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Subject: Interleukin-5 (IL-5) Inhibitors

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DESCRIPTION:

Benralizumab (Fasenra)

Benralizumab (Fasenra™), a humanized IL-5 receptor alpha-directed cytolytic monoclonal antibody, was approved by the U.S. Food and Drug Administration (FDA) in November 2017 for the add-on maintenance treatment of patients aged 12 years and older with severe asthma with an eosinophilic phenotype. Benralizumab was given an orphan drug designation for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) in November 2018.

The safety and effectiveness of benralizumab was established in three double-blind, randomized, placebo-controlled trials in individuals with severe asthma. Study data from SIROCCO and CALIMA demonstrated that add-on benralizumab treatment significantly reduced the annual exacerbation rate and improved lung function compared with placebo in adults and adolescents with severe, uncontrolled asthma with eosinophilic phenotype. Study data from ZONDA showed that benralizumab in adults significantly reduced the glucocorticoid dose from baseline, but found no significant improvement in FEV1 at 28 weeks.

SIROCCO, an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, evaluated the efficacy and safety of benralizumab in patients with severe, uncontrolled asthma with eosinophilia. (n=1205). Participants were required to have a diagnosis of asthma for at least 1 year and have at least two exacerbations while on high-dosage inhaled corticosteroids and long-acting β2-agonists (ICS plus LABA) in the previous year. Patients were randomly assigned (1:1:1) to benralizumab 30 mg either every 4 weeks (Q4W; n=400) or every 8 weeks with the first three doses every 4 weeks (Q8W; n=398) or placebo (n=407) for 48 weeks as add on to their standard treatment. Patients were stratified 2:1 according to blood eosinophil counts of at least 300 cells per µL and less than 300 cells per µL. The primary endpoint was annual exacerbation rate ratio versus placebo, and key secondary endpoints were prebronchodilator FEV1 and total asthma symptom score at week 48, for patients with blood eosinophil counts of at least 300 cells per µL. Efficacy analyses were by intention to treat (based on the full analysis set). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when given Q4W (rate ratio 0.55 [95% CI 0.42-0.71], p<0.0001) or Q8W (rate ratio 0.49 [95% CI 0.37-0.64], p<0.0001). Both benralizumab dosing regimens significantly improved prebronchodilator FEV1 in patients at week 48 compared with placebo (least-squares mean change from baseline: Q4W group

0.106 L [95% CI 0.016-0.196]; Q8W group 0.159 L [95% CI 0.068-0·249]). Compared with placebo, asthma symptoms were improved by the Q8W regimen (least-squares mean difference -0.25 [95% CI -0.45 to -0.06]), but not the Q4W regimen (-0.08 [95% CI -0.27 to 0.12]). The most common adverse events were worsening asthma (105 [13%] of 797 benralizumab-treated patients vs 78 [19%] of 407 placebo-treated patients) and nasopharyngitis (93 [12%] vs 47 [12%]).

CALIMA, a phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, evaluated 1306 participants with severe asthma uncontrolled by medium-dosage to high-dosage inhaled corticosteroids plus long-acting β_2-agonists (ICS plus LABA), elevated blood eosinophil counts, and a history of two or more exacerbations in the previous year. Patients were randomly assigned (1:1:1) to receive 56 weeks of benralizumab 30 mg every 4 weeks (Q4W; n=425), benralizumab 30 mg every 8 weeks with the first three doses 4 weeks apart (Q8W; n=441), or placebo (n=440). Patients were stratified (2:1) by baseline blood eosinophil counts 300 cells per µL or greater and less than 300 cells per µL, respectively. The primary endpoint was annual exacerbation rate ratio versus placebo for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils 300 cells per µL or greater (intention-to-treat analysis). Key secondary endpoints were pre-bronchodilator FEV1 and total asthma symptom score. Benralizumab resulted in significantly lower annual exacerbation rates with the Q4W regimen (rate 0.60 [95% CI 0.48-0.74], rate ratio 0.64 [95% CI 0.49-0.85], p=0.0018, n=241) and Q8W regimen (rate 0.66 [95% CI 0.54-0.82], rate ratio 0.72 [95% CI 0.54-0.95], p=0.0188, n=239) compared with placebo (rate 0.93 [95% CI 0.77-1.12], n=248). Benralizumab also significantly improved pre-bronchodilator FEV1 (Q4W and Q8W) and total asthma symptom score (Q8W only) in these patients. The most common adverse events were nasopharyngitis (90 [21%] in the Q4W group, 79 [18%] in the Q8W group, and 92 [21%] in the placebo group) and worsening asthma (61 [14%] in the Q4W group, 47 [11%] in the Q8W group, and 68 [15%] in the group).

ZONDA, a 28-week multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, evaluated 220 individuals with severe asthma associated with eosinophilia Patients received benralizumab 30 mg every 4 weeks (Q4W; n=72), benralizumab 30 mg every 8 weeks with the first three doses 4 weeks apart (Q8W; n=73), or placebo (n=75). The two benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group (P<0.001 for both comparisons). The odds of a reduction in the oral glucocorticoid dose were more than 4 times as high with benralizumab as with placebo. Among the secondary outcomes, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than the rate with placebo (marginal rate, 0.83 vs. 1.83, p=0.003), and benralizumab administered every 8 weeks resulted in an annual exacerbation rate that was 70% lower than the rate with placebo (marginal rate, 0.54 vs. 1.83, p<0.001). At 28 weeks, there was no significant effect of either benralizumab regimen on the FEV1, as compared with placebo. The effects on various measures of asthma symptoms were mixed, with some showing significant changes in favor of benralizumab and others not showing significant changes. Frequencies of adverse events were similar between each benralizumab group and the placebo group.

Depemokimab (Exdensur)

Depemokimab (Exdensur), an interleukin-5 antagonist, was approved by the U.S. Food and Drug Administration (FDA) in December 2025 for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Depemokimab is not indicated for treatment of other eosinophilic conditions or relief of acute bronchospasm or status asthmaticus.

The safety and efficacy of depemokimab were evaluated in two randomized, double-blind, placebo-controlled studies (SWIFT-1, SWIFT2) 52 weeks in duration involving 762 patients age 12 years and older with asthma who were required to have a blood eosinophil count of at least 300 eosinophils/mcL, and at least two asthma exacerbations requiring systemic corticosteroid use over the past 12 months despite medium- to high-dose ICS plus at least one controller medication. Maintenance oral corticosteroids (OCS) (up to 10 mg of prednisone per day or equivalent) were allowed. Depemokimab 100 mg was administered subcutaneously once every six months for a total of 2 doses over the treatment period.

The primary endpoint for both studies was the annualized rate of clinically significant asthma exacerbations over 52 weeks. Clinically significant asthma exacerbations were defined as worsening of asthma requiring use of systemic corticosteroids (single IM corticosteroid dose, oral steroids for three or more days), hospitalization, or emergency department visit.

In SWIFT-1 and SWIFT-2, the annualized rate of asthma exacerbations was significantly lower in patients receiving depemokimab compared to placebo. During the 52-week treatment period, fewer patients experienced exacerbations in the depemokimab group (32% and 32%) compared to the placebo group (46% and 50%) in SWIFT-1 and SWIFT-2, respectively. The annualized rate of clinically significant asthma exacerbations in SWIFT-1 was 0.46 in the depemokimab group and 1.11 in the placebo group (rate ratio: 0.42 (95%CI: 0.30, 0.59), p<0.001). The annualized rate of clinically significant asthma exacerbations in SWIFT-2 was 0.56 in the depemokimab group and 1.08 in the placebo group (rate ratio: 0.52 (95%CI: 0.36, 0.73), p<0.001). In a secondary endpoint from SWIFT-1 and SWIFT-2, patients treated with depemokimab experienced numerically fewer exacerbations requiring hospitalization and/or ED visits (1% and 4%) compared with placebo (8% and 10%), respectively.

Across clinical trials, depemokimab was well tolerated, with patients experiencing a similar rate and severity of side effects as those receiving placebo. The most common adverse reactions (incidence ≥4% and more common than placebo) were upper respiratory tract infection, allergic rhinitis, influenza, arthralgia, and pharyngitis. In the pooled safety population, injection site reactions occurred in 1% and <1% patients receiving depemokimab and placebo, respectively.

Mepolizumab (Nucala)

Mepolizumab (Nucala), a humanized IL-5 antagonist monoclonal antibody, was approved by the U.S. Food and Drug Administration (FDA) in November 2015 for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. In December 2017, mepolizumab was approved for treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA). In 2019, a single-dose, prefilled auto-injector and prefilled syringe became commercially available for self-administration.

The safety and effectiveness of mepolizumab was established in three multicenter, double-blind, randomized, placebo-controlled trials and two open-label extension studies of the initial trials in individuals with severe eosinophilic asthma confirmed by blood eosinophils ≥ 150 cells/microliter at initiation of treatment or blood eosinophils ≥ 300 cells/microliter in the past 12 months. Study data confirms the efficacy of mepolizumab in reducing exacerbations that require hospitalization and/or emergency department visits and improvement in asthma control (that is, a longer time to the first exacerbation) and quality of life measures.

DREAM, an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging dose selection trial, evaluated the efficacy and safety of mepolizumab on rates of exacerbation in individuals with severe recurrent asthma exacerbations and evidence of eosinophilic inflammation (e.g., sputum eosinophils, peripheral blood eosinophilia, or elevated exhaled nitric oxide) (n=621). Participants were required to be on background maintenance therapy with a high-dose ICS for the prior 12 months (with or without oral corticosteroids) plus an additional controller (LABA, leukotriene inhibitor, or theophylline) medication. Subjects received either intravenous mepolizumab at 75 mg, 250 mg, or 750 mg or placebo at 4-week intervals to week 48 (13 infusions). The primary outcome, an annualized rate of clinically significant asthma exacerbations, was decreased in all mepolizumab groups compared with placebo with the greatest reduction in the 750 mg group (52% reduction; 95% CI 36%-64%; p<0.0001). The effects of mepolizumab on symptoms and quality of life and pulmonary function (FEV1) did not differ significantly from those reported with placebo. The frequency of serious adverse events was similar across treatment groups. There were no reports of serious life-threatening anaphylactic reactions.

SIRIUS, a phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, evaluated 135 participants with severe asthma and peripheral blood eosinophilia (300 eosinophils/mcL during the 12 months prior to study entry or 150 eosinophils/mcL during the optimization phase) despite maintenance oral glucocorticoid treatment (5 mg to 35 mg of prednisone or its equivalent per day). Subjects received either mepolizumab 100 mg or placebo administered subcutaneously every 4 weeks

for 20 weeks. The primary efficacy outcome was the percentage reduction in daily oral glucocorticoid dose during weeks 20-24 compared with baseline dose while maintaining control of asthma. The likelihood of a reduction in the glucocorticoid dose was 2.39 times greater in the mepolizumab group (95% CI, 1.25-4.56; p=0.008). The median percentage reduction from baseline in the daily oral glucocorticoid dose was 50% in the mepolizumab group compared with no reduction in the placebo group (p=0.007). Mepolizumab was associated with a decrease in the number of asthma exacerbations (annualized rates were 1.44 per year in the mepolizumab group vs. 2.12 per year in the placebo group; rate ratio, 0.68; 95% CI, 0.47 to 0.99; p=0.04) and improved control of asthma symptoms. The most frequently reported adverse events were headache and nasopharyngitis (both groups). Local injection-site reactions were increased in the mepolizumab 100-mg subcutaneous treatment group compared with placebo.

MENSA, a 32-week phase III, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial, evaluated 576 individuals aged 12 years or older with severe asthma. Participants with severe asthma and markers of eosinophilic airway inflammation (peripheral blood eosinophil count 150/mcL at screening or 300/mcL at some point in the previous year) despite high-dose IHS (with or without systemic glucocorticoids) received either mepolizumab 75 mg intravenously, mepolizumab 100 mg subcutaneously, or placebo every 4 weeks for 32 weeks. Study participants were required to have a FEV1 of less than 80% of the predicted value (in the case of adults) or an FEV1 of less than 90% of the predicted value or a ratio of the FEV1 to the forced vital capacity (FVC) of less than 0.8 (in the case of adolescents under the age of 18 years). The primary outcome was the annualized frequency of clinically significant exacerbations, defined as worsening of asthma that required the treating physician to administer systemic glucocorticoids for at least 3 days, an emergency department visit, or hospitalization.

The rate of asthma exacerbations was reduced by 47% (95% CI, 28 to 60) in the intravenous mepolizumab group compared with placebo and by 53% (95% CI, 36 to 65) in the subcutaneous mepolizumab group compared with placebo (p<0.001 for both comparisons). At week 32, the mean increase in FEV1 from baseline was reported as 100 mL greater with intravenous mepolizumab compared with placebo (p=0.02) and 98 mL greater with subcutaneous mepolizumab compared with placebo (p=0.03). Adverse events during treatment, including nasopharyngitis and headache, were similar across all groups.

A total of 136 subjects with EGPA were evaluated in a randomized, placebo-controlled, multicenter, 52-week trial. Subjects were 18 years of age and older and had been diagnosed with EGPA for at least 6 months based on the history or presence of: asthma plus eosinophilia (>1.0x10^9/Liter and/or >10% of leucocytes) plus at least two of the following additional features of EGPA; a biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation; neuropathy, mono or poly (motor deficit or nerve conduction abnormality); pulmonary infiltrates, non-fixed; sino-nasal abnormality; cardiomyopathy (established by echocardiography or Magnetic Resonance Imaging); glomerulonephritis (hematuria, red cell casts, proteinuria); alveolar hemorrhage (by bronchoalveolar lavage); palpable purpura; anti neutrophil cytoplasmic anti-body (ANCA) positive (Myeloperoxidase or proteinease 3). Subjects also were required to have a history of relapsing or refractory disease.

Subjects received 300 mg of mepolizumab or placebo administered subcutaneously once every 4 weeks while continuing their stable oral corticosteroid therapy. Starting at Week 4, the oral corticosteroid 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. Mepolizumab compared with placebo significantly increased the proportion of patients achieving remission at both 36 and 48 weeks (32% vs 3%), and at 52 weeks (19% vs 1%)

Reslizumab (Cinqair)

Reslizumab (Cinqair), an interleukin-5 antagonist, was approved by the U.S. Food and Drug Administration (FDA) in March 2016 for add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype. Reslizumab is not indicated for treatment of other eosinophilic conditions or relief of acute bronchospasm or status asthmaticus.

The safety and efficacy of reslizumab were evaluated in 2 randomized, double-blind, placebo-controlled studies (Studies I, II) 16 to 52 weeks in duration involving 953 patients age 12 years and older with asthma who were required to have a blood eosinophil count of at least 400/mcL (within 3 to 4 weeks of dosing), and at least 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. The majority of patients (82%) were on medium-high dose inhaled corticosteroids plus a long-acting beta agonist (ICS/LABA) at baseline. Maintenance oral corticosteroids (OCS) (up to 10 mg of prednisone per day or equivalent) were allowed; 106 (11%) patients were on OCS at baseline. Reslizumab 3 mg/kg administered once every 4 weeks for a total of 13 doses was compared with placebo.

The primary endpoint for Studies I and II was the frequency of asthma exacerbations for each patient during the 52-week treatment period. An asthma exacerbation was defined as a worsening of asthma that required at least 1 of the following medical interventions: 1) Either the use of a systemic corticosteroid, or ≥ 2-fold an increase in the use of ICS for 3 or more days, and/or 2) Asthma-related emergency treatment including at least 1 of the following: an unscheduled visit to their healthcare professional for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms; a visit to the emergency room for asthma-related treatment; or an asthma-related hospitalization.

In Studies I and II, reslizumab significantly reduced the annual rate of clinical asthma exacerbations compared with placebo (0.84 vs 1.81 events per patient/year). One or more exacerbations occurred in 32% of the reslizumab group and 50% of the placebo arm. Reslizumab produced a significantly greater change in FEV1 from baseline to week 16 (0.23 vs 0.11 L). Clinically important changes in patient-reported asthma control scores and quality of life scores were also significantly improved with reslizumab.

POSITION STATEMENT:

Drug Waste Reduction: Additional medical necessity criteria for dose optimization may apply depending on the requested dose and member's benefit. Refer to 09-J5000-54, Medical Coverage Guideline Drug Waste Reduction.

Site of Care: If benralizumab (Fasenra), mepolizumab (Nucala), or reslizumab (Cinqair) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46, Site of Care Policy for Select Non-Oncology Medications.

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary. This statement applies to benralizumab (Fasenra) pen and mepolizumab (Nucala) prefilled auto-injectors and syringes.

Benralizumab (Fasenra)

Initiation of benralizumab (Fasenra) **meets the definition of medical necessity** for members diagnosed with any of the following conditions when **ALL** associated criteria are met:

1. Severe Eosinophilic Asthma
    a. Member's diagnosis has been confirmed by **ONE** of the following – laboratory documentation must be provided:

i. Member has a baseline (prior to therapy with benralizumab) blood eosinophilic count of 150 cells/microliter or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids

ii. Member has a fraction of exhaled nitric oxide (FeNO) of 20 parts per billion or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids

iii. Member has sputum eosinophils 2% or higher while on high dose inhaled corticosteroids or daily oral corticosteroids

b. **ONE** of the following:

i. Member has a history of uncontrolled asthma while on asthma control therapy (e.g., inhaled corticosteroids [ICS], ICS/long-acting beta-2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline) as demonstrated by **ONE** of the following:

- Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months
- Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months
- Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered
- The member has baseline (prior to therapy with benralizumab) Forced Expiratory Volume (FEV1) that is less than 80% of predicted

ii. Member's medication history indicates use of a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma within the past 12 months (treatment on samples is not approvable)

c. **ONE** of the following:

i. Member is **NOT** currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including benralizumab) **AND** is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days

ii. Member is currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including benralizumab) **AND ONE** of the following:

- Member is currently treated with an inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days that is adequately dosed to control symptoms
- Member is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days

iii. Member has an intolerance or hypersensitivity to inhaled corticosteroid therapy

iv. Member has an FDA labeled contraindication to **ALL** inhaled corticosteroids

d. **ONE** of the following:

i. Member is currently being treated for at least 3 months **AND** has been adherent for 90 days within the past 120 days with **ONE** of the following:

- A long-acting beta-2 agonist (LABA)

- A leukotriene receptor antagonist (LTRA)
- Long-acting muscarinic antagonist (LAMA)
- Theophylline

ii. Member has an intolerance or hypersensitivity to therapy to **ONE** LABA, LTRA, LAMA, or theophylline

iii. Member has an FDA labeled contraindication to **ALL** LABA, LTRA, LAMA, AND theophylline therapies

e. Member will continue asthma control therapy in combination with benralizumab

f. Benralizumab is not used in combination with depemokimab (Exdensur), dupilumab (Dupixent), mepolizumab (Nucala), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

g. Benralizumab is prescribed by a board certified (or board eligible) allergist, immunologist, or pulmonologist

h. Dose does not exceed either of the following:

i. Initial dose: 30 mg every 4 weeks x 3 doses

ii. Maintenance dose: 30 mg every 8 weeks

i. Member is 6 years of age or older

2. Eosinophilic Granulomatosis with Polyangiitis (EGPA)

a. Use will be for treatment of relapsing or refractory disease or treatment for maintenance of disease remission

b. Member does not have severe disease with organ- or life-threatening manifestations (e.g., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia)

c. Member's diagnosis is confirmed by the presence of **ALL** of the following:

i. Asthma

ii. Eosinophilia (defined as eosinophils greater than 1,000 cells per microliter **OR** greater than 10% of leucocytes) – laboratory documentation must be provided

iii. Two of the following – documentation from the medical record must be provided:

- Biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation
- Mononeuropathy or polyneuropathy
- Nonfixed pulmonary infiltrates
- Abnormalities of paranasal sinuses

d. **ONE** of the following:

i. Member is currently treated within the past 90 days with oral corticosteroids for at least 4 weeks **AND** the member will continue oral corticosteroid therapy in combination with benralizumab

ii. Member has an intolerance or hypersensitivity to **ONE** oral corticosteroid

iii. Member has an FDA labeled contraindication to **ALL** oral corticosteroids

e. Benralizumab is not used in combination with depemokimab (Exdensur), dupilumab (Dupixent), mepolizumab (Nucala), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

f. Benralizumab is prescribed by a board certified (or board eligible) allergist, immunologist, pulmonologist, or rheumatologist

g. Dose does not exceed 30 mg every 4 weeks

h. Member is 18 years of age or older

3. Other FDA-approved or NCCN supported diagnosis (not previously listed above)

    a. When **ONE** of the following is met:

        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

        ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

    b. Dose does not exceed the maximum FDA-approved dosing

Approval duration: 6 months

Continuation of benralizumab (Fasenra) **meets the definition of medical necessity** for members diagnosed with any of the following conditions when **ALL** associated criteria are met:

1. Severe Eosinophilic Asthma

    a. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for severe eosinophilic asthma, OR the member has previously met all indication-specific initiation criteria

    b. Member has a clinical benefit to treatment with benralizumab as demonstrated by at least **ONE** of the following – documentation from the medical record must be provided:

        i. Increase in percent predicted Forced Expiratory Volume (FEV1)

        ii. Decrease in the dose of inhaled corticosteroids required to control the patient's asthma

        iii. Decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma

        iv. Decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma

    c. Member is currently treated and is compliant with asthma control therapy (e.g., inhaled corticosteroids [ICS], ICS/long-acting beta-2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline)

    d. Benralizumab is prescribed by or in consultation with a board certified (or board eligible) allergist, immunologist, or pulmonologist

    e. Benralizumab is not used in combination with depemokimab (Exdensur), dupilumab (Dupixent), mepolizumab (Nucala), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

    f. Dose does not exceed 30 mg every 8 weeks

    g. Member is 6 years of age or older

2. Eosinophilic Granulomatosis with Polyangiitis (EGPA)

a. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for EGPA, OR the member has previously met all indication-specific initiation criteria

b. Member achieves remission of EGPA – documentation from the medical record must be provided

c. **ONE** of the following:

i. Member is currently treated within the past 90 days with oral corticosteroids for at least 4 weeks **AND** the member will continue oral corticosteroid therapy in combination with benralizumab

ii. Member has an intolerance or hypersensitivity to **ONE** oral corticosteroid

iii. Member has an FDA labeled contraindication to **ALL** oral corticosteroids

d. Benralizumab is not used in combination with depemokimab (Exdensur), dupilumab (Dupixent), mepolizumab (Nucala), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

e. Benralizumab is prescribed by a board certified (or board eligible) allergist, immunologist, pulmonologist, or rheumatologist

f. Dose does not exceed 30 mg every 4 weeks

g. Member is 18 years of age or older

3. Other FDA-approved or NCCN supported diagnosis (not previously listed above)

a. When **ONE** of the following is met:

i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. Dose does not exceed the maximum FDA-approved dosing

Approval duration: 12 months

<u>Depemokimab (Exdensur)</u>

Initiation of depemokimab (Exdensur) meets the definition of **medical necessity** for members diagnosed with any of the following conditions when **ALL** associated criteria are met:

1. Severe Eosinophilic Asthma

a. Member's diagnosis has been confirmed by **ONE** of the following – laboratory documentation must be provided:

i. Member has a baseline (prior to therapy with reslizumab) blood eosinophilic count of 150 cells/microliter or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids

ii. Member has a fraction of exhaled nitric oxide (FeNO) of 20 parts per billion or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids

iii. Member has sputum eosinophils 2% or higher while on high dose inhaled corticosteroids or daily oral corticosteroids

b. **ONE** of the following:

i. Member has a history of uncontrolled asthma while on asthma control therapy as demonstrated by **ONE** of the following:

- Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months
- Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months
- Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered
- The member has baseline (prior to therapy with depemokimab) Forced Expiratory Volume (FEV1) that is less than 80% of predicted

ii. Member's medication history indicates use of a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma within the past 12 months (treatment on samples is not approvable)

c. ONE of the following:

i. Member is **NOT** currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including depemokimab) **AND** is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days

ii. Member is currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including depemokimab) **AND ONE** of the following:

- Member is currently treated with an inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days that is adequately dosed to control symptoms
- Member is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days

iii. Member has an intolerance or hypersensitivity to **ONE** inhaled corticosteroid therapy

iv. Member has an FDA labeled contraindication to **ALL** inhaled corticosteroids

d. **ONE** of the following:

i. Member is currently being treated for at least 3 months **AND** has been adherent for 90 days within the past 120 days with **ONE** of the following:

- A long-acting beta-2 agonist (LABA)
- A leukotriene receptor antagonist (LTRA)
- Long-acting muscarinic antagonist (LAMA)
- Theophylline

ii. Member has an intolerance or hypersensitivity to therapy to **ONE** LABA, LTRA, LAMA, or theophylline

iii. Member has an FDA labeled contraindication to **ALL** LABA, LTRA, LAMA, **AND** theophylline therapies

e. **ONE** of the following:

i. Member has tried and had an inadequate response to benralizumab (Fasenra) **AND** mepolizumab (Nucala) **AND** reslizumab (Cinqair) after at least a 3-month trial of each product – documentation from the medical record must be provided

ii. Member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to benralizumab (Fasenra) **AND** mepolizumab (Nucala) **AND** reslizumab (Cinqair) – documentation from the medical record must be provided

iii. Member has an FDA labeled contraindication to benralizumab (Fasenra) **AND** mepolizumab (Nucala) **AND** reslizumab (Cinqair) – documentation from the medical record must be provided

f. Member will continue asthma control therapy in combination with depemokimab

g. Depemokimab is prescribed by a board certified (or board eligible) allergist, immunologist, or pulmonologist

h. Depemokimab is not used in combination with benralizumab (Fasenra), dupilumab (Dupixent), mepolizumab (Nucala), reslizumab (Cinqair), tezepelumab (Tezspire), or omalizumab (Xolair, Omlyclo)

i. Dose does not exceed 100 mg every 6 months

j. Member is 12 years of age or older

2. Other FDA-approved or NCCN supported diagnosis (not previously listed above)

a. When **ONE** of the following is met:

i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. Dose does not exceed the maximum FDA-approved dosing

Approval duration: 6 months

Continuation of depemokimab (Exdensur) meets the definition of **medical necessity** for members diagnosed with any of the following conditions when **ALL** associated criteria are met:

1. Severe Eosinophilic Asthma

a. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for severe eosinophilic asthma, OR the member has previously met all indication-specific initiation criteria

b. Member has a clinical benefit to treatment with depemokimab as demonstrated by at least **ONE** of the following – documentation from the medical record must be provided:

i. Increase in percent predicted Forced Expiratory Volume (FEV1)

ii. Decrease in the dose of inhaled corticosteroids required to control the patient's asthma

iii. Decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma

iv. Decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma

c. Member is currently treated and is compliant with asthma control therapy (e.g., inhaled corticosteroids [ICS], ICS/long-acting beta-2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline)

d. Depemokimab is prescribed by a board certified (or board eligible) allergist, immunologist, or pulmonologist

e. Depemokimab is not used in combination with benralizumab (Fasenra), dupilumab (Dupixent), mepolizumab (Nucala), reslizumab (Cinqair), tezepelumab (Tezspire), or omalizumab (Xolair, Omlyclo)

f. Dose does not exceed 100 mg every 6 months

g. Member is 12 years of age or older

2. Other FDA-approved or NCCN supported diagnosis (not previously listed above)

   a. When **ONE** of the following is met:

      i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

      ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

   b. Dose does not exceed the maximum FDA-approved dosing

Approval duration: 12 months

<u>Mepolizumab (Nucala)</u>

Initiation of mepolizumab (Nucala) **meets the definition of medical necessity** for members diagnosed with any of the following conditions when ALL associated criteria are met:

1. Severe Eosinophilic Asthma

   a. Member's diagnosis has been confirmed by **ONE** of the following – laboratory documentation must be provided:

      i. Member has a baseline (prior to therapy with mepolizumab) blood eosinophilic count of 150 cells/microliter or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids

      ii. Member has a fraction of exhaled nitric oxide (FeNO) of 20 parts per billion or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids

      iii. Member has sputum eosinophils 2% or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids

   b. **ONE** of the following:

      i. Member has a history of uncontrolled asthma while on asthma control therapy (e.g., inhaled corticosteroids [ICS], ICS/long-acting beta-2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline) as demonstrated by **ONE** of the following:

- Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months
- Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months
- Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered
- The member has baseline (prior to therapy with mepolizumab) Forced Expiratory Volume (FEV1) that is less than 80% of predicted

ii. Member's medication history indicates use of a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma within the past 12 months (treatment on samples is not approvable)

c. **ONE** of the following:

i. Member is **NOT** currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including mepolizumab) **AND** is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days

ii. Member is currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including mepolizumab) **AND ONE** of the following:

- The member is currently treated with an inhaled corticosteroid for at least 3 months that is adequately dosed to control symptoms **AND** has been adherent for 90 days within the past 120 days
- The member is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days

iii. Member has an intolerance or hypersensitivity to **ONE** inhaled corticosteroid therapy

iv. Member has an FDA labeled contraindication to **ALL** inhaled corticosteroids

d. **ONE** of the following:

i. Member is currently being treated for at least 3 months **AND** has been adherent for 90 days within the past 120 days with **ONE** of the following:

- A long-acting beta-2 agonist (LABA)
- A leukotriene receptor antagonist (LTRA)
- Long-acting muscarinic antagonist (LAMA)
- Theophylline

ii. Member has an intolerance or hypersensitivity to therapy to **ONE** LABA, LTRA, LAMA, or theophylline

iii. Member has an FDA labeled contraindication to **ALL** LABA, LTRA, LAMA, **AND** theophylline therapies

e. Member will continue asthma control therapy in combination with mepolizumab

f. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

g. Mepolizumab is prescribed by a board certified (or board eligible) allergist, immunologist, or pulmonologist

h. Dose does not exceed

i. 6 to 11 years of age: 40 mg every 4 weeks

ii. 12 years and older: 100 mg every 4 weeks

i. Member is 6 years of age or older

2. Chronic Obstructive Pulmonary Disease (COPD)

a. Member's diagnosis has been confirmed by spirometry with a post-bronchodilator FEV1/FVC ratio less than 0.7 – documentation from the medical record must be provided

b. Member has a baseline (prior to therapy with mepolizumab) blood eosinophil count of 300 cells/microliter or higher – documentation from the medical record must be provided

c. **ONE** of the following:

i. Member has a history of inadequately controlled COPD while on COPD inhaled maintenance therapy as demonstrated by **ONE** of the following:

- Frequent COPD exacerbations (i.e., 2 or more moderate exacerbations) requiring one or more courses of systemic corticosteroids within the past 12 months
- A severe COPD exacerbation requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months

ii. Member's medication history indicates use of a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of COPD within the past 12 months (treatment on samples is not approvable)

d. **ONE** of the following:

i. Member is currently treated with an inhaled corticosteroid (ICS) for at least 3 months **AND** has been adherent for 90 days within the past 120 days

ii. Member has an intolerance or hypersensitivity to **ONE** inhaled corticosteroid

iii. Member has an FDA labeled contraindication to **ALL** inhaled corticosteroids

e. Member is currently treated with a long-acting muscarinic antagonist (LAMA) **AND** a long-acting beta-2 agonist (LABA) used in combination (LAMA/LABA dual therapy) for at least 3 months **AND** has been adherent for 90 days within the past 120 days

f. Member will continue COPD inhaled maintenance therapy (i.e., ICS/LAMA/LABA triple therapy, LAMA/LABA dual therapy) in combination with mepolizumab

g. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

h. Mepolizumab is prescribed by a board certified (or board eligible) allergist, immunologist, or pulmonologist

i. Dose does not exceed 100 mg every 4 weeks

j. Member is 18 years of age or older

3. Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
    a. There is information indicating the member's diagnosis was confirmed by **ONE** of the following:
        i. Anterior rhinoscopy
        ii. Nasal endoscopy
        iii. Computed tomography (CT) of the sinuses
    b. Member has at least **TWO** of the following symptoms consistent with chronic rhinosinusitis (CRS):
        i. Nasal discharge (rhinorrhea or post-nasal drainage)
        ii. Nasal obstruction or congestion
        iii. Loss or decreased sense of smell (hyposmia)
        iv. Facial pressure or pain
    c. Member has had symptoms consistent with CRS for at least 12 consecutive weeks
    d. **ONE** of the following:
        i. Member has tried and had an inadequate response to **ONE** intranasal corticosteroid (e.g., fluticasone, Sinuva) after at least a 4-week duration of therapy
        ii. Member has an intolerance or hypersensitivity to **ONE** intranasal corticosteroid (e.g., fluticasone, Sinuva)
        iii. Member has an FDA labeled contraindication to **ALL** intranasal corticosteroids
    e. **BOTH** of the following:
        i. Member is currently treated with standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids)
        ii. Member will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with mepolizumab
    f. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)
    g. Mepolizumab is prescribed by a board certified (or board eligible) allergist, immunologist, otolaryngologist (ear, nose, and throat specialist), or pulmonologist
    h. Dose does not exceed 100 mg every 4 weeks
    i. Member is 18 years of age or older
4. Eosinophilic Granulomatosis with Polyangiitis (EGPA)
    a. Use will be for treatment of relapsing or refractory disease or treatment for maintenance of disease remission
    b. Member does not have severe disease with organ- or life-threatening manifestations (e.g., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia)
    c. Member's diagnosis is confirmed by the presence of **ALL** of the following:
        i. Asthma
        ii. Eosinophilia (defined as eosinophils greater than 1,000 cells per microliter OR greater than 10% of leucocytes) – laboratory documentation must be provided

iii. Two of the following – documentation from the medical record must be provided:

- Biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation
- Mononeuropathy or polyneuropathy
- Nonfixed pulmonary infiltrates
- Abnormalities of paranasal sinuses

d. **ONE** of the following:

i. Member is currently treated within the past 90 days with oral corticosteroids for at least 4 weeks **AND** the member will continue oral corticosteroid therapy in combination with mepolizumab

ii. Member has an intolerance or hypersensitivity to **ONE** oral corticosteroid

iii. Member has an FDA labeled contraindication to **ALL** oral corticosteroids

e. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

f. Mepolizumab is prescribed by a board certified (or board eligible) allergist, immunologist, pulmonologist, or rheumatologist

g. Dose does not exceed 300 mg every 4 weeks

h. Member is 18 years of age or older

5. Hypereosinophilic Syndrome (HES)

a. Member's diagnosis has been confirmed by **ONE** of the following – laboratory documentation must be provided

a. Member has a peripheral blood eosinophil count greater than 1000 cells/microliter

b. Member has a percentage of eosinophils in bone marrow section exceeding 20% of all nucleated cells

b. Member has a history of two or more HES flares within the past 12 months – documentation from the medical record must be provided

c. Secondary (reactive, non-hematologic) causes of eosinophilia have been excluded (e.g., infection, allergy/atopy, medications, collagen vascular disease, metabolic [e.g., adrenal insufficiency], solid tumor/lymphoma)

d. Member has evidence of hypereosinophilia-related organ damage (e.g., fibrosis of lung, heart, digestive tract, skin, etc.; thrombosis with or without thromboembolism; cutaneous erythema, edema/angioedema, ulceration, pruritis, or eczema; peripheral or central neuropathy with chronic or recurrent neurologic deficit; other organ system involvement such as liver, pancreas, kidney) – documentation from the medical record must be provided

e. Member does **NOT** have FIP1L1-PDGFRA-positive disease

f. Member is currently treated with a maximally tolerated oral corticosteroid or has an intolerance, hypersensitivity, or FDA labeled contraindication to oral corticosteroid therapy

g. Member is currently treated with hydroxyurea, interferon-a, or another immunosuppressive agent (e.g., azathioprine, cyclosporine, methotrexate, tacrolimus)

OR has an intolerance, hypersensitivity, or FDA labeled contraindication to hydroxyurea, interferon-a, and all other immunosuppressive agents (e.g., azathioprine, cyclosporine, methotrexate, tacrolimus)

h. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

i. Mepolizumab is prescribed by a board certified (or board eligible) allergist, hematologist, immunologist, pulmonologist, or rheumatologist

j. Dose does not exceed 300 mg every 4 weeks

k. Member is 12 years of age or older

6. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
    a. When **ONE** of the following is met:
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
        ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
    b. Dose does not exceed the maximum FDA-approved dosing

Approval duration: 6 months

Continuation of mepolizumab (Nucala) **meets the definition of medical necessity** for members diagnosed with any of the following conditions when **ALL** associated criteria are met:

1. Severe Eosinophilic Asthma
    a. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for severe eosinophilic asthma, OR the member has previously met all indication-specific initiation criteria
    b. Member has a clinical benefit to treatment with mepolizumab as demonstrated by at least **ONE** of the following – documentation from the medical record must be provided:
        i. Increase in percent predicted Forced Expiratory Volume (FEV1)
        ii. Decrease in the dose of inhaled corticosteroids required to control the patient's asthma
        iii. Decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma
        iv. Decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma
    c. Member is currently treated and is compliant with asthma control therapy (e.g., inhaled corticosteroids [ICS], ICS/long-acting beta-2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline)
    d. Mepolizumab is prescribed by or in consultation with a board certified (or board eligible) allergist, immunologist, or pulmonologist

e. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

f. Dose does not exceed

i. 6 to 11 years of age: 40 mg every 4 weeks

ii. 12 years and older: 100 mg every 4 weeks

g. Member is 6 years of age or older

2. Chronic Obstructive Pulmonary Disease (COPD)

a. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for COPD, OR the member has previously met all indication-specific initiation criteria

b. Member has a clinical benefit to treatment with mepolizumab as evidenced by a reduction in the number of moderate (i.e., those requiring treatment with oral corticosteroids) or severe (i.e., those requiring hospitalization) exacerbations – documentation from the medical record must be provided

c. Member is currently treated with a long-acting muscarinic antagonist (LAMA) **AND** a long-acting beta-2 agonist (LABA) used in combination (LAMA/LABA dual therapy) for at least 3 months **AND** has been adherent for 90 days within the past 120 days

d. Member will continue COPD inhaled maintenance therapy (i.e., ICS/LAMA/LABA triple therapy, LAMA/LABA dual therapy) in combination with mepolizumab

e. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

f. Mepolizumab is prescribed by a board certified (or board eligible) allergist, immunologist, or pulmonologist

g. Dose does not exceed 100 mg every 4 weeks

h. Member is 18 years of age or older

3. Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

a. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for CRSwNP, OR the member has previously met all indication-specific initiation criteria

b. Member has a clinical benefit to treatment with mepolizumab as evidenced by a reduction in disease severity (e.g., reduction in nasal congestion, nasal polyp size, anterior or posterior rhinorrhea, sinonasal inflammation, facial pressure/pain; improved sese of smell; or reduction in corticosteroid use) – documentation from the medical record must be provided

c. **BOTH** of the following:

i. Member is currently treated with standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids)

ii. Member will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with mepolizumab

d. Mepolizumab is prescribed by or in consultation with a board certified (or board eligible) allergist, immunologist, otolaryngologist (ear, nose, and throat specialist), or pulmonologist

e. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

f. Dose does not exceed 100 mg every 4 weeks

g. Member is 18 years of age or older

4. Eosinophilic Granulomatosis with Polyangiitis (EGPA)

    a. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for EGPA, OR the member has previously met all indication-specific initiation criteria

    b. Member achieves remission of EGPA – documentation from the medical record must be provided

    c. **ONE** of the following:

        i. Member is currently treated within the past 90 days with oral corticosteroids for at least 4 weeks **AND** the member will continue oral corticosteroid therapy in combination with mepolizumab

        ii. Member has an intolerance or hypersensitivity to **ONE** oral corticosteroid

        iii. Member has an FDA labeled contraindication to **ALL** oral corticosteroids

    d. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

    e. Mepolizumab is prescribed by a board certified (or board eligible) allergist, immunologist, pulmonologist, or rheumatologist

    f. Dose does not exceed 300 mg every 4 weeks

    g. Member is 18 years of age or older

5. Hypereosinophilic Syndrome (HES)

    a. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for HES, OR the member has previously met all indication-specific initiation criteria

    b. Member has a 50% reduction in HES flares – documentation from the medical record must be provided

    c. Member is currently treated with a maximally tolerated oral corticosteroid or has an intolerance, hypersensitivity, or FDA labeled contraindication to oral corticosteroid therapy

    d. Member is currently treated with hydroxyurea, interferon-a, or another immunosuppressive agent (e.g., azathioprine, cyclosporine, methotrexate, tacrolimus) **OR** has an intolerance, hypersensitivity, or FDA labeled contraindication to hydroxyurea, interferon-a, and all other immunosuppressive agents (e.g., azathioprine, cyclosporine, methotrexate, tacrolimus)

    e. Mepolizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), omalizumab (Xolair, Omlyclo), tezepelumab (Tezspire), or reslizumab (Cinqair)

    f. Mepolizumab is prescribed by a board certified (or board eligible) allergist, hematologist, immunologist, pulmonologist, or rheumatologist

    g. Dose does not exceed 300 mg every 4 weeks

h. Member is 12 years of age or older

6. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
    a. When **ONE** of the following is met:
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
        ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
    b. Dose does not exceed the maximum FDA-approved dosing

Approval duration: 12 months

Reslizumab (Cinqair)

Initiation of reslizumab (Cinqair) meets the definition of **medical necessity** for members diagnosed with any of the following conditions when **ALL** associated criteria are met:

1. Severe Eosinophilic Asthma
    a. Member's diagnosis has been confirmed by **ONE** of the following – laboratory documentation must be provided:
        i. Member has a baseline (prior to therapy with reslizumab) blood eosinophilic count of 150 cells/microliter or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids
        ii. Member has a fraction of exhaled nitric oxide (FeNO) of 20 parts per billion or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids
        iii. Member has sputum eosinophils 2% or higher while on high dose inhaled corticosteroids or daily oral corticosteroids
    b. **ONE** of the following:
        i. Member has a history of uncontrolled asthma while on asthma control therapy as demonstrated by **ONE** of the following:
            - Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months
            - Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months
            - Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered
            - The member has baseline (prior to therapy with reslizumab) Forced Expiratory Volume (FEV1) that is less than 80% of predicted
        ii. Member's medication history indicates use of a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma within the past 12 months (treatment on samples is not approvable)
    c. ONE of the following:

i. Member is **NOT** currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including reslizumab) **AND** is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days

ii. Member is currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including reslizumab) **AND ONE** of the following:

- Member is currently treated with an inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days that is adequately dosed to control symptoms
- Member is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days

iii. Member has an intolerance or hypersensitivity to **ONE** inhaled corticosteroid therapy

iv. Member has an FDA labeled contraindication to **ALL** inhaled corticosteroids

d. **ONE** of the following:

i. Member is currently being treated for at least 3 months **AND** has been adherent for 90 days within the past 120 days with **ONE** of the following:

- A long-acting beta-2 agonist (LABA)
- A leukotriene receptor antagonist (LTRA)
- Long-acting muscarinic antagonist (LAMA)
- Theophylline

ii. Member has an intolerance or hypersensitivity to therapy to **ONE** LABA, LTRA, LAMA, or theophylline

iii. Member has an FDA labeled contraindication to **ALL** LABA, LTRA, LAMA, **AND** theophylline therapies

e. **ONE** of the following:

i. Member has tried and had an inadequate response to both benralizumab (Fasenra) **AND** mepolizumab (Nucala) after at least a 3-month trial of each product – documentation from the medical record must be provided

ii. Member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to both benralizumab (Fasenra) **AND** mepolizumab (Nucala) – documentation from the medical record must be provided

iii. Member has an FDA labeled contraindication to both benralizumab (Fasenra) **AND** mepolizumab (Nucala) – documentation from the medical record must be provided

f. Member will continue asthma control therapy in combination with reslizumab

g. Reslizumab is prescribed by a board certified (or board eligible) allergist, immunologist, or pulmonologist

h. Reslizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), mepolizumab (Nucala), tezepelumab (Tezspire), or omalizumab (Xolair, Omlyclo)

i. Dose does not exceed 3 mg/kg every 4 weeks

j. Member is 18 years of age or older

2. Other FDA-approved or NCCN supported diagnosis (not previously listed above)

    a. When **ONE** of the following is met:

        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

        ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

    b. Dose does not exceed the maximum FDA-approved dosing

Approval duration: 6 months

Continuation of reslizumab (Cinqair) meets the definition of **medical necessity** for members diagnosed with any of the following conditions when **ALL** associated criteria are met:

1. Severe Eosinophilic Asthma

    a. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for severe eosinophilic asthma, OR the member has previously met all indication-specific initiation criteria

    b. Member has a clinical benefit to treatment with reslizumab as demonstrated by at least **ONE** of the following – documentation from the medical record must be provided:

        i. Increase in percent predicted Forced Expiratory Volume (FEV1)

        ii. Decrease in the dose of inhaled corticosteroids required to control the patient's asthma

        iii. Decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma

        iv. Decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma

    c. Member is currently treated and is compliant with asthma control therapy (e.g., inhaled corticosteroids [ICS], ICS/long-acting beta-2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline)

    d. Reslizumab is prescribed by a board certified (or board eligible) allergist, immunologist, or pulmonologist

    e. Reslizumab is not used in combination with benralizumab (Fasenra), depemokimab (Exdensur), dupilumab (Dupixent), mepolizumab (Nucala), tezepelumab (Tezspire), or omalizumab (Xolair, Omlyclo)

    f. Dose does not exceed 3 mg/kg every 4 weeks

    g. Member is 18 years of age or older

2. Other FDA-approved or NCCN supported diagnosis (not previously listed above)

    a. When **ONE** of the following is met:

        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. Dose does not exceed the maximum FDA-approved dosing

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

FDA-approved

Benralizumab (Fasenra)

- 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen

Depemokimab (Exdensur)

- 100 mg once every 6 months administered by subcutaneous (SC) injection

Mepolizumab (Fasenra)

- Asthma:
  - 12 years of age and older: 100 mg administered subcutaneously once every 4 weeks
  - 6 to 11 years of age: 40 mg administered subcutaneously once every 4 weeks
- Chronic Rhinosinusitis with Nasal Polyps
  - 100 mg administered subcutaneously once every 4 weeks
- EGPA: 300 mg as 3 separate 100-mg injections administered subcutaneously once every 4 weeks
- HES: 300 mg as 3 separate 100-mg injections administered subcutaneously once every 4 weeks

Reslizumab (Cinqair)

- Do not administer as an intravenous push or bolus
- Administer in a healthcare setting by a healthcare professional prepared to manage anaphylaxis
- Recommended dosage regimen is 3 mg/kg once every 4 weeks by intravenous infusion over 20-50 minutes

Dose Adjustments

Benralizumab (Fasenra)

- None

Depemokimab (Exdensur)

- None

Mepolizumab (Fasenra)

- None

Reslizumab (Cinqair)

- None

Drug Availability

Benralizumab (Fasenra)

- Injection: 10 mg/0.5 mL and 30 mg/mL solution in a single-dose prefilled syringe
- Injection: 30 mg/mL solution in a single-dose prefilled autoinjector

Depemokimab (Exdensur)

- Injection: 100 mg/mL solution in a single-dose, prefilled pen
- Injection: 100 mg/mL solution in a single-dose, prefilled syringe with needle guard

Mepolizumab (Fasenra)

- 100 mg of lyophilized powder in a single-dose vial for reconstitution
- 100 mg/mL, single-dose, prefilled autoinjector or single-dose prefilled syringe

Reslizumab (Cinqair)

- Injection: 100 mg/10 mL (10 mg/mL) solution in single-use vials

PRECAUTIONS:

Boxed Warning

Benralizumab (Fasenra)

- None

Depemokimab (Exdensur)

- None

Mepolizumab (Fasenra)

- None

Reslizumab (Cinqair)

- Anaphylaxis: Anaphylaxis has been observed with infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose.

Contraindications

Benralizumab (Fasenra)

- Known hypersensitivity to benralizumab or excipients

Depemokimab (Exdensur)

- None

Mepolizumab (Fasenra)

- History of hypersensitivity to mepolizumab or excipients in the formulation

Reslizumab (Cinqair)

- Known hypersensitivity to reslizumab or any of its excipients

Precautions/Warnings

Benralizumab (Fasenra)

- Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash)
- Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy; decrease corticosteroids gradually, if appropriate
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before initiation of therapy; if patients become infected while receiving therapy and do not respond to anti-helminth treatment, discontinue until the parasitic infection resolve

Depemokimab (Exdensur)

- Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash)
- Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy; decrease corticosteroids gradually, if appropriate

Mepolizumab (Fasenra)

- Hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration
- Herpes zoster infections have occurred
- Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy
- Treat patients with pre-existing helminth infections before therapy

Reslizumab (Cinqair)

- Malignancy
- Reduction in Corticosteroid Dosage
- Parasitic (Helminth) Infection

BILLING/CODING INFORMATION:

HCPCS Coding

J0517	Injection, benralizumab, 1 mg
J2182	Injection, mepolizumab, 1 mg
J2361	Injection, depemokimab-ulaa, 1 mg
J2786	Injection, reslizumab, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity: Benralizumab

J82.83	Eosinophilic asthma
M30.1	Polyarteritis with lung involvement [Churg-Strauss]

ICD-10 Diagnosis Codes That Support Medical Necessity: Depemokimab

D72.110-D72.119	Hypereosinophilic syndrome [HES]
J32.0 - J32.9	Chronic sinusitis [with nasal polyposis]
J33.0 – J33.9	Nasal polyp
J44.0-J44.9	Other chronic obstructive pulmonary disease
J82.83	Eosinophilic asthma
M30.1	Polyarteritis with lung involvement [Churg-Strauss]

ICD-10 Diagnosis Codes That Support Medical Necessity: Mepolizumab

D72.110-D72.119	Hypereosinophilic syndrome [HES]
J32.0 - J32.9	Chronic sinusitis [with nasal polyposis]
J33.0 – J33.9	Nasal polyp
J44.0-J44.9	Other chronic obstructive pulmonary disease
J82.83	Eosinophilic asthma
M30.1	Polyarteritis with lung involvement [Churg-Strauss]

ICD-10 Diagnosis Codes That Support Medical Necessity: Reslizumab

J82.83	Eosinophilic asthma

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

FEV1:

- expiratory volume in 1 second

FVC:

- vital capacity

PEF:

- expiratory flow

Mild Intermittent Asthma:

- < or = to 2 times a week
- and normal PEF between exacerbations
- brief (from a few hours to a few days); intensity may vary
- symptoms < or = to 2 times a month
- or PEF > or = to 80% predicted
- variability < 20%

Mild Persistent Asthma:

- > 2 times a week but < 1 time a day
- may affect activity
- symptoms > 2 times a month
- or PEF > or = to 80% predicted
- variability 20 to 30 %

Moderate Persistent Asthma:

- symptoms
- symptoms > one time a week
- use of inhaled short-acting beta2-agonist
- may affect activity
- > or = to 2 times a week; may last days
- or PEF > 60% but less than 80% predicted
- variability > 30%

Severe Persistent Asthma:

- symptoms (i.e., coughing, dyspnea, wheezing)
- physical activity
- exacerbations
- nighttime symptoms
- or PEF < or = 60% predicted
- variability > 30%

RELATED GUIDELINES:

Omalizumab (Xolair®), 09-J0000-44

Tezepelumab-ekko (Tezspire), 09-J4000-13

Dupilumab (Dupixent®) Injection, 09-J2000-80

OTHER:

Table 1 - Low, medium and high ICS doses: adults/adolescents (GINA 2020, Box 3-6A)

Inhaled Corticosteroid	Total daily ICS dose (mcg)		
	Low	Medium	High
Beclomethasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclomethasone dipropionate (pMDI, extrafine particle, HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	100	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100-250	>250-500	>500
Mometasone furoate (DPI)	200	200	400
Mometasone furoate (pMDI, standard particle, HFA)	200-400	200-400	>400
DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; pMDI: pressurized metered dose inhaler (non-CFC)			

Table 2 - Low, medium and high ICS doses: children 6-11 years (GINA 2020, Box 3-6B)

Inhaled Corticosteroid	Total daily ICS dose (mcg)		
	Low	Medium	High
Beclomethasone dipropionate (pMDI, standard particle, HFA)	100-200	>200-400	>400
Beclomethasone dipropionate (pMDI, extrafine particle, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100-200	>200-400	>400
Budesonide (nebules)	250-500	>500-1000	>1000
Ciclesonide (pMDI, extrafine particle, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50	50	N/A
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100	100	200
DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; pMDI: pressurized metered dose inhaler (non-CFC)			

Table 3 - Low, medium and high ICS doses: children 5 years and younger (GINA 2020, Box 3-6B)

Inhaled Corticosteroid	Total daily ICS dose (mcg)		
	Low	Medium	High
Beclomethasone dipropionate (pMDI, standard particle, HFA)	100-200	>200-400	>400
Beclomethasone dipropionate (pMDI, extrafine particle, HFA)	50-100	>100-200	>200
Budesonide (nebules)	250-500	>500-1000	>1000
Ciclesonide (pMDI, extrafine particle, HFA)	N/A	N/A	N/A
Fluticasone furoate (DPI)	N/A	N/A	N/A
Fluticasone propionate (pMDI, standard particle, HFA)	100-200	>200-500	>500
Mometasone furoate (pMDI, standard particle, HFA)	100	100	200
DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; pMDI: pressurized metered dose inhaler (non-CFC)			

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/11/26.

GUIDELINE UPDATE INFORMATION:

03/15/26	New Medical Coverage Guideline: Merging MCGs 09-J2000-92, Benralizumab (Fasenra), 09-J2000-54, Mepolizumab (Fasenra), 09-J2000-63, Reslizumab (Cinqair) IV infusion; adding Depemokimab (Exdensur).
04/15/26	Revision to guideline; Updated Position Statement.
06/01/26	Revision: Added Drug Waste Reduction statement to the Position Statement.
07/01/26	Revision: Added HCPCS code J2361 and removed code J3590.