Medical Policy

BlueCross BlueShield of Kansas
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Title: Injectable Asthma Agents

See also: *Xolair (omalizumab)*

- **Prime Therapeutics will review Prior Authorization requests**

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Injectable-Asthma.pdf

Link to Drug List (Formulary):
https://www.bcbsks.com/drugs/

Professional
Original Effective Date: June 1, 2016
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Institutional
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Current Effective Date: May 1, 2018

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DESCRIPTION

The intent of the Injectable Asthmas Agents Prior Authorization (PA) criteria is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies. For the diagnosis of severe eosinophilic asthma, the program requires diagnosis as determined by blood or sputum eosinophilic counts and require the patient to currently be receiving maximally tolerated inhaled corticosteroids (ICS) plus a controller agent. For a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA), a patient must have a 6 month history of EGPA that has contains relapsing or refractory disease. The patient's diagnosis of EGPA must be confirmed by several parameters and the patient must be currently on maximally tolerated oral corticosteroid therapy and have tried and failed an oral immunosuppressant or have a documented intolerance, FDA labeled contraindication, or hypersensitivity to these prerequisites. The requested dose must be within the FDA maximum dose for the patient's indication and the requested agent will not be used in combination with Xolair or another IL-5 inhibitor indicated for the requested indication. For renewal of therapy, the program will require the patient has had clinical response from the requested agent, will continue to receive standard therapy (e.g. ICS or a controller medication), the dose is within FDA labeling for the patient's diagnosis, and that the requested agent will not be used in combination with Xolair or another IL-5 inhibitor indicated for the requested indication.

Target Agents

- **Cinqair**® (reslizumab)
- **Fasenra**™ (benralizumab)
- **Nucala**® (mepolizumab)

FDA Approved Indications and Dosage[1,9,10]

Agent(s)	Indication* ^	Dose and administration
Cinqair® (reslizumab)	As add-on maintenance treatment of patients with severe asthma 18 years and older and with an eosinophil phenotype	3 mg/kg once every 4 weeks by intravenous infusion
Fasenra™ (benralizumab)	Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype	30 mg administered once every 4 weeks for the first 3 doses, then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen
Nucala® (mepolizumab)	As add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)	**Severe Asthma**: 100 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen **EGPA**: 300 mg administered once every 4 weeks by subcutaneous injection as 3 separate 100 mg injections into the upper arm, thigh, or abdomen

* Not for treatment of other eosinophilic conditions or for relief of acute bronchospasms or status asthmaticus
^ Benralizumab, mepolizumab and reslizumab have not been studied for use in combination with Xolair (omalizumab)

POLICY

Prior Authorization Criteria for Approval

Initial Evaluation

Cinqair (reslizumab), **Fasenra** (benralizumab), and **Nucala** (mepolizumab) will be approved when ALL of the following are met:

1. ONE of the following:
   - A. The patient has a diagnosis of severe eosinophilic asthma and ALL of the following:
     - i. The patient is within the FDA labeled age for the requested agent:
       - a. Cinqair: 18 years of age or over
       - b. Fasenra: 12 years of age or over
       - c. Nucala: 12 years of age or over

       AND
     - ii. The patient's diagnosis has been confirmed by ONE of the following eosinophilic counts for the requested agent:
       - a. If the requested agent is Cinqair, the patient has a blood eosinophilic count greater than or equal to 400 cells/MicroLiter within the previous 12 months

         OR
       - b. If the requested agent is Fasenra, the patient has a blood eosinophilic count greater than or equal to 150 cells/microLiter

         OR
       - c. If the requested agent is Nucala, the patient has ONE of the following:
         1) Blood eosinophilic count greater than or equal to 150 cells/microLiter prior to initiation (within the previous 6 weeks) of therapy with the requested agent

            OR
         2) Blood eosinophilic count greater than or equal to 300 cells/microLiter within the previous 12 months

            OR
         3) Sputum eosinophilic count greater than 3%

       AND
     - iii. ONE of the following:
       - a. If the requested agent is Fasenra AND the patient is aged 12 years to 17 years, the patient has a baseline Forced Expiratory Volume (FEV1) that is less than 90% of predicted

         OR
       - b. The patient has a baseline FEV_1 that is less than 80% of predicted

       AND
     - iv. The patient has ONE of the following:

a. Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months
OR
b. Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months
OR
c. Controlled asthma that worsens when the doses of inhaled or systemic corticosteroids are tapered

AND

v. ONE of the following:
a. The patient is currently treated with a maximally tolerated inhaled corticosteroid within the past 90 days
OR
b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to inhaled corticosteroids

