Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

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):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
Original Effective Date: June 1, 2016
Revision Date(s): June 1, 2016; October 1, 2016; May 15, 2017
Current Effective Date: October 1, 2016

Institutional
Original Effective Date: June 1, 2016
Revision Date(s): June 1, 2016; October 1, 2016; May 15, 2017
Current Effective Date: October 1, 2016

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

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. The program will require the patient has a diagnosis of severe eosinophilic asthma as determined by blood or sputum eosinophilic counts. The program will also require the patient has and is currently receiving maximally tolerated inhaled corticosteroids (ICS) plus a controller medication as recommended in the National Asthma Education and Prevention Program (NAEPP) expert panel guidelines and the Global Initiative for Asthma (GINA) guidelines. 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 asthma. 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 asthma.

Target Drugs

- **Cinqair**® (reslizumab)
- **Nucala**® (mepolizumab)

FDA Approved Indications and Dosage[1,9]

Agent(s)	Indication* ^	Dose and administration
Nucala® (mepolizumab)	As add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype	**Severe eosinophilic asthma**: 100 mg administered subcutaneously every 4 weeks
Cinqair® (reslizumab)	As add-on maintenance treatment of patients 18 years and older with severe asthma, and with an eosinophil phenotype	**Severe eosinophilic asthma**: 3 mg/kg once every 4 weeks by intravenous infusion

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

POLICY

Prio Authorization Criteria for Approval

Initial Evaluation

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

1. The patient does not have any FDA labeled contraindications to the requested agent
   AND
2. The patient has ONE of the following diagnoses:
   a. Severe eosinophilic asthma
      OR
   b. Another FDA approved indication
   AND
3. If the diagnosis is severe eosinophilic asthma, the patient meets ALL of the following:
   a. The patient is within the FDA labeled age for the requested agent:
      i. Cinqair: 18 years of age or over
      ii. Nucala: 12 years of age or over
      AND
   b. The patient's diagnosis has been confirmed by ONE of the following eosinophilic counts for the requested agent:
      i. If requesting Cinqair, the patient has a blood eosinophilic count greater than or equal to 400 cells/MicroLiter within the previous 12 months
         OR
      ii. If requesting 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
   c. The patient has a baseline Forced Expiratory Volume (FEV_1) less than 80% predicted
      AND

d. The patient has ONE of the following:
    i. Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months
    OR
    ii. Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months
    OR
    iii. Controlled asthma that worsens when the doses of inhaled or systemic corticosteroids are tapered

AND

e. ONE of the following:
    i. The patient is currently treated with a maximally tolerated inhaled corticosteroid
    OR
    ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to inhaled corticosteroids

AND

f. ONE of the following:
    i. The patient is currently treated with ONE of the following:
        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
    ii. 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

AND

4. 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)
AND

5. BOTH of the following:
    a. If the requested agent is subject to quantity limit (i.e. Nucala), 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
    AND
    b. If the requested agent is not subject to quantity limit (i.e. Cinqair), the dose is within FDA labeling

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

Renewal Evaluation

Cinqair® (reslizumab) 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. The patient does not have any FDA labeled contraindications to the requested agent
    AND
3. If the diagnosis is severe eosinophilic asthma, the patient meets ALL of the following:
    a. The patient has had clinical response or disease stabilization as defined by ONE of the following:
        i. Increase in percent predicted Forced Expiratory Volume (FEV_1) from baseline
        OR
        ii. Decrease in the dose of inhaled corticosteroids required to control the patient's asthma
        OR
        iii. Decrease in need for treatment with systemic corticosteroids
        OR
        iv. Decrease in number of hospitalizations or visits to urgent care or emergency room due to exacerbations of asthma
    AND

b. ONE of the following:
    i. 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)
    OR
    ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL standard therapies

AND

4. 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)
AND
5. BOTH of the following:
    a. If the requested agent is subject to quantity limit (i.e. Nucala), 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

    AND

    b. If the requested agent is not subject to quantity limit (i.e. Cinqair), the dose is within FDA labeling.

