PREMERA BLUE CROSS

PHARMACY / MEDICAL POLICY – 5.01.559

IL-5 Inhibitors

Effective Date:	Dec. 1, 2020	RELATED MEDICAL POLICIES:
Last Revised:	Nov. 10, 2020	5.01.513 Xolair® (omalizumab)
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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

Drug	Medical Necessity
Nucala® (mepolizumab) SC	**Nucala® (mepolizumab) may be considered medically necessary for the labeled indication of add-on maintenance treatment of patients with severe asthma aged 6 years and**

Drug	Medical Necessity
Managed under Pharmacy and Medical benefit	**older, and with an eosinophilic phenotype, when the following conditions are met:** 1. Patient has a history of 2 or more exacerbations in the previous year, requiring bursts of systemic steroids and commonly requiring urgent care visits,* ER visits and/or hospitalizations, despite regular use of high-dose inhaled corticosteroids (such as those listed in the **table** below), plus at least one additional controller (such as long-acting beta agonists (LABAs) salmeterol or formoterol. **AND** 2. Patient has had AT LEAST ONE of the following 3 criteria in the previous 12 months: ○ Blood **eosinophil count greater than 150 cells/mcL **OR** ○ Sputum **eosinophil count greater than or equal to 3% **OR** ○ Patient has oral corticosteroid dependent asthma and is not able to discontinue use of oral corticosteroids for blood eosinophil or sputum eosinophil tests **AND** 3. Nucala® (mepolizumab) is not used in combination with Dupixent® (dupilumab) or Xolair® (omalizumab) when the medications are being used for the treatment of asthma ***Note:** Urgent care visits are not always required, since some patients are given a standing prescription for a systemic steroid that they can fill when exacerbations occur, eliminating the need for an unnecessary urgent care visit that could actually delay initiation of the steroid burst. ****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 150 cells/mcL or 3%, respectively), this suggests that the patient is unresponsive to their regular maintenance (inhaled or oral) corticosteroid treatment. **Nucala® (mepolizumab) may be considered medically necessary for the labeled indication of treatment of adult**

Drug	Medical Necessity
	patients with eosinophilic granulomatosis with polyangiitis (EGPA) when all of the following conditions are met: 1. Patient is over 18 years old **AND** 2. Patient has a history or presence of asthma **AND** 3. A blood eosinophil level of ≥10% OR absolute eosinophil count ≥1500 cells/microL **AND** 4. 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 >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) **Nucala® (mepolizumab) may be considered medically necessary for the labeled indication of treatment of adult and pediatric patients with hypereosinophilic syndrome (HES) when all of the following conditions are met:** 1. Patient is 12 years of age and older **AND** 2. Documented history for ≥ 6 months without an identifiable non-hematologic secondary cause (eg, drug hypersensitivity,

Drug	Medical Necessity
	parasitic helminth infection, HIV infection, non-hematologic malignancy) **AND** 3. A blood eosinophil level of ≥1,000 cells/microL **AND** 4. 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** 5. Nucala® (mepolizumab) is prescribed by or in consultation with a hematologist
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 patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype, when the following conditions are met:** 1. Patient has a history of 2 or more exacerbations in the previous year, requiring bursts of systemic steroids and commonly requiring urgent care visits,* ER visits and/or hospitalizations, despite regular use of high-dose inhaled corticosteroids (such as those listed in the **table** below), plus at least one additional controller (such as long-acting beta agonists (LABAs) salmeterol or formoterol. **AND** 2. Patient has had AT LEAST ONE of the following 3 criteria in the previous 12 months: ○ Blood **eosinophil count greater than 150 cells/mcL **OR** ○ Sputum **eosinophil count greater than or equal to 3% **OR** ○ Patient 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
	3. Fasenra® (benralizumab) is not used in combination with Dupixent® (dupilumab) or Xolair® (omalizumab) when the medications are being used for the treatment of asthma *__Note:__ Urgent care visits are not always required, since some patients are given a standing prescription for a systemic steroid that they can fill when exacerbations occur, eliminating the need for an unnecessary urgent care visit that could actually delay initiation of the steroid burst. **__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 150 cells/mcL or 3%, respectively), this suggests that the patient is unresponsive to their regular maintenance (inhaled or oral) corticosteroid treatment.
Cinqair® (reslizumab) IV **Managed under Medical benefit**	**Cinqair® (reslizumab) may be considered medically necessary for the labeled indication of add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype, when the following conditions are met:** 1. Patient has a history of 2 or more exacerbations in the previous year, requiring bursts of systemic steroids and commonly requiring urgent care visits,* ER visits and/or hospitalizations, despite regular use of high-dose inhaled corticosteroids (such as those listed in the **table** below), plus at least one additional controller (such as long-acting beta agonists (LABAs) salmeterol or formoterol. **AND** 2. Patient has had AT LEAST ONE of the following 3 criteria in the previous 12 months: ○ Blood **eosinophil count greater than 150 cells/mcL **OR** ○ Sputum **eosinophil count greater than or equal to 3% **OR** ○ Patient 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
	3. Cinqair® (reslizumab) is not used in combination with Dupixent® (dupilumab) or Xolair® (omalizumab) when the medications are being used for the treatment of asthma *Note: Urgent care visits are not always required, since some patients are given a standing prescription for a systemic steroid that they can fill when exacerbations occur, eliminating the need for an unnecessary urgent care visit that could actually delay initiation of the steroid burst. **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 150 cells/mcL or 3%, respectively), this suggests that the patient 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 as long as the medical necessity criteria are met and chart notes demonstrate that the patient continues to show a positive clinical response to therapy as documented by any of the following parameters:** • Decrease in requirement for oral steroids, exacerbation frequency, ER and urgent care visits, hospitalizations **OR** • Decrease in frequency and severity of asthma symptoms

Length of Approval	
Approval	**Criteria**
	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 as long as the medical necessity criteria are met and chart notes demonstrate that the patient 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

Documentation Requirements
The patient'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 inhalation 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

High Dose Regimens of Inhaled Corticosteroids			
Drug Name	**Low Dose**	**Medium Dose**	**High Dose**
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 (Asmanex DPI) 110 mcg per inhalation 220 mcg per inhalation	110 to 220 mcg 1 to 2 inhalations 1 inhalation	>220 to 440 mcg 2 inhalations	>440 mcg >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.

Evidence Review

Description

Asthma

Asthma is a chronic disease that causes 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 patient is unable to get enough oxygen. Severe attacks can make the patient 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] Patients 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 patients, 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 patients with persistent asthma. In spite of these available therapies, there are patients who remain poorly controlled on maximum therapy (including oral corticosteroids) and there are patients 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 patients. Unlike omalizumab, a monoclonal antibody that is effective in treating IgE related asthma,

mepolizumab is designed to prevent exacerbations in patients 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 also high affinity, preventing the association of IL-5 with the eosinophil receptor IL-5Ra and thus preventing the inflammatory cascade.

Efficacy

Mepolizumab is a recently-approved 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 patients were randomized on a 1:1:1:1 ratio to placebo, 75mg mepolizumab IV, 250mg IV, and 750mg IV. Standard background treatment included ≥ 880 mcg/day fluticasone equivalent +/- oral corticosteroids (OCS) and other controllers. Eosinophilic asthma was defined as having an eosinophil count ≥ 300 cells/mcL, sputum eosinophils 3%, exhaled NO ≥ 50 ppb, or deterioration of control in the last 12 months following < 26% reduction in inhaled corticosteroid (ICS). Patients 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 patients (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 patients with recurrent exacerbations on high-dose ICS and with eosinophil counts of ≥ 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 patients 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 patients with high eosinophil counts. Patients 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 patients. 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 patient 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 patients off of 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 patient 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)

	Baseline eosinophils ≥ 300 cells/µL (primary analysis group)		Baseline eosinophils < 300 cells/µL (secondary analysis group)	
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 the 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
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 patient 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 similar to 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, patient 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

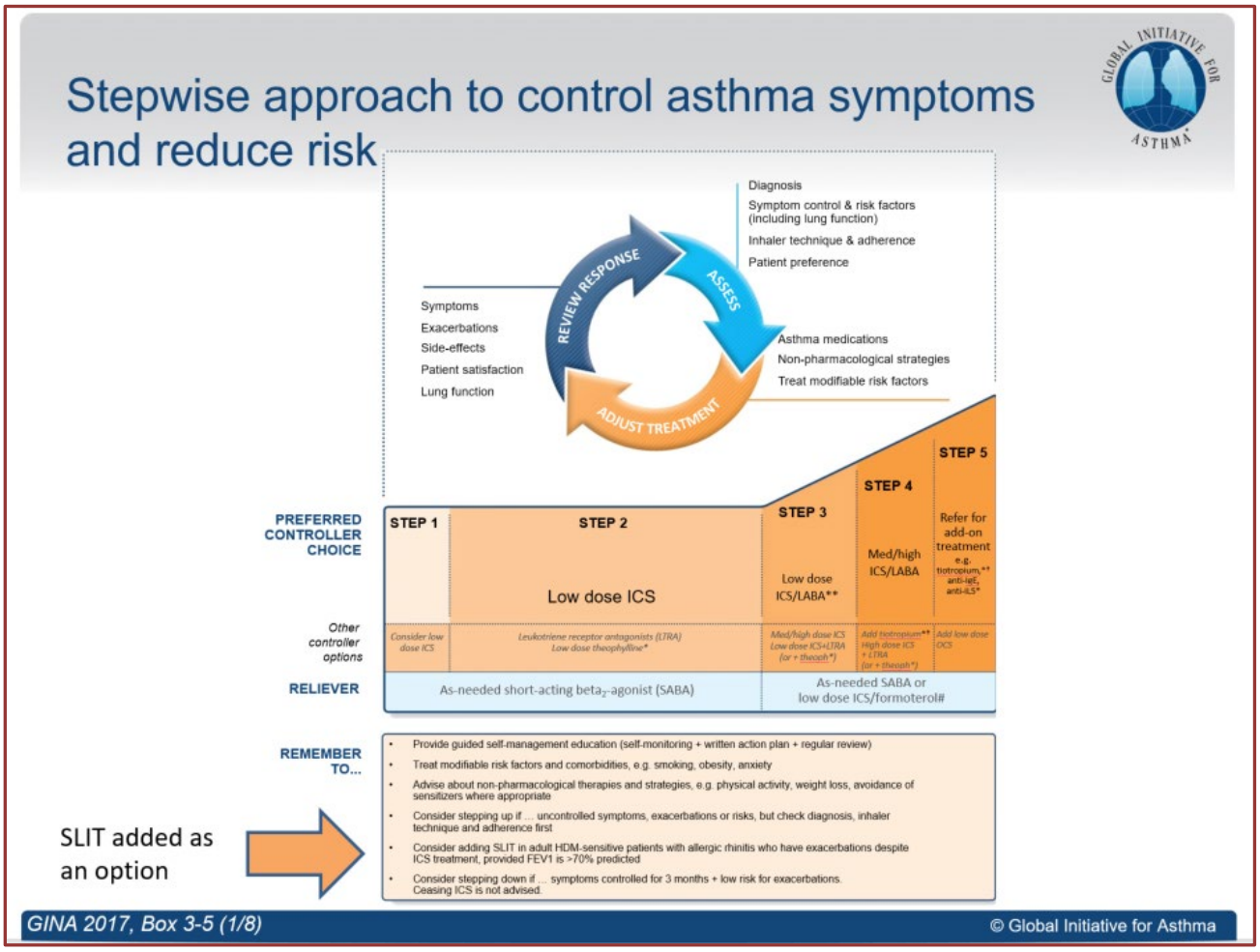
Two serious safety signals, anaphylaxis and muscle toxicity, were identified in the pooled safety data from the placebo-controlled asthma studies. Three (of five) cases of anaphylaxis reported in the reslizumab group were deemed related to treatment. Potentially life-threatening creatine phosphokinase (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 patient 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]. See figure below.



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 (similar to 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.

References

1. 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.
2. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198–1207.
3. Bel EH, Wenzel SE, Thompson PJ, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. N Engl J Med. 2014; 371:1189-1197.
4. Chaudhry S, Abugov R. Joint Clinical and Statistical Briefing Document. FDA Pulmonary-Allergy Drugs Advisory Committee Meeting June 11, 2015. Available: **https://wayback.archive-it.org/7993/20170404155602/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM462804.pdf** Accessed November 18, 2020.
5. Donald Y.M. Leung, and Stanley J. Szefler. Diagnosis and management of steroid-resistant asthma. Clin. Chest Med. 1997;18(3): 611-625.
6. CDC. Most recent data on Asthma. Available: **http://www.cdc.gov/asthma/most_recent_data.htm** Accessed November 18, 2020.
7. Menzella F, Lusuardi M, Galeone C, Taddei S, Zucchi L. Profile of anti-IL-5 mAb mepolizumab in the treatment of severe refractory asthma and hypereosinophilic diseases. J Asthma Allergy. 2015; 8: 105–114.
8. Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. Respirology. 2006;11:54–61.

9. European Medicines Agency. Withdrawal assessment report for Bosatria. Accessible: **http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500060631.pdf** Accessed November 18, 2020.

10. Wenzel SE. Eosinophils in asthma – closing the loop or opening the door? N Engl J Med. 2009;360(10):1026–1028.

11. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. Am J Respir Crit Care Med. 2003;167(2):199–204.

12. Flood-Page 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;176:1062–1071.

13. Zia-Amirhosseini P, Minthorn E, Benincosa LJ, et al. Pharmacokinetics and pharmacodynamics of SB-240563, a humanized monoclonal antibody directed to human interleukin-5, in monkeys. J Pharmacol Exp Ther. 1999;291(3):1060–1067.

14. Liu Y, Zhang S, Li DW, Jiang SJ. Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. PLoS One. 2013;8(3):e59872.

15. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009;360:973–984.

16. Haldar P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. J Allergy Clin Immunol. 2014;133(3):921–923.

17. Nowak RM, Parker JM, Silverman RA, et al. A randomized trial of benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, after acute asthma. Am J Emerg Med. 2015;33(1):14–20.

18. Prazma CM, Wenzel S, Barnes N, Douglass JA, Hartley BF, Ortega H. Characterization of an OCS-dependent severe asthma population treated with mepolizumab. Thorax. 2014;69(12):1141–1142.

19. Tanaka H, Komai M, Nagao K, et al. Role of interleukin-5 and eosinophils in allergen-induced airway remodeling in mice. Am J Respir Cell Mol Biol. 2004;31:62.

20. Fanta C, Bochner B, Hollingsworth H. Treatment of intermittent and mild persistent asthma in adolescents and adults. UpToDate [online database]. Last updated March, 2016. Available at: **http://www.uptodate.com/contents/treatment-of-intermittent-and-mild-persistent-asthma-in-adolescents-and-adults?source=search_result&search=Treatment+of+intermittent+and+mild+persistent+asthma+in+adolescents+and+adults&selectedTitle=1%7E150** Accessed November 18, 2020.

21. Fitzgerald JM, Bleeker ER, Nair P, et al. Benralizumab, an anti-interleukin-5alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled Phase 3 trial. Lancet 2016;388:2128-42.

22. Bleeker, ER, Fitzgerald JM, Cahnez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2 agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115-27.

23. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 2017;376:2448-58.

24. Nowak RM, Parker JM, Silverman RA, et al. A randomized trial of benralizumab, an interleukin 5 receptor monoclonal antibody, after acute asthma. Am J Emerg Med. 2015 Jan;33(1):14-20.

25. Castro M, Wenzel SE, Bleeker ER, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med. 2014 Nov;2(11):879-90.

26. Park HS, Kim MK, Imai N, et al. A Phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. Int Arch Allergy Immunol 2016;169:135-45.

27. Ferguson GT, Fitzgerald JM, Bleeker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2017;5:568-76.

28. Brightling CE, Bleeker ER, Panetierri RA, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med. 2014 November;2(11):891-901.

29. Sanofi and Regeneron announce positive dupilumab topline results from phase 3 trial in uncontrolled persistent asthma. Available at: **https://www.sanofigenzyme.com/en/about-us/newsroom/2017/2017-09-11-06-42-00** Accessed November 18, 2020.

30. **https://www.astrazeneca.com/our-focus-areas/respiratory.html** Accessed November 18, 2020.

31. **https://clinicaltrials.gov/ct2/show/NCT02417961** Accessed November 18, 2020.

32. Nucala® (mepolizumab) for injection, for subcutaneous use, prescribing information. GlaxoSmithKline, Research Triangle Park, NC. September 2019.

33. A look at mepolizumab for treating severe eosinophilic asthma. Available at: **www.icer-review.org** Accessed November 18, 2020.

34. Goldman M, Hirsch I, Zangrilli JG, Newbold P, Xu X. the association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase 3 SIROCCO and CALIMA studies. Curr Med Res Opin 2017;33(9):1605-13.

35. Fitzgerald JM, Bleeker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Lancet Resp Med 2017 Sep 8. pii S2213-2600(17)30344-2 doi S2213-2600(17)30344-2. 10.1016/S2213-2600(17)30344-2. [Epub ahead of print]

36. Center for Disease Control and Prevention; Asthma Data, Statistics, and Surveillance. Available at: **http://www.cdc.gov/asthma/asthmadata.htm** Accessed November 18, 2020.

37. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. Lancet 2002;360(9347):1715-21.

38. Patterson M, Borish L, Kennedy J. The past, present, and future of monoclonal antibodies to IL-5 and eosinophilic asthma. J Asthma Allergy 2015. Nov3;8:125-34.

39. Fasenra™ (benralizumab) for injection, for subcutaneous injection, preliminary prescribing information. AstraZeneca Pharmaceuticals, Wilmington, DE, October, 2019.

40. Global Initiative for Asthma; Global Strategy for Asthma Management and Prevention 2017. Available at: **www.ginasthma.org** Accessed November 18, 2020.

41. Castro M, Mathur S, Hargreave F, et al. Reslizumab for inadequately controlled asthma with elevated eosinophil counts: results from two multicenter, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3:355-66.

42. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma. Am J Respir Crit Care Med 184;1125-32.

43. Mathur S, Castro M, Hargreave F, et al. Efficacy of reslizumab in patients with poorly controlled eosinophilic asthma: subgroup analysis of patients with nasal polyps. J Allergy Clin Immunol 127;2:AB84. (abstract 313)

44. Food and Drug Administration; Briefing Document for Pulmonary-Allergy Advisory Committee Meeting. BLA 761033. Dec 9, 2015.

45. Murphy K, Jacobs J, Bjermer L, Shalit Y, Garin M. Long-Term Safety and Efficacy of Reslizumab in Patients with Inadequately Controlled, Moderate-To-Severe Asthma and Elevated Blood Eosinophil Counts: An Open-Label Extension Study. Am J Respir Crit Care Med 191;2015:A6455.

46. Patterson M, Borish L, Kennedy J. The past, present, and future of monoclonal antibodies to IL-5 and eosinophilic asthma. J Asthma Allergy 2015. Nov3;8:125-34.

47. Cherian S, Konstantinova T, Hu J, Khan SH. Safety Profile of Dual Biologic Therapy with Omalizumab and a Second Biologic Agent. Journal of Allergy and Clinical Immunology. 2020;145(2).

48. Ortega G, Tongchinsub P, Carr T. Combination Biologic Therapy for Severe Persistent Asthma. Annals of Allergy, Asthma & Immunology. 2019;123(3):309-311.

49. Thomes R, Darveaux J. Combination Biologic Therapy in Severe Asthma: A Case Series. Annals of Allergy, Asthma & Immunology. 2018;121(5).

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).
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

Date	Comments
	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.

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.

PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማሪኛ (Amharic):
ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በአከፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):
يحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):
Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):
Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):
Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti apliksayonyo wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):
ແຈ້ງການນີ້ມີຂໍ້ມູນສຳຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສຳຄັນກ່ຽວກັບຄຳຮ້ອງສະໝັກ ຫຼື ຄວາມຄຸ້ມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີສຳຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດຳເນີນການຕາມກຳນົດເວລາສະເພາະເພື່ອຮັກສາຄວາມຄຸ້ມຄອງປະກັນສຸຂະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເລື່ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄວ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໂທຫາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):
សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្ងៃជាក់ច្បាស់នានា ដើម្បីនឹងរក្សាទុកការជានាវ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញផ្លែ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):
ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਜਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀ ਜਸਹਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ਼ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫ਼ਤ ਵਿੱਚ ਤੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):
این اعلامیه حاوی اطلاعات مهم میباشد .این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید .شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید .شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کاربران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócic uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):
Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastre de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):
Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'amatalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):
Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).