AND

vi. ONE of the following:
a. The patient is currently treated with ONE of the following within the past 90 days:
1) A long-acting beta-2 agonist (LABA)
OR
2) A leukotriene receptor antagonist (LRTA)
OR
3) Long-acting muscarinic antagonist (LAMA)
OR
4) Theophylline
OR
b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a long-acting beta-2 agonist (LABA), leukotriene receptor antagonist (LRTA), long-acting muscarinic antagonist (LAMA), AND theophylline

OR

B. The patient has a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) and ALL of the following:
i. The requested agent is Nucala
AND
ii. The patient is 18 years of age or over
AND
iii. The patient has a history of EGPA for at least 6 months with a history of relapsing or refractory disease
AND
iv. The patient's diagnosis of EGPA was confirmed by ONE of the following:

a. The patient meets 4 of the following:
   1) History of asthma (wheezing or the finding of diffuse high pitched wheezes in expiration)
   2) Greater than 10% eosinophils on differential leukocyte count
   3) Mononeuropathy (including multiplex) or polyneuropathy
   4) Migratory or transient pulmonary opacities detected radiographically
   5) Paranasal sinus abnormality
   6) Biopsy containing blood vessel showing the accumulation of eosinophils in extravascular areas

OR

b. The patient meets ALL of the following:
   1) Medical history of asthma

   AND

   2) Peak peripheral blood eosinophilia > 1500 cells/microL

   AND

   3) Systemic vasculitis involving two or more extra-pulmonary organs

AND

v. ONE of the following:
   a. The patient is currently on maximally tolerated oral corticosteroid therapy within the past 90 days

   OR

   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to oral corticosteroid therapy

AND

vi. ONE of the following:
   a. The patient has tried and failed an oral immunosuppressant (i.e., azathioprine, methotrexate) in the past 90 days

   OR

   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to immunosuppressants

OR

C. Another FDA approved indication

AND

2. The patient will NOT receive the requested agent in combination with Xolair or with another interleukin 5 (IL-5) inhibitor (e.g. Cinqair, Fasenra, Nucala) for the requested indication

AND

3. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

4. ONE of the following:

A. The requested agent is subject to quantity limit (i.e. Fasenra, Nucala), AND ONE of the following:
   i. The quantity (dose) requested is within the program quantity limit
   OR
   ii. The quantity (dose) requested is above the program limit, within FDA approved labeling, and the prescribed dose cannot be achieved using a lesser quantity of a higher strength
   OR
B. The requested agent is NOT subject to quantity limit (i.e. Cinqair) AND the requested dose is within FDA labeling for the requested indication

Length of Approval: 6 months for severe eosinophilic asthma
12 months for EGPA and all other FDA approved indications

For Fasenra, approve loading dose for new starts and the maintenance dose for the remainder of the 6 months

Renewal Evaluation
Cinqair® (reslizumab), **Fasenra** (benralizumab), and **Nucala**® (mepolizumab) will be approved when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the Prime Therapeutics PA process
   AND
2. ONE of the following:
   A. The patient has a diagnosis of severe eosinophilic asthma, and BOTH of the following:
      i. The patient has had clinical response or disease stabilization as defined by ONE of the following:
         a. Increase in percent predicted Forced Expiratory Volume (FEV_1) from baseline
         OR
         b. Decrease in the dose of inhaled corticosteroids required to control the patient's asthma
         OR
         c. Decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma
         OR
         d. Decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma
      AND
      ii. ONE of the following:

a. The patient is currently treated and is compliant with standard therapy (e.g. inhaled corticosteroids, long-acting beta-2 agonist (LABA), leukotriene receptor antagonist (LRTA), long-acting muscarinic antagonist (LAMA), theophylline) within the past 90 days
OR
b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL standard therapies

OR

B. The patient has a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) AND ALL of the following:
i. The requested agent is Nucala
AND
ii. The patient has had clinical response or disease stabilization as defined by ONE of the following:
a. Remission achieved with the requested agent
OR
b. Decrease in corticosteroid maintenance dose required for control of symptoms related to EGPA
OR
c. Decrease in hospitalization due to symptoms of EGPA
OR
d. Dose of maintenance corticosteroid therapy and/or immunosuppressant therapy was not increased
AND
iii. ONE of the following:
a. The patient is currently treated and is compliant with maintenance therapy with oral corticosteroids within the past 90 days
OR
b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to oral corticosteroids

OR

C. The patient has another FDA approved indication

3. The patient will NOT receive the requested agent in combination with Xolair or with another interleukin 5 (IL-5) inhibitor (e.g., Cinqair, Fasenra, Nucala) for the requested indication
AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
5. ONE of the following:
A. The requested agent is subject to quantity limit (i.e. Fasenra, Nucala), AND ONE of the following:
i. The quantity (dose) requested is within the program quantity limit

OR

ii. The quantity (dose) requested is above the program limit, within FDA approved labeling, and the prescribed dose cannot be achieved using a lesser quantity of a higher strength

OR

B. The requested agent is NOT subject to quantity limit (i.e. Cinqair) AND the requested dose is within FDA labeling for the requested indication

Length of approval: 12 months

Agent	Loading dose
Fasenra (benralizumab)	30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection

Agent	Contraindications
Cinqair (reslizumab)	▪ History of known hypersensitivity to reslizumab or any of its excipients
Fasenra (benralizumab)	▪ Known hypersensitivity to benralizumab or excipients
Nucala (mepolizumab)	▪ History of hypersensitivity to mepolizumab or excipients in the formulation

Brand (generic)	Quantity Limit
Cinqair® (reslizumab)	
100 mg/10 mL single use vial	N/A
Fasenra (benralizumab)	
30 mg/mL pre-filled syringe	1 syringe/56 days
Nucala® (mepolizumab)	
100 mg powder for injection	Severe eosinophilic asthma: 1 vial/28 days EGPA: 3 vials/28 days

RATIONALE

Asthma

Asthma is a chronic inflammatory disorder of the airways.[2,4] It is characterized by variable and recurring clinical symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.[2] Symptoms of asthma include wheezing, coughing, recurrent difficulty breathing, shortness of breath, and chest tightness[2,4]. Generally, these symptoms will occur or worsen with exercise, exposure to allergens and irritants, infections, exercise, changes in weather, stress, or menstrual cycles.[2] The National Asthma Education and Prevention Program (NAEPP) Expert Panel guidelines recommend the use of detailed medical history, physical examination, and spirometry to make a diagnosis of asthma. In addition, differential diagnosis of asthma should be considered.[2]

Markers of asthma that is not adequately controlled in patients receiving therapy include limitation of normal activities, poor lung function with FEV1 of <80% predicted, at least 2 episodes per year of asthma exacerbations requiring oral systemic corticosteroids.[2] More frequent and intense exacerbations (e.g. requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control.[2]

The Global Initiative for Asthma (GINA) guidelines l guidelines recommend a stepwise approach for managing asthma.[4] Long-term goals for asthma management are to achieve good control of symptoms, maintain normal activity level and to minimize the future risk of exacerbations, fixed airflow limitation and side-effects.[3] IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic asthma and the development and persistence of inflammation. GINA guidelines define moderate asthma as that which is well controlled with low dose ICS in combination with a LABA.[4] Severe asthma is defined as "asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or which remains uncontrolled despite this therapy.[2] Early initiation of low dose inhaled corticosteroid (ICS) in patients with asthma has led to greater improvement in lung function than if initiation of ICS after symptoms have been present for more than 2 to 4 years.[4]

GINA recommends as-needed relieve inhaler, short acting b-agonist (SABA) as Step 1. SABAs are highly effective for the quick relief of asthma symptoms. However, there is insufficient evidence for use of SABA alone for the treatment of asthma. SABA monotherapy for the treatment of asthma should be reserved for patients with occasional daytime symptoms (less than twice a month) of short duration with no night waking and with normal lung function. Step 2 is the recommendation of treatment with ICS. At low doses, ICS reduces asthma symptoms, increases lung function, improves quality of life, and reduces the risk of exacerbations and asthma-related hospitalizations or death. Leukotriene receptor antagonists (LTRA) are less effective than ICS. Step 3 involves one or two maintenance inhalers and an as-needed reliever. Combination low dose ICS and long acting b-agonist (LABA) as maintenance treatment plus an as-needed SABA or low dose ICS with formoterol (budesonide or beclometasone) with a reliever treatment are options recommended. Step 4 involves 2 or more maintenance agents with an as-needed reliever. Combination low dose ICS with formoterol or medium dose ICS with LABA and an as-needed SABA are recommended options. Step 5 includes higher level care and/or add-on treatment. Depending on treatment options used in previous steps, long acting muscarinic antagonists (LAMA) such as tiotropium, omalizumab, or anti-interluekin-5 (mepolizumab and reslizumab) are additional pharmacologic options as add-on therapy.[4]

Severe Asthma Phenotype and Eosinophilic Asthma Subphenotype

Severe asthma is defined as "asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy."[4] Despite the availability of multiple asthma treatments, a substantial proportion of patients with severe asthma continue to have uncontrolled disease.[8] Thirty to forty percent of severe asthma patients still need regular bursts of systemic steroids to control their asthma.[7] Severe asthma has a considerable amount of variability in its pattern of inflammation, and this variability causes multiple phenotypical differences that influence treatment response.[2]

Eosinophilic asthma is a subphenotype of severe asthma characterized by elevated sputum and blood eosinophil levels as well as increased asthma severity, atopy, late-onset disease, and steroid refractoriness.[5] Several biomarkers including blood eosinophilic counts and sputum eosinophilic counts are used in diagnosing severe asthma with an eosinophilic phenotype.[5] As with other severe forms of asthma, the Gold Standard/International Guidelines treatment for severe asthma, including eosinophilic asthma, is high dose ICS plus a long acting beta-2 agonist (LABA), leukotriene modifier or theophylline and/or continuous systemic corticosteroids as background therapy.[4,5] Newer therapies that specifically target formation of eosinophils may also be utilized. Cinquair (reslizumab), Fasenra (benralizumab), and Nucala (mepolizumab) are examples of such agents FDA indicated for severe eosinophilic asthma.[1,9]

Cinqair Efficacy[9]

The efficacy of Cinqair (reslizumab) was established in four randomized, double-blind, placebo controlled studies (studies I-IV).

Study I and II

These studies included a total of 953 patients with asthma and blood eosinophil count of at least 400 cell/microLiter measured within 3 to 4 weeks of dosing with reslizumab (3 mg/kg every 4 weeks). Patients were also required to have had at least 1 asthma exacerbation requiring systemic corticosteroids within the past 12 months. The primary end point for these studies was frequency of asthma exacerbation. Patients receiving reslizumab had significant reductions in the rate of all asthma exacerbations compared to placebo.

	Treatment Arm	Asthma Exacerbation Rate	Rate Ratio (95% CI)
All exacerbations			
Study I	CINQAIR 3 mg/kg (n=245)	0.90	0.5
	Placebo (n=244)	1.80	(0.37, 0.67)
Study II	CINQAIR 3 mg/kg (n=232)	0.86	0.41
	Placebo (n=232)	2.11	(0.28, 0.59)

Study III and IV

These studies primarily assessed effects of reslizumab on lung function. Their primary endpoint was mean change in FEV1 from baseline.

Mean Change (95% CI) from Baseline in FEV_1 in mL Over 16 Weeks (Difference from CINQAIR and Placebo) in Patients with Severe Asthma with an Eosinophilic Phenotype

Study	FEV_1 Change in mL
Study I	137 (76, 198)
Study II	93 (30, 155)
Study III	160 (60, 259)
Study IV[a]	76 (-6,158)

a Study IV evaluated asthma patients unselected for blood eosinophils

Lung function was evaluated in study I and II however; it was a primary end point as in study III and IV

Study IV enrolled patients unselected for blood eosinophils (80% of the patients has blood eosinophils less than 400 cells/microLiter). The results demonstrate that reslizumab given to patients with inadequately controlled asthma unselected for blood eosinophil count does not produce a statistically significant effect on lung function.

Cinqair Safety[9]
Adverse events associated with reslizumab include oropharyngeal pain as well as creatine phosphokinase (CPK) elevations and muscle related adverse reactions. Reslizumab is contraindicated in patients with known hypersensitivity to reslizumab or any of its excipients. It also carries a boxed warning for anaphylaxis. Therapy with reslizumab should be discontinued immediately if a patient experiences anaphylaxis.

Fasenra Efficacy[10]
Benralizumab was approved through 3 confirmatory clinical trials.

Trial 1 and Trial 2, were randomized, double-blind, parallel-group, placebo-controlled, exacerbation trials in patients 12 years of age and older and 48 and 56 weeks in duration, respectively. The trials randomized a total of 2510 patients. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months, ACQ-6 score of 1.5 or more at screening, and reduced lung function at baseline [prebronchodilator FEV1 below 80% in adults, and below 90% in adolescents] despite regular treatment with high dose inhaled corticosteroid (ICS) (Trial 1) or with medium or high dose ICS (Trial 2) plus a long-acting beta agonist (LABA) with or without oral corticosteroids (OCS) and additional asthma controller medications. Patients were stratified by geography, age, and blood eosinophils count (≥300 cells/µL or <300 cells/µL). Benralizumab administered once every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter as add-on to background treatment was evaluated compared to placebo.
All subjects continued their background asthma therapy throughout the duration of the trials.

Trial 3 was a randomized, double-blind, parallel-group, OCS reduction trial in 220 asthma patients. Patients were required treatment with daily OCS (7.5 to 40 mg per day) in addition to regular use of high-dose ICS and LABA with or without additional controller(s). The trial included an 8-week run-in period during which the OCS was titrated to the minimum effective dose without losing asthma control. For the purposes of the OCS dose titration, asthma control was assessed by the investigator based on a patient's FEV1, peak expiratory flow, nighttime awakenings, short-acting bronchodilator rescue medication use or any other symptoms that would require an increase in OCS dose. Baseline median OCS dose was similar across all treatment groups. Patients were required to have blood eosinophil counts greater than or equal to 150 cells/µL and a history of at least one exacerbation in the past 12 months. The baseline median OCS dose was 10 mg (range: 8 to 40 mg) for all 3 treatment groups (placebo, benralizumab every 4 weeks, and benralizumab every 4 weeks for the first 3 doses, and then once every 8 weeks.

The primary endpoint for Trials 1 and 2 was the rate of asthma exacerbations in patients with baseline blood eosinophil counts of greater than or equal to 300 cells/µL who were taking high-dose ICS and LABA. Asthma exacerbation was defined as a worsening of asthma requiring use of oral/systemic corticosteroids for at least 3 days, and/or emergency department visits requiring use of oral/systemic corticosteroids and/or hospitalization. For patients on maintenance oral

corticosteroids, an asthma exacerbation requiring oral corticosteroids was defined as a temporary increase in stable oral/systemic corticosteroids for at least 3 days or a single depo-injectable dose of corticosteroids. In Trial 1, 35% of patients receiving benralizumab experienced an asthma exacerbation compared to 51% on placebo. In Trial 2, 40% of patients receiving benralizumab experienced an asthma exacerbation compared to 51% on placebo.

Fasenra Safety[10]

Adverse reactions from clinical trials, which were more common in benralizumab than placebo include headache and pyrexia. Injection site reactions (e.g., pain, erythema, pruritus, papule) were also reported with benralizumab. Benralizumab is contraindication in those with known hypersensitivity to benralizumab or excipients.

Nucala Efficacy[1]

The efficacy of mepolizumab for the treatment of severe eosinophilic asthma was established in three double blind, randomized, placebo controlled trials: A dose-ranging and exacerbation reduction trial (trial 1) and two confirmatory trials (trial 2 and 3). Trial 1 was 52 weeks long and enrolled subjects with uncontrolled asthma despite use of high dose inhaled corticosteroids (ICS) plus additional controller(s). The subjects were defined as having eosinophilic asthma if they had one of the following: blood eosinophilic count greater than or equal to 300 cells/mcL, sputum eosinophil count greater than 3%, exhaled nitric oxide concentration greater than or equal to 50 parts per billion, or deterioration of asthma control after less than or equal to 25% reduction in regular maintenance ICS or oral corticosteroids. The trial randomized the subjects to either the mepolizumab or placebo arms. Those in the mepolizumab arm received one of three intravenous (IV) doses: 75 mg, 250 mg, and 750 mg each dosed once every four weeks. This trial provided support for subsequent trials of mepolizumab dosed at 75 mg IV and 100 mg administered subcutaneously every four weeks.

Trial 2 was a 32-week placebo- and active-controlled trial in subjects with asthma not adequately controlled on high-dose inhaled corticosteroids plus additional controller(s) with or without oral corticosteroids. Subjects were required to have blood eosinophils of greater than or equal to 150 cells/mcL at screening (within 6 weeks of dosing) or blood eosinophils of greater than or equal to 300 cells/mcL within 12 months of enrollment. Subjects were randomized to receive mepolizumab dosed at 75 mg or placebo each of which was administered every 4 weeks for 32 weeks. The primary end point for trial 1 and 2 was frequency of asthma exacerbations. Asthma exacerbations were defined as worsening of asthma symptoms requiring systemic corticosteroids and/or hospitalization and/or emergency department visits. Compared to placebo, subjects receiving mepolizumab experienced significantly fewer exacerbations and had a longer time to first exacerbation.

Rate of exacerbations per year in Trial 1 and 2[1]

Trial	Treatment Group	Rate	Difference	Rate Ratio
Trial 1	Placebo (n=155)	2.40		
	Mepolizumab 75 mg IV (n=153)	1.24	1.16	0.52 (0.39, 0.69)
Trial 2	Placebo (n=191)	1.74		
	Mepolizumab 75 mg IV (n=191)	0.93	0.81	0.53 (0.40, 0.72)
	Mepolizumab 100 mg SC (n= 194)	0.83	0.91	0.47 (0.35, 0.64)

Trial 3 was a 24 week oral corticosteroid-reduction study in asthma patients who required daily oral corticosteroids in addition to regular controller medications. The primary end point was percent reduction of oral corticosteroid dose during weeks 20 to 24 without loss of asthma control. The trial subjects received mepolizumab (n=69) or placebo (n=66) once every 4 weeks for 24 weeks. The baseline mean oral corticosteroid use was similar between the Nucala and placebo group. Overall, mepolizumab achieved greater reduction in oral corticosteroid use while maintaining asthma control when compared to placebo. However, the difference between the mepolizumab and placebo groups was not statistically significant.

Reduction in oral corticosteroid (OCS) dose[1]

Reduction in OCS dose	Mepolizumab (% of patients)	Placebo (% of patients)
90 – 100%	23	11
75 – <90%	17	8
50 – <75%	13	15
>0 – 50%	10	11
No decrease	36	56

Nucala Safety[1]

The most common adverse events in clinical trials were bronchitis, fatigue, headache, nasopharyngitis, and sinusitis. Subjects receiving mepolizumb had higher incidence of injection site reactions than those receiving placebo. Mepolizumab is contraindicated in patients with history of hypersensitivity to mepolizumab or excipients in the formulation.

Eosinophilic Granulomatosis With Polyangiitis (EGPA)

EGPA, also known as Churg-Strauss Syndrome, is a rare systemic vasculitis disease with main clinical features of late-onset allergic rhinitis and asthma, increased blood eosinophil count, and vasculitis manifestations, some of which can be life threatening.[12] The diagnosis of EGPA is typically suspected based on clinical findings, such as eosinophilia count ≥ 1500/microL, asthma, and allergic rhinitis.[13] Once EGPA is suspected based on clinical findings of asthma with eosinophilia, asthma with systemic manifestations or even eosinophilia with extrapulmonary disease, a biopsy demonstrating small or medium sized vessel vasculitis strongly supports the diagnosis of EGPA. Skin, nerve, and muscle are among the most common biopsied tissues, but endomyocardial, renal, and gastrointestinal biopsies may also be useful. Antineutrophil cytoplasm antibody (ANCA) testing is also recommended. ANCA positivity is highly suggestive of EGPA but ANCA negative results do not rule out its diagnosis. ANCA testing results define EGPA patient subgroups. ANCA-positive patients are more likely to have a vasculitis phenotype with glomerulonephritis, mononeuritis multiplex, and relapses. Despite fewer relapses, ANCA negative patients tend to have poorer prognosis, possibly because of their high frequency of cardiomyopathy.[12]

There are two types of classifications used for the diagnosis of EGPA. The first and most commonly used classification is by the American College of Rheumatology (ACR). ACR has established six criteria for the classification of EGPA in a patient with documented vasculitis. The presence of four or more of these criteria can establish a diagnosis of EGPA:

- Asthma (a history of wheezing or finding or diffuse high pitched wheezes on expiration)
- Greater than 10 percent eosinophils on the differential leukocyte count
- Mononeuropathy (including multiplex) or polyneuropathy

- Migratory or transient opacities detected radiographically
- Paranasal sinus abnormality
- Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas

The Lanham criteria is also used for the diagnosis of EGPA. The Lanham criteria requires the patient to have asthma, peak peripheral blood eosinophilia in excess of 1500 cells/microL, and systemic vasculitis involving two or more extra-pulmonary organs.

Glucocorticosteroids are the mainstay of therapy for EGPA.[12,14] The maintenance glucocorticoid dose should be adapted to tightly control each patient's needs to prevent relapses of systemic manifestations and control asthma. Immunosuppressive therapy is used as add on therapy for patients with life and/or organ manifestations (i.e. heart, GI, central nervous system, alveolar hemorrhage and/or glomerulonephritis) to induce remission.[12] Cyclophosphamide is used in combination with glucocorticosteroids for patients with severe, multiorgan disease. Maintenance therapy with azathioprine or methotrexate is recommended for patients with life and/or organ threatening disease manifestations after remission has been achieved. Maintenance therapy with an immunosuppressant can be started 2 -3 weeks after the last cyclophosphamide pulse or a few days after oral cyclophosphamide.

Glucocorticoid therapy alone maybe suitable for patients without life and/or organ threatening disease manifestations. However, additional immunosuppressants can be considered for select patients when prednisone dose cannot be tapered to less than 7.5 mg/day after 3-4 months of therapy or for patients with recurrent disease.[12] First line immunosuppressants used are azathioprine and methotrexate. Other, second line therapy options are mycophenolate, hydroxyurea, intravenous immune globulin, rituximab, interferon-alpha, anti-IgE therapy (omalizumab), and anti-IL-5 antibodies (mepolizumab).[14]

Nucala Efficacy[1]

A total of 136 subjects with EGPA were evaluated in a randomized, placebo-controlled, multicenter, 52-week trial. Subjects enrolled had a diagnosis of EGPA for at least 6 months prior to enrollment with a history of relapsing or refractory disease and were on a stable dosage of oral prednisolone or prednisone of greater than or equal to 7.5 mg/day (but not greater than 50 mg/day) for at least 4 weeks prior to enrollment. Subjects received 300 mg of mepolizumab or placebo administered subcutaneously once every 4 weeks while continuing their stable OCS therapy. Starting at Week 4, OCS was tapered during the treatment period at the discretion of the investigator. The co-primary endpoints were the total accrued duration of remission over the 52-week treatment period, defined as Birmingham Vasculitis Activity Score (BVAS) = 0 (no active vasculitis) plus prednisolone or prednisone dose less than or equal to 4 mg/day, and the proportion of subjects in remission at both Week 36 and Week 48 of treatment. The BVAS is a clinician-completed tool to assess clinically active vasculitis that would likely require treatment, after exclusion of other causes.

A significantly higher proportion of subjects receiving mepolizumab achieved remission at both Week 36 and Week 48 compared with placebo. In addition, significantly more subjects receiving mepolizumab achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week study treatment period compared with placebo (19% for mepolizumab versus 1% for placebo; OR 19.7; 95% CI: 2.3, 167.9).

The time to first relapse (defined as worsening related to vasculitis, asthma, or sino-nasal symptoms requiring an increase in dose of corticosteroids or immunosuppressive therapy or hospitalization) was significantly longer for subjects receiving mepolizumab compared with placebo with a hazard ratio of 0.32 (95% CI: 0.21, 0.5). Additionally, subjects receiving mepolizumab had a reduction in rate of relapse compared with subjects receiving placebo (rate ratio 0.50; 95% CI: 0.36, 0.70 for mepolizumab compared with placebo). The incidence and number of relapse types (vasculitis, asthma, sino-nasal) were numerically lower with mepolizumab compared with placebo.

Subjects receiving mepolizumab had a significantly greater reduction in average daily OCS dose compared with subjects receiving placebo during Weeks 48 to 52.

REVISIONS	
06-01-2016	Published 04-25-2016. Effective 06-01-2016.
	Policy added to the bcbsks.com web site.
10-01-2016	Published 09-01-2016. Effective 10-01-2016.
	In Title section revised title to "Injectable Asthma Agents" from "Nucala (mepolizumab)". ▪ Added "See also: Xolair (omalizumab)"
	Description section updated adding Cinquair (reslizumab) as a Target Drug
	In Policy section: <u>Initial Evaluation</u> ▪ In Initial Evaluation added "Cinquar (reslizumab) and" to read "Cinqair (reslizumab) and Nucala (mepolizumab) will be approved with ALL of the following are met:" ▪ Added Item 3 a and 3 a i to read "The patient is within the FDA labeled age for the requested agent: Cinqair: 18 years of age or over" ▪ In Item 3 a ii added "Nucala" and removed "The patient is" to read "Nucala: 12 years of age or over" ▪ In Item 3 b added "for the requested agent" to read "The patient's diagnosis has been confirmed by ONE of the following eosinophilic counts for the requested agent" ▪ Added Items 3 b i and 3 b ii to read "If requesting Cinqair, the patient has a blood eosinophilic count greater than or equal to 400 cells/MicroLiter within the previous 12 months AND If requesting Nucala, the patient has one of the following:" ▪ In Item 4 added "(e.g. Cinqair, Nucala)" to read "The patient will not receive the requested agent in combination with Xolair or with another interleukin 5 (IL-5) inhibitor indicated for asthma (e.g. Cinqair, Nucala)" ▪ In Item 5 revised "ONE" to "BOTH" and added "a. If the requested agent is subject to quantity limit (i.e. Nucala), ONE of the following:" and "b. If the requested agent is not subject to quantity limit (i.e. Cinqair), the dose is within FDA labeling" <u>Renewal Evaluation</u> ▪ In Renewal Evaluation added "Cinquar (reslizumab) and" to read "Cinqair (reslizumab) and Nucala (mepolizumab) will be approved with ALL of the following are met:" ▪ In Item 4 added "(e.g. Cinqair, Nucala)" to read "The patient will not receive the requested agent in combination with Xolair or with another interleukin 5 (IL-5) inhibitor indicated for asthma (e.g. Cinqair, Nucala)" ▪ In Item 5 revised "ONE" to "BOTH" and added "a. If the requested agent is subject to quantity limit (i.e. Nucala), ONE of the following:" and "b. If the requested agent is not subject to quantity limit (i.e. Cinqair), the dose is within FDA labeling" ▪ Added Cinquair (reslizumab) to the Contraindications and Quantity Limit chart.

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	Rationale section updated
	References updated
05-15-2017	In Description section: ▪ FDA Approved Indications and Dosage chart updated
	Rationale section updated
	References updated
12-11-2017	Policy published 01-05-2018. Policy retro-effective to 12-11-2017.
	In Description section: ▪ In Target Agents added Fasenra (benralizumab) ▪ Updated FDA Approved Indications and Dosage chart adding Fasenra
	In Policy section: Initial Evaluation ▪ Added "Fasenra (benralizumab)" to read "Cinqair (reslizumab), Fasenra (benralizumab), and Nucala (mepolizumab) will be approved when ALL of the following are met:" ▪ In Item 3 a added "ii. Fasenra: 12 years of age or over" ▪ Added "For Fasenra, approve loading dose for new starts and the maintenance dose for the remainder of the 6 months" Renewal Evaluation ▪ Added "Fasenra (benralizumab)" to read "Cinqair (reslizumab), Fasenra (benralizumab), and Nucala (mepolizumab) will be approved when ALL of the following are met:" ▪ Added Loading Dose chart ▪ Updated Contraindications and Quantity Limit charts
	References updated
05-01-2018	Description section updated
	In Policy section: Initial Evaluation ▪ In Item 1 A ii b added "If the requested agent is Fasenra, the patient has a blood eosinophilic count greater than or equal to 150 cells/microliter" ▪ In Item 1 A iii a added "If the requested agent is Fasenra AND the patient is aged 12 years to 17 years, the patient has a baseline Forced Expiratory Volume (FEV1) that is less than 90% of predicted" ▪ In Items 1 A v a and I A bi a added "within the past 90 days" ▪ Added "B. The patient has a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) and ALL of the following: i. The requested agent is Nucala AND ii.The patient is 18 years of age or over AND iii. The patient has a history of EGPA for at least 6 months with a history of relapsing or refractory disease AND iv. The patient's diagnosis of EGPA was confirmed by ONE of the following: a. The patient meets 4 of the following: 1) History of asthma (wheezing or the finding of diffuse high pitched wheezes in expiration) 2) Greater than 10% eosinophils on differential leukocyte count 3) Mononeuropathy (including multiplex) or polyneuropathy 4) Migratory or transient pulmonary opacities detected radiographically 5) Paranasal sinus abnormality 6) Biopsy containing blood vessel showing the accumulation of eosinophils in extravascular areas OR b. The patient meets ALL of the following: 1) Medical history of asthma AND 2) Peak peripheral blood eosinophilia > 1500 cells/microL AND

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	3) Systemic vasculitis involving two or more extra-pulmonary organs AND v. ONE of the following: a. The patient is currently on maximally tolerated oral corticosteroid therapy within the past 90 days OR b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to oral corticosteroid therapy AND vi. ONE of the following: a. The patient has tried and failed an oral immunosuppressant (i.e., azathioprine, methotrexate) in the past 90 days OR b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to immunosuppressants OR C. Another FDA approved indication ▪ In Items 2 and 4 B revised wording to add "for the requested indication" away from "indicated for asthma" to be more generalized ▪ In Length of Approval added "EGPA and" to read "12 months for EGPA and all other FDA approved indications" <u>Renewal Evaluation</u> ▪ In Item 2 A i c added "due to exacerbations of asthma" to read "Decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma" ▪ In Item 2 A i d added "need for mechanical ventilation" to read "Decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma" ▪ In Items 2 A ii a added "within the past 90 days" ▪ Added "B. The patient has a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) AND ALL of the following: i. The requested agent is Nucala AND ii. The patient has had clinical response or disease stabilization as defined by ONE of the following: a Remission achieved with the requested agent OR b Decrease in corticosteroid maintenance dose required for control of symptoms related to EGPA OR c Decrease in hospitalization due to symptoms of EGPA OR d Dose of maintenance corticosteroid therapy and/or immunosuppressant therapy was not increased AND iii. ONE of the following: a The patient is currently treated and is compliant with maintenance therapy with oral corticosteroids within the past 90 days OR b The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to oral corticosteroids OR C. The patient has another FDA approved indication" ▪ Updated Contraindications chart ▪ Updated Quantity Limit chart
	Rationale section updated
	References updated

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