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Subject: Benralizumab (Fasenra)

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DESCRIPTION:

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.

Evidence-based practice guidelines or position statements from the American Academy of Allergy, Asthma and Immunology (AAAAI), European Respiratory Society/American Thoracic Society (ERS/ATS), Global Initiative for Chronic Obstructive Lung Disease (GOLD), and National Heart, Lung and Blood

Institute (NHLBI) have not been updated to include recommendations surrounding the use of benralizumab.

POSITION STATEMENT:

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

1. Severe eosinophilic asthma
    a. Member meets **ONE** of the following:
        i. 18 years of age and older: FEV1 is less than 80% of the predicted value
        ii. 12 to 17 years of age: FEV1 is less than 90% of the predicted value OR FEV1/FVC ratio is less than 0.8
    b. Member's symptoms remain uncontrolled or inadequately controlled despite treatment with at least ONE of the following:
        i. 12 months of high-dose inhaled corticosteroids (see table 1) used in combination with a long-acting beta agonist (e.g., formoterol fumarate (Foradil), salmeterol xinafoate (Serevent)) for a minimum of 3 months
        ii. 12 months of high-dose inhaled corticosteroids (see table 1) used in combination with a leukotriene modifier (e.g., montelukast, zafirlukast) for a minimum of 3 months
        iii. 12 months of high-dose inhaled corticosteroids (see table 1) used in combination with theophylline for a minimum of 3 months
        iv. 6 months of high-dose inhaled corticosteroids (see table 1) with daily oral corticosteroids used in combination with at least one additional controller medication (i.e., long-acting beta agonist, leukotriene modifier, theophylline) for a minimum of 3 months
    c. Member has a history of two or more exacerbations requiring systemic glucocorticoids while being treated with a high-dose inhaled corticosteroid in the past year
    d. Member's eosinophil count is at least 150 cells/microliter during the previous six weeks OR at least 300 cells/microliter during the previous year – laboratory documentation must be provided
    e. Benralizumab is not used in combination with mepolizumab (Nucala), omalizumab (Xolair) or reslizumab (Cinqair)
    f. Benralizumab is prescribed by a board certified (or board eligible) allergist, immunologist, or pulmonologist
    g. 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
    h. Member is 12 years of age or older
2. Eosinophilic granulomatosis with polyangiitis (EGPA)
    a. Member has relapsing or refractory disease
    b. Member's diagnosis is confirmed by the presence of **ALL** of the following:
        i. Asthma

ii. Eosinophilia (defined as eosinophils greater than 1,500/mm3 **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

c. Member's symptoms remain uncontrolled or inadequately controlled despite treatment with oral corticosteroids

d. Benralizumab is not used in combination with mepolizumab (Nucala), omalizumab (Xolair) or reslizumab (Cinqair)

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

f. 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

g. Member is 12 years of age or older

Approval duration: 12 months

Continuation of benralizumab (Fasenra) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of severe eosinophilic asthma or EGPA, OR the member has previously met all indication-specific initiation criteria
2. **ONE** of the following:
    a. Member has a beneficial response to treatment with benralizumab for severe eosinophilic asthma as demonstrated by at least **ONE** of the following and supported by documentation from the medical record:
        i. Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids)
        ii. Increase in predicted FEV1 from pretreatment baseline
        iii. Reduction in reported asthma-related symptoms, such as, asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing
    b. Member achieves remission of EGPA
3. Benralizumab is not used in combination with mepolizumab (Nucala), omalizumab (Xolair) or reslizumab (Cinqair)
4. Dose does not exceed 30 mg every 8 weeks

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 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

Dose Adjustments

- None

Drug Availability

- Injection: 30 mg/mL solution in a single-dose prefilled syringe

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Known hypersensitivity to benralizumab or excipients

Precautions/Warnings

- 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

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0517	Injection, benralizumab, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

J82	Pulmonary eosinophilia, not elsewhere classified
M30.1	Polyarteritis with lung involvement [Churg-Strauss]

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: BCBSF 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.

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:

Mepolizumab (Nucala), 09-J2000-54

Omalizumab (Xolair®), 09-J0000-44

Reslizumab (Cinqair®) IV infusion, 09-J2000-63

OTHER:

TABLE 1 **Definition of high daily dose of various inhaled corticosteroids in relation to patient age**	
Inhaled corticosteroid	**Threshold daily dose in mcg considered as high**

	Age 6–12 years	Age >12 years
Beclomethasone dipropionate	≥ 800 (DPI or CFC MDI)	≥ 2000 (DPI or CFC MDI)
	≥ 320 (HFA MDI)	≥ 1000 (HFA MDI)
Budesonide	≥ 800 (MDI or DPI)	≥ 1600 (MDI or DPI)
Ciclesonide	≥ 160 (HFA MDI)	≥ 320 (HFA MDI)
Fluticasone propionate	≥ 500 (HFA MDI or DPI)	≥ 1000 (HFA MDI or DPI)
Mometasone furoate	≥ 500 (DPI)	≥ 800 (DPI)
Triamcinolone acetonide	≥ 1200	≥ 2000
Notes: 1) Designation of high doses is provided from manufacturers' recommendations where possible. 2) As chlorofluorocarbon (CFC) preparations are being taken from the market, medication inserts for hydrofluoroalkane (HFA) preparations should be carefully reviewed by the clinician for the equivalent correct dosage. DPI: dry powder inhaler; MDI: metered-dose inhaler		

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/09/19.

GUIDELINE UPDATE INFORMATION:

01/15/18	New Medical Coverage Guideline.
02/15/18	Review of guideline; no changes.
06/15/18	Revision of guideline; updated ICD10 Codes.
01/01/19	Revision: HCPCS code updates. Added J0517 and removed J3590.
2/15/19	Review of guideline; updated position statement and references.