Length of approval: 12 months

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

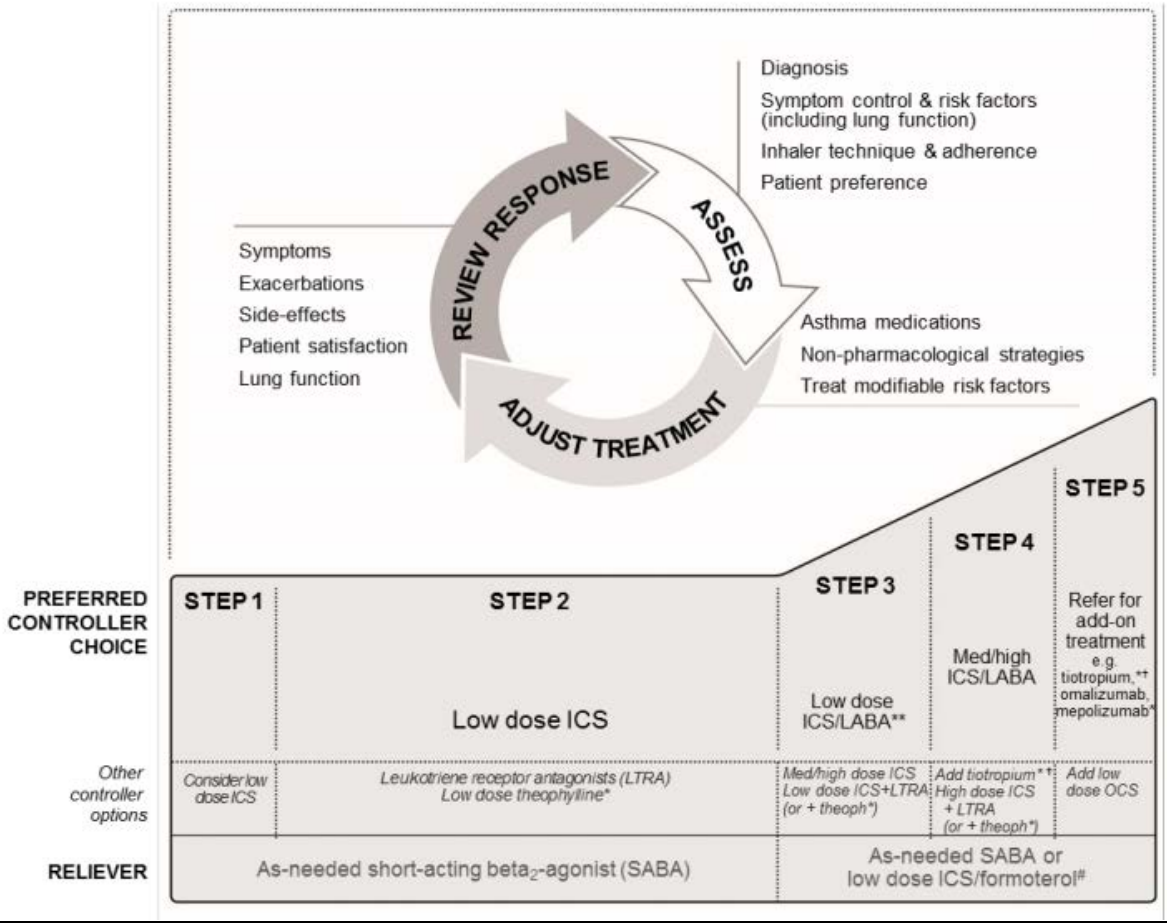
Brand (generic)	Quantity Limit
Cinqair® (reslizumab)	
100 mg/10 mL single use vial	N/A
Nucala® (mepolizumab)	
100 mg powder for injection	1 vial/28 days

RATIONALE

Asthma

Asthma is a complex disorder characterized by variable and recurring clinical symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.[2] Symptoms of asthma include wheezing, coughing, recurrent difficulty breathing, and chest tightness. 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. Once a definitive diagnosis of asthma is made, the goal of disease management is reduction of impairment from asthma and reduction of risk (i.e. prevent recurrent exacerbations, prevent loss of lung function, and provide optimal pharmacotherapy).[2,4] The Global Initiative for Asthma (GINA) guidelines and NAEPP Expert Panel guidelines recommend a stepwise approach for managing asthma.[2,3] Inhaled corticosteroids are considered the most effective long term therapy for control and management of asthma.[2] The patient's asthma can be considered to be well controlled when asthma symptoms are twice a week or less; the rescue bronchodilator medication is used twice a week or less; there is no nocturnal or early morning awaking due to asthma symptoms; there are no limitations of work, school, or exercise; and the Forced Expiratory Volume (FEV1) is normal or the patient's personal best.[6] 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]

2016 GINA Guidelines on Stepwise Approach to Treatment of Asthma[4]



Key: ICS-inhaled corticosteroid, LABA-long acting beta agonist, SABA-short acting beta agonist, LTRA-leukotriene receptor antagonist

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 (Figure 1), 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. Nucala (mepolizumab) and Cinquair (reslizumab) are is an examples of such agents FDA indicated for severe eosinophilic asthma.[1,9]

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 safety of mepolizumab was established in three double blind, randomized, placebo controlled trials. The most common adverse events were bronchitis, fatigue, headache, nasopharyngitis, and sinusitis. Subjects receiving mepolizumb had higher incidence of injection site reactions than those receiving placebo.[1] Mepolizumab is contraindicated in patients with history of hypersensitivity to mepolizumab or excipients in the formulation.

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 excipeients. It also carries a boxed warning for anaphylaxis. Therapy with reslizumab should be discontinued immediately if a patient experiences anaphylaxis.

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: Initial Evaluation ▪ 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

REVISIONS	
	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" Renewal Evaluation ▪ 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.
	Rationale section updated
	References updated
05-15-2017	In Description section: ▪ FDA Approved Indications and Dosage chart updated
	Rationale section updated
	References updated

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