L1-PDGFRA fusion gene).[24] Mepolizumab 750 mg IV for 36 months resulted in significantly more patients reducing their prednisone dose ≤ 10 mg per day compared with placebo (84% of patients vs. 43% of patients, P < 0.001). In an open-label extension of this study (mean exposure to mepolizumab of 251 weeks), 62% of patients were prednisone-free without other hypereosinophilic syndrome medications for ≥ 12 weeks.[25] Dosing intervals of IV mepolizumab varied in the extension study; the most common dosing interval was every 9 to 12 weeks. SC Nucala has not been studied in this patient population. IV mepolizumab is available from the manufacturer on a compassionate use basis for patients with life-threatening HES who have failed prior therapies.[26]

7. Nasal Polyps. There are limited data regarding the use of Nucala in patients with nasal polyps. One small (n = 30), randomized, double-blind study compared mepolizumab 750 mg IV (every 28 days for two doses) with placebo for the treatment of severe nasal polyposis.27 At Week 8, mepolizumab IV was found to significantly improve the change in the total polyp score from baseline compared with placebo (60% improvement vs. 10% improvement, respectively; P = 0.018). Non-significant improvements in patients' loss of smell, postnasal drip, and congestion were observed with mepolizumab IV at Week 8 vs. the placebo group; rhinorrhea remained at the same level regardless of treatment. No studies of SC Nucala have been conducted in this patient population. Additional, well-controlled trials are needed to determine the role of Nucala in the treatment of nasal polyposis.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

CFR		
WAC	WAC 284-43-2050	
RCW		
Contract Citation	☐ WAH	
	☐ IMC	

	☐ MA	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
Other Requirements		
NCQA Elements		
References	1. Product Information: NUCALA(R) subcutaneous injection, mepolizumab subcutaneous injection. GlaxoSmithKline LLC (per manufacturer), Philadelphia, PA, December 2017. Accessed February 2018. 2. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated April 2016. Available at: http://www.ginasthma.org. Accessed on: February 14, 2018. 3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343-373. 4. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380:651-659. 5. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371:1198-1207. 6. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189-1197. 7. Data on file. Biomarkers Used in studies for Nucala to identify subjects and evaluate efficacy. GlaxoSmithKline; November 2015. 8. Flood-Paige P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med. 2007;176(11):1062-1071. 9. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med. 2016;4(7):549-556. 10. Oldhoff JM, Darsow U, Werfel T, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy. 2005;60(5):693-696. 11. Oldhoff JM, Darsow U, Werfel T, et al. No effect of anti-interleukin-5 therapy (mepolizumab) on the atopy patch test in atopic dermatitis patients. Int Arch Allergy Immunol. 2006;141(3):290-294. 12. Mukherjee M, Sehmi R, Nair P. Anti-IL5 therapy for asthma and beyond. WAO Journal. 2014;7(32):1-14. 13. Cinqair® injection for intravenous use [prescribing information]. Frazer, PA: Teva Respiratory, LLC; March 2016.	

	14. Xolair® subcutaneous injection [prescribing information]. South San Francisco, CA and East Hanover, NJ: Genentech, Inc. and Novartis Pharmaceuticals Corporation; July 2016. 15. Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. J Allergy Clin Immunol 2006;118(6):1312-1319. 16. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic esophagitis: a randomized, placebo-controlled, double-blind trial. Gut. 2010;59:21-30. 17. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology. 2011;141(5):1593-1604. 18. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol. 2013;108(5):679-692. 19. Joint Task Force on Practice Parameters: American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology. Food allergy: a practice parameter update – 2014. J Allergy Clin Immunol. 2014;134:1016-1025. 20. Kim S, Marigowda G, Oren E, et al. Mepolizumab as a steroid sparing treatment option in patients with Churg-Strauss Syndrome. J Allergy Clin Immunol. 2010;125(6):1336-1343. 21. Moosig F, Gross WL, Herrmann K, et al. Targeting interleukin-5 in refractory and relapsing Churg-Strauss Syndrome. Ann Intern Med. 2011;155(5):341-343. 22. Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med. 2015;26(7):545-553. 23. Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. J Allergy Clin Immunol. 2004;113(1):115-119. 24. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med. 2008;358(12):1215-1228. 25. Roufosse FE, Kahn JE, Gleich GJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. J Allergy Clin Immunol. 2013;131(2):461-467. 26. Gotlib J. World Health Organization-defined eosinophilic disorders: 2015 update on diagnosis, risk stratification, and

	management. Am J Hematol. 2015;90(11):1077-1089. 27. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol. 2011;128:989-995. 28. Product Information: FASENRA™ subcutaneous injection, benralizumab subcutaneous injection. AstraZeneca Pharmaceuticals LP (per manufacturer), Wilmington, DE, 2017. 29. Product Information: XOLAIR® subcutaneous injection powder, omalizumab subcutaneous injection powder. Genentech Inc (per manufacturer), South San Francisco, CA, 2016. 30. Product Information: CINQAIR® intravenous injection, reslizumab intravenous injection. Teva Pharmaceuticals (per manufacturer), Frazer, PA, 2016 OTHER REFERENCES UTILIZED • Liacouras CA, Furata GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011 Jul;128(1):3-20.e6.

Revision History

Revision Date	Revision Description	Revision Made By
06/12/2018	Created to mirror HCA policy	Jennifer Farley, PharmD
08/10/2018	Approval	UM Pharmacy Subcommittee