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Benralizumab

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: Benralizumab (Fasenra®) may be self-administered (see Policy Guidelines). For self-administered medications, please refer to the applicable pharmacy benefit plan.

Eosinophilic Asthma
Benralizumab (Fasenra®) **may be considered medically necessary** for the add-on maintenance treatment of severe eosinophilic asthma when the following criteria are met:

- Individual is 6 years of age and older; AND
- There is documented and current use of an inhaled corticosteroid (ICS) in combination with a long acting beta2-agonist (LABA), leukotriene receptor antagonist [LTRA], theophylline or long-acting muscarinic antagonist (LAMA); AND
- The individual has uncontrolled asthma while on control therapy as evidenced by 2 or more exacerbations requiring systemic glucocorticoids, frequent ER visits, or hospitalizations (see **NOTE 2**); AND
- Eosinophil count of the following:
  - 150 cells/µL or more in peripheral blood at screening; or
  - 300 cells/µL or more during the previous year.

NOTE 2: Individuals who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering off corticosteroids, will also meet this definition of severe asthma. For definition of uncontrolled asthma see Description section.

Eosinophilic Granulomatosis with Polyangiitis
Benralizumab (Fasenra®) **may be considered medically necessary** for individuals 18 years and older with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome) when one of the following criteria is met:

- Eosinophil count of 1,000 cells/microliter or greater; OR
- >10% leukocytes.

Benralizumab (Fasenra®) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications, including but not limited to:

- Relief of acute bronchospasm or status asthmaticus.

Policy Guidelines

Self-Administration

- Not applicable to plans regulated by the Illinois Department of Insurance or Medicare or Medicaid plans.
- The U.S. Food and Drug Administration (FDA) has deemed the drug(s) or biological product(s) in this medical policy to be appropriate for self-administration or for administration by a caregiver (i.e., not a healthcare professional), excluding individuals less than 12 years of age.

Description

Monoclonal antibodies (mAbs), omalizumab, mepolizumab, reslizumab, tezepelumab-ekko, and dupilumab are currently available for use as add-on treatment for severe asthma. These mAbs either bind or block the offending triggers to reduce allergic cascade and airway inflammation when eosinophils are the causative factor. Benralizumab (Fasenra®), an interleukin-5-receptor alpha directed cytolytic monoclonal antibody, offers a different mechanism of action that delivers rapid, direct, and nearly complete eosinophil depletion, with early and sustained efficacy responses. This treatment offers a different choice among the currently available therapies for severe asthma with an eosinophilic phenotype. (2) Monoclonal antibodies have also shown promise in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA). Trial results suggest that targeting eosinophils as a therapeutic strategy in EGPA can lead to a high percentage of patients with remission and a low percentage having relapse despite substantial reductions in the use of oral glucocorticoids, providing further evidence of the critical role of eosinophils in the pathophysiological processes underlying EGPA. (3)

Background
According to the Asthma and Allergy Foundation of America, asthma affects more than 27 million Americans. (4) This is 8.7 percent of adults and 6.2 percent of children per 2022 statistics. (5) Asthma has been increasing since the early 1980s in all age, sex, and racial groups. It is a chronic disease that causes the airways to become inflamed, making it hard to breathe. There is no cure for asthma. The best way to manage asthma is to avoid triggers, take medications to prevent symptoms, and prepare to treat asthma episodes if they occur. (4)

Asthma symptoms can appear when the individual is exposed to a trigger. A trigger is something that the individual is sensitive to, which causes swelling, mucous production and narrowing within the airways. Common asthma triggers are pollen, chemicals, extreme weather changes, smoke, dust mites, stress, and exercise.

Asthma comprises a number of distinct phenotypes, mainly eosinophilic and non-eosinophilic asthma, based on the cell-profile of induced sputum samples. Response to asthma treatments may be different based on the different types of inflammation.

<u>Definition of Uncontrolled Asthma</u>
At least one of the following:

- Poor symptom control: Asthma Control Questionnaire (ACQ) score consistently >1.5, Asthma Control Test (ACT) score <20 (or ‘‘not well controlled’’ by the National Asthma Education and Prevention Program (NAEPP) /Global Initiative for Asthma (GINA) guidelines);
- Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids (CS) (>3 days each) in the previous year;
- Serious exacerbations: at least 1 hospitalization, intensive care unit (ICU) stay, or mechanical ventilation in the previous year;
- Airflow limitation: after appropriate bronchodilator withhold, forced expiratory volume in 1 second (FEV_1) <80% predicted (in the face of reduced FEV_1/forced vital capacity [FVC] defined as less than the lower limit of normal). (6)

Eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome) is a rare antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The incidence of EGPA ranges between 0.5 and 4.2 cases per million people per year and its prevalence between 10 and 14 cases per million inhabitants globally. The disease usually evolves through three different phases: a prodromic ‘allergic’ phase, which can last for several years and is marked by asthma and chronic rhinosinusitis; an eosinophilic phase, during which eosinophilia and end-organ involvement appear; and a vasculitic phase, characterized by clinical manifestations due to small-vessel vasculitis (for example, mononeuritis multiplex and glomerulonephritis). However, these phases often overlap, do not necessarily develop in the aforementioned sequence and some patients do not manifest vasculitic complications. (7)

Benralizumab

Benralizumab is a humanized afucosylated, monoclonal antibody (IgG1, kappa) that directly binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα). The IL-5 receptor is expressed on the surface of eosinophils and basophils. Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. By binding to the IL-5Rα chain, benralizumab reduces eosinophils through antibody-dependent cell-mediated cytotoxicity. (1)

Regulatory Status

- On November 14, 2017, benralizumab (Fasenra®) was approved by the U.S. Food and Drug Administration (FDA) on as an add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.
- On April 11, 2024, the FDA expanded the previous indication for use as an add on-maintenance treatment for severe eosinophilic asthma to include the treatment of patients 6 to 11 years old.
- On September 18, 2024, the FDA approved benralizumab (Fasenra®) for the treatment of adult patients with EGPA. (8)

FDA Recommended Dosages (1)

Asthma

In adult and adolescent patients 12 years of age and older, dosing is 30 mg/mL administered subcutaneously every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter.

In pediatric patients 6 to 11 years of age, dosing is dependent on body weight. Dosage for benralizumab (Fasenra®) is 10 mg/0.5 mL if <35 kg and 30 mg/mL if ≥35 kg given subcutaneously every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter.

Eosinophilic Granulomatosis with Polyangiitis
Adult patient dosing is 30 mg/mL administered once every 4 weeks by subcutaneous injection.

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for benralizumab (Fasenra®).

Benralizumab (Fasenra®) for Severe Eosinophilic Asthma (1)
Adult and Adolescent Population Aged 12 Years and Older
The efficacy of Fasenra for the add-on maintenance treatment of severe asthma, and with an eosinophilic phenotype was evaluated in two randomized, double-blind, parallel-group, placebo-controlled, exacerbation trials, SIROCCO (NCT01928771) and CALIMA (NCT01914757), for 48 and 56 weeks in duration, respectively. Furthermore, the effects of Fasenra in the reduction of oral corticosteroid use and effect on lung function were evaluated in clinical trials, ZONDA (NCT02075255) and a 12-week lung function trial (NCT02322775), respectively.

SIROCCO and CALIMA were randomized, double-blind, parallel-group, placebo-controlled, exacerbation trials in patients 12 years of age and older and 48 and 56 weeks in duration, respectively. The trials randomized a total of 2,510 patients. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months, Asthma Control Questionnaire-6 (ACQ-6) score of 1.5 or more at screening, and reduced lung function at baseline (pre-bronchodilator forced expiratory volume in 1 second [FEV_1] below 80% in adults, and below 90% in adolescents) despite regular treatment with high dose inhaled corticosteroid (ICS) (SIROCCO) or with medium or high dose ICS (CALIMA) plus a long-acting beta agonist (LABA) with or without oral corticosteroids (OCS) and additional asthma controller medications. Patients were stratified by geography, age, and blood eosinophils count (≥300 cells/µL or <300 cells/µL). Fasenra administered once every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter as add-on to background treatment was evaluated compared to placebo.

All subjects continued their background asthma therapy throughout the duration of the trials.

ZONDA was a randomized, double-blind, parallel-group, OCS reduction trial in 220 adult patients with asthma. Patients were required treatment with daily OCS (7.5 to 40 mg per day) in addition to regular use of high-dose ICS and LABA with or without additional controller(s). The

trial included an 8-week run-in period during which the OCS was titrated to the minimum effective dose without losing asthma control. For the purposes of the OCS dose titration, asthma control was assessed by the investigator based on a patient's FEV_1, peak expiratory flow, nighttime awakenings, short-acting bronchodilator rescue medication use or any other symptoms that would require an increase in OCS dose. Baseline median OCS dose was similar across all treatment groups. Patients were required to have blood eosinophil counts greater than or equal to 150 cells/µL and a history of at least one exacerbation in the past 12 months. The baseline median OCS dose was 10 mg (range: 8 to 40 mg) for all 3 treatment groups (placebo, Fasenra every 4 weeks, and Fasenra every 4 weeks for the first 3 doses, and then once every 8 weeks).

While 2 dosing regimens were studied in SIROCCO, CALIMA, and ZONDA, the recommended dosing regimen is 30 mg Fasenra administered every 4 weeks for the first 3 doses, then every 8 weeks thereafter.

Exacerbations

The primary endpoint for SIROCCO and CALIMA was the rate of asthma exacerbations in patients with baseline blood eosinophil counts of greater than or equal to 300 cells/µL who were taking high-dose ICS and LABA. Asthma exacerbation was defined as a worsening of asthma requiring use of oral/systemic corticosteroids for at least 3 days, and/or emergency department visits requiring use of oral/systemic corticosteroids and/or hospitalization. For patients on maintenance oral corticosteroids, an asthma exacerbation requiring oral corticosteroids was defined as a temporary increase in stable oral/systemic corticosteroids for at least 3 days or a single depo-injectable dose of corticosteroids. In SIROCCO, 35% of patients receiving Fasenra experienced an asthma exacerbation compared to 51% on placebo. In CALIMA, 40% of patients receiving Fasenra experienced an asthma exacerbation compared to 51% on placebo (Table 1).

Table 1. Rate of Exacerbations, SIROCCO and CALIMA (ITT Population)[*]

Trial	**Treatment**	**Exacerbations per year**		
		Rate	**Difference**	**Rate Ratio (95% CI)**
All exacerbations				
SIROCCO	FASENRA[†] (n=267)	0.74	-0.78	0.49 (0.37, 0.64)
	Placebo (n=267)	1.52	--	--
CALIMA	FASENRA[†] (n=239)	0.73	-0.29	0.72 (0.54, 0.95)
	Placebo (n=248)	1.01	--	--
Exacerbations requiring hospitalization/emergency room visit				
SIROCCO	FASENRA[†] (n=267)	0.09	-0.16	0.37 (0.20, 0.67)
	Placebo (n=267)	0.25	--	--
CALIMA	FASENRA[†] (n=239)	0.12	0.02	1.23 (0.64, 2.35)
	Placebo (n=248)	0.10	--	--
Exacerbations requiring hospitalization				
SIROCCO	FASENRA[†] (n=267)	0.07	-0.07	0.48 (0.22, 1.03)

	Placebo (n=267)	0.14	--	--
CALIMA	FASENRA[†] (n=239)	0.07	0.02	1.48 (0.65, 3.37)
	Placebo (n=248)	0.05	--	--

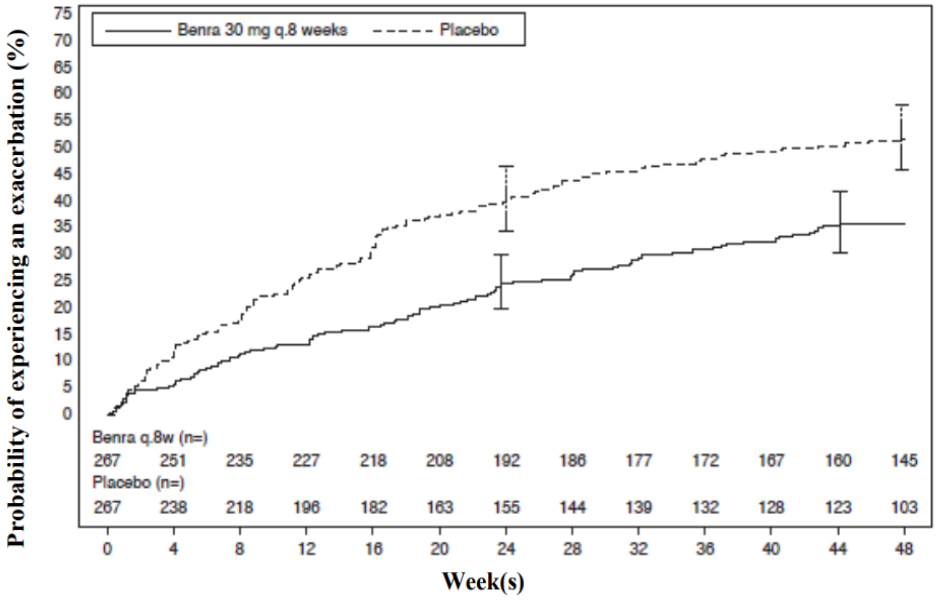
CI: confidence interval; ITT: intention to treat.

[*] Baseline blood eosinophil counts of greater than or equal to 300 cells/µL and taking high-dose ICS.

[†] Fasenra 30 mg administered every 4 weeks for the first 3 doses, and every 8 weeks thereafter.

The time to first exacerbation was longer for the patients receiving Fasenra compared with placebo in SIROCCO (Figure 1). Similar findings were seen in CALIMA.

Figure 1. Kaplan-Meier Cumulative Incidence Curves for Time to First Exacerbation, SIROCCO



Subgroup analyses from SIROCCO and CALIMA identified patients with a higher prior exacerbation history and baseline blood eosinophil count as potential predictors of improved treatment response. Reductions in exacerbation rates were observed irrespective of baseline peripheral eosinophil counts; however, patients with a baseline blood eosinophil count ≥300 cells/µL showed a numerically greater response than those with counts <300 cells/µL. In both trials patients with a history of 3 or more exacerbations within the 12 months prior to Fasenra randomization showed a numerically greater exacerbation response than those with fewer prior exacerbations.

Oral Corticosteroid Reduction

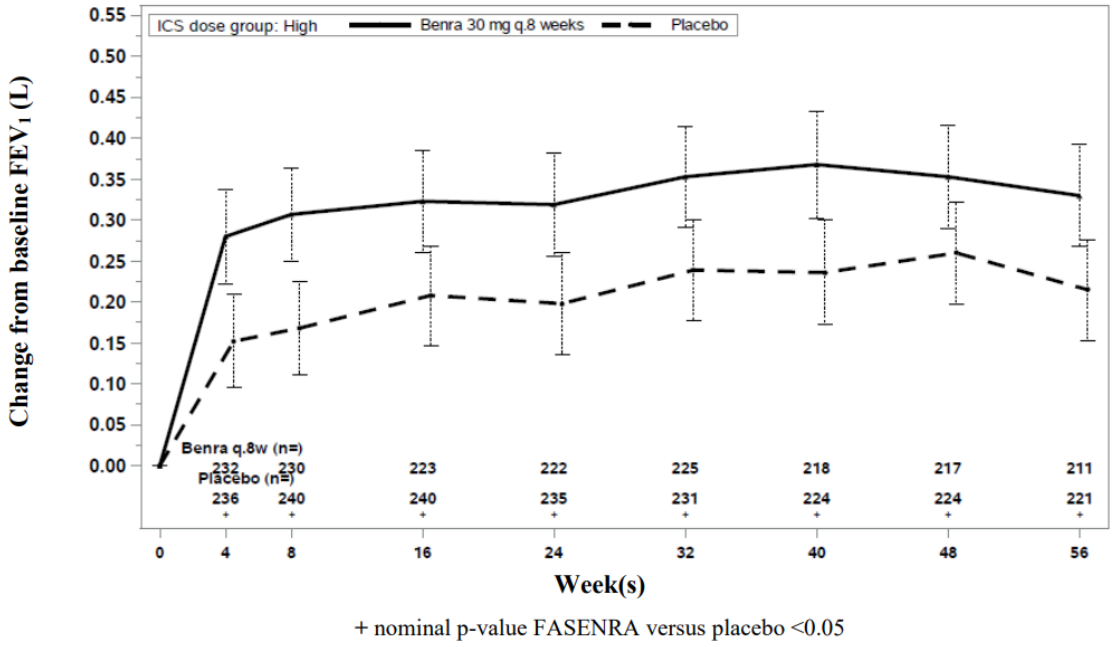
ZONDA evaluated the effect of Fasenra on reducing the use of maintenance oral corticosteroids in adult patients with asthma. The primary endpoint was percent reduction from baseline of the final OCS dose during Weeks 24 to 28, while maintaining asthma control (see definition of asthma control in trial description). Compared to placebo, patients receiving Fasenra achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. The median percent reduction in daily OCS dose from baseline was 75% in patients

receiving Fasenra (95% confidence interval [CI]: 60, 88) compared to 25% in patients receiving placebo (95% CI: 0, 33). Reductions of 50% or higher in the OCS dose were observed in 48 (66%) patients receiving Fasenra compared to those receiving placebo 28 (37%). The proportion of patients with a mean final dose less than or equal to 5 mg at Weeks 24 to 28 was 59% for Fasenra and 33% for placebo (odds ratio 2.74, 95% CI: 1.41, 5.31). Only patients with an optimized baseline OCS dose of 12.5 mg or less were eligible to achieve a 100% reduction in OCS dose during the study. Of those patients, 52% (22 of 42) receiving Fasenra and 19% (8 of 42) on placebo achieved a 100% reduction in OCS dose. Exacerbations resulting in hospitalization and/or ER visit were also assessed as a secondary endpoint. In this 28-week trial, patients receiving Fasenra had 1 event while those on placebo had 14 events (annualized rate 0.02 and 0.32, respectively; rate ratio of 0.07, 95% CI: 0.01, 0.63).

Lung Function

Change from baseline in mean FEV_1 was assessed in SIROCCO, CALIMA, and ZONDA as a secondary endpoint. Compared with placebo, Fasenra provided consistent improvements over time in the mean change from baseline in FEV_1 (Figure 2 and Table 2).

Figure 2. Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L), CALIMA



ICS: inhaled corticosteroid; FEV_1: forced expiratory volume in 1 second.

Table 2. Change from Baseline in Mean Pre-Bronchodilator FEV_1 (L) at End of Trial*

Trial	Difference from Placebo in Mean Change from Pre-Bronchodilator Baseline FEV_1 (L) (95% CI)
SIROCCO	0.159 (0.068, 0.249)
CALIMA	0.116 (0.028, 0.204)
ZONDA	0.112 (-0.033, 0.258)

CI: confidence interval; FEV_1: forced expiratory volume in 1 second.

* Week 48 in SIROCCO, Week 56 in CALIMA, Week 28 in ZONDA.

Subgroup analyses also showed greater improvements in FEV_1 in patients with higher baseline blood eosinophil counts and more frequent prior exacerbation history.

The clinical program for Fasenra also included a 12-week, randomized, double-blind, placebo-controlled lung function trial conducted in 211 adult patients with mild to moderate asthma. Patients were treated with placebo or benralizumab 30 mg SC every 4 weeks for 3 doses. Lung function, as measured by the change from baseline in FEV_1 at Week 12 was improved in the benralizumab treatment group compared to placebo.

Patient Reported Outcomes
The ACQ-6 and Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12) were assessed in SIROCCO, CALIMA, and ZONDA. The responder rate for both measures was defined as improvement in score of 0.5 or more as threshold at the end of SIROCCO, CALIMA, and ZONDA (48, 56, and 28 weeks, respectively). In SIROCCO, the ACQ-6 responder rate for Fasenra was 60% vs 50% placebo (odds ratio 1.55; 95% CI: 1.09, 2.19). In CALIMA, the ACQ-6 responder rate for Fasenra was 63% vs 59% placebo (odds ratio 1.16; 95% CI: 0.80, 1.68). In SIROCCO, the responder rate for AQLQ(S)+12 for Fasenra was 57% vs 49% placebo (odds ratio 1.42; 95% CI: 0.99, 2.02), and in CALIMA, 60% Fasenra vs 59% placebo (odds ratio of 1.03; 95% CI: 0.70, 1.51). Similar results were seen in ZONDA.

Pediatric Patients 6 to 11 Years of Age
Use of Fasenra in pediatric patients aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in pediatric patients aged 6 to 11 years. The effectiveness of Fasenra in pediatric patients 6 to 11 years of age is extrapolated from efficacy in three clinical trials (SIROCCO, CALIMA, and ZONDA) with support from pharmacokinetic analysis and pharmacodynamic response in pediatric patients aged 6 to 11 years compared to adults and adolescents. TATE is a 48-week, open-label, pharmacokinetic and pharmacodynamic trial that was conducted in 28 patients aged 6 to 11 years (mean age 9 years; 6-8 years, n=11; 9-11 years n=17; 32% female, White 29%, Asian 32%, Black or African American 29%) with severe asthma, and with an eosinophilic phenotype.

Based upon the pharmacokinetic data from TATE, a subcutaneous dose of 10 mg (patients <35 kg) and subcutaneous dose of 30 mg (patients ≥35 kg) of benralizumab administered every 4 weeks for the first 3 doses, then every 8 weeks thereafter in patients aged 6 to 11 years was determined to have similar or higher exposure, respectively, to adults and adolescents administered a subcutaneous dose of 30 mg with the same dosing regimen. The pharmacodynamic response observed in TATE for pediatric patients aged 6 to 11 years was similar to that observed in adults and adolescents. No new safety signals were observed from TATE and safety for the higher drug exposure is supported by safety data from SIROCCO and CALIMA in adults and adolescents, and ZONDA in adults, who received 30 mg of Fasenra every 4 weeks for 1 year.

Benralizumab (Fasenra®) for Eosinophilic Granulomatosis with Polyangiitis (1)

The efficacy of Fasenra for eosinophilic granulomatosis with polyangiitis (EGPA) was evaluated in a randomized, double-blind, active-controlled, noninferiority clinical trial (MANDARA [NCT04157348]) of 52-weeks duration. The trial enrolled a total of 140 adults aged 18 years and older with EGPA. Patients were required to have asthma, eosinophilia (1,000 cells/uL or >10% of leukocytes) and a history of relapsing or refractory disease treated with background prednisolone/prednisone with or without immunosuppressive therapy. Patients were randomized to receive Fasenra 30 mg administered subcutaneously every 4 weeks or mepolizumab 300 mg administered subcutaneously every 4 weeks in addition to continued background therapy. Starting at Week 4, the oral corticosteroid (OCS) dose was tapered at the discretion of the investigator. The MANDARA trial was a non-inferiority trial and was not designed to assess whether Fasenra was superior to mepolizumab. The pre-specified noninferiority (NI) margin was a treatment difference of -25%. The secondary endpoints (accrued duration of remission, relapse, OCS reduction and the asthma control questionnaire-6) were not included in the pre-specified multiple testing procedure for statistical significance.

Remission

The primary endpoint in MANDARA was the proportion of patients in remission, defined as Birmingham Vasculitis Activity Score (BVAS)=0 (no active vasculitis) plus prednisolone/ prednisone dose ≤4 mg/day, at both Week 36 and Week 48. The BVAS is a clinician-completed tool, that is divided into 9 organ-based systems, to assess clinically active vasculitis that would likely require treatment, after exclusion of other causes. As shown in Table 3, Fasenra demonstrated noninferiority to mepolizumab for the primary endpoint of remission and the components of remission.

Table 3. Remission and Components of Remission in Patients with EGPA in MANDARA Trial

	Remission (OCS≤4 mg/day + BVAS=0)		**OCS≤4 mg/day**		**BVAS=0**	
	FASENRA[*] N=70	**Mepo[†] N=70**	**FASENRA[*] N=70**	**Mepo[†] N=70**	**FASENRA[*] N=70**	**Mepo[†] N=70**
Patients in remission at both Weeks 36 and 48						
Patients, n (%)[‡]	41 (59)	40 (57)	43 (62)	41 (58)	58 (83)	59 (84)
Differences in remission rate (%)[‡] (95% CI)	2.7 (-13, 18)[§]	-- --	4.1 (-11, 19)	-- --	-1.2 (-13, 11)	-- --

EGPA: eosinophilic granulomatosis with polyangiitis; OCS: oral corticosteroid; BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval.

N=number of patients in analysis.

[*] Fasenra 30 mg administered subcutaneously every 4 weeks.

[†] Mepolizumab (Mepo) 300 mg administered subcutaneously every 4 weeks.

[‡] Model adjusted percentages.

§ NI margin -25% with 2.5% 1 sided significance level. Since the lower bound of the 95% CI for the treatment difference was >-25%, effectiveness of Fasenra was demonstrated to be noninferior to the effectiveness of mepolizumab.

Using an alternative remission definition of BVAS=0 plus prednisolone/prednisone ≤7.5 mg/day, consistent efficacy between groups for these endpoints was observed.

Accrued Duration of Remission

Total accrued duration of remission was similar in Fasenra compared to mepolizumab (odds ratio 1.4, 95% CI: 0.75, 2.5). Results for accrued duration of remission are shown in Table 4. The proportion of patients achieving remission within the first 24 weeks of treatment and remaining in remission through Week 52 was 42% for Fasenra and 37% for mepolizumab (difference in responder rate 5.5%, 95% CI: -9.3, 20). This result was not statistically significant as there was no pre-specified multiple testing procedure.

Table 4. Accrued Duration of Remission in Patients with EGPA in the MANDARA Trial

	Remission (OCS≤4 mg/day + BVAS=0)		**OCS≤4 mg/day**		**BVAS=0**	
	FASENRA* N=70	**Mepo† N=70**	**FASENRA* N=70**	**Mepo† N=70**	**FASENRA* N=70**	**Mepo† N=70**
Accrued duration over 52 weeks‡, n (%)						
0 weeks§	9 (13)	15 (21)	9 (13)	12 (17)	0	0
>0 to <12 weeks	12 (17)	10 (14)	10 (14)	12 (17)	0	2 (3)
12 to <24 weeks	8 (11)	8 (11)	9 (13)	8 (11)	2 (3)	2 (3)
24 to <36 weeks	21 (30)	19 (27)	19 (27)	18 (26)	6 (9)	7 (10)
≥36 weeks	20 (29)	18 (26)	23 (33)	20 (29)	62 (89)	59 (84)
Odds ratio¶ (95% CI)	1.4 (0.75, 2.5)	-- --	1.4 (0.74, 2.5)	-- --	1.5 (0.54, 4.2)	-- --

EGPA: eosinophilic granulomatosis with polyangiitis; OCS: oral corticosteroid; BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval.

* Fasenra 30 mg administered subcutaneously every 4 weeks.

† Mepolizumab (Mepo) 300 mg administered subcutaneously every 4 weeks.

‡ Not included in the pre-specified multiple testing procedure for statistical significance.

§ Did not achieve remission at any point.

¶ An odds ratio >1 favors Fasenra. This result was not statistically significant as there was no pre-specified multiple testing procedure.

Relapse

The hazard ratio for time to first relapse (defined as worsening related to vasculitis, asthma, or sino-nasal symptoms requiring an increase in dose of corticosteroids or immunosuppressive therapy or hospitalization) was 0.98 (95% CI: 0.53, 1.8). Relapse was observed in 30% of patients on Fasenra and 30% of patients on mepolizumab. The annualized relapse rate was 0.50 for patients receiving Fasenra versus 0.49 for patients receiving mepolizumab (rate ratio 1.0, 95% CI: 0.56, 1.9). The types of relapse were consistent for patients receiving Fasenra or mepolizumab.

Oral Corticosteroid Reduction

During Weeks 48 to 52, a 100% reduction in the OCS dose was observed in 41% of patients receiving Fasenra compared to 26% of those receiving mepolizumab (difference 16%, 95% CI: 0.67, 31). During Weeks 48 to 52, reductions of 50% or higher were observed in 86% of patients receiving Fasenra compared to 74% of those receiving mepolizumab (difference 12%, 95% CI: -0.57, 25). These results were not statistically significant as there was no pre-specified multiple testing procedure.

Asthma Control Questionnaire-6 (ACQ-6)

ACQ-6 is a 6-item questionnaire that is completed by the patient to measure the adequacy of asthma control and change in asthma control. The ACQ-6 responder rate during Weeks 48 to 52 (defined as a decrease in score of 0.5 or more compared with baseline) was 42% for Fasenra and 48% for mepolizumab (difference -6.2%, 95% CI: -19, 6.2).

Summary of Evidence

Based on the clinical studies provided to the U.S. Food and Drug Administration (FDA) for approval, benralizumab (Fasenra®) may be considered medically necessary for the FDA labeled indication for add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma, and with an eosinophilic phenotype. It is not to be used for relief of acute bronchospasm or status asthmaticus. Benralizumab (Fasenra®) is also approved to treat adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) (formerly known as Churg–Strauss syndrome). Benralizumab (Fasenra®) is considered experimental, investigational and/or unproven for all other non-FDA approved indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0517

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. FDA – Benralizumab (Fasenra) Product Label (9/2024). U.S. Food and Drug Administration. Available at <https://www.accessdata.fda.gov> (accessed July 14, 2025).

Other:

2. Fitzgerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 trial. Lancet. Oct 29, 2016; 388(10056):2128-2141. PMID 27609406
3. Wechsler ME, Nair P, Terrier B, et al. Benralizumab versus mepolizumab for eosinophilic granulomatosis with polyangiitis. N Engl J Med. Mar 7 2024; 390(10):911-921. PMID 38393328.
4. Asthma and Allergy Foundation of America. Asthma. 2022. Available at <https://www.aafa.org> (accessed July 17, 2025).
5. Centers for Disease Control and Prevention - Asthma Surveillance Data (August 20, 2024). Available at <https://www.cdc.gov> (accessed July 17, 2025).
6. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014; 43:343-373. PMID 24337046
7. Emmi G, Bettiol A, Gelain E, et al. Evidence-Based Guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. Nat Rev Rheumatol. Jun 2023; 19(6):378-393. PMID 37161084
8. Drugs.com. Fasenra FDA Approval History. October 2, 2024. Available at <https://www.drugs.com> (accessed July 14, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2026	Document updated with literature review. The following changes were made to Coverage: 1) Added NOTE 1; 2) Revised coverage criteria for severe eosinophilic asthma; 3) Added Coverage for adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis per FDA label; 4) Revised experimental, investigational and/or unproven statement to read "Benralizumab (Fasenra®) is considered experimental, investigational and/or

	unproven for all other non-Food and Drug Administration approved indications, including but not limited to: Relief of acute bronchospasm or status asthmaticus". References 3, 7 and 8 added; others updated/removed.
04/15/2025	Document updated. The following change was made to Coverage: Added "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 of a formulation that cannot be self-administered is considered not medically necessary unless the patient has a physical or cognitive limitation that makes the utilization of a self-administered formulation unsafe or otherwise not feasible, as demonstrated by BOTH of the following: Inability to self-administer the medication, AND lack of caregiver or support system for assistance with administration of self-administered products." No new references added.
03/15/2024	Document updated with literature review. The following change was made to Coverage: Modified medically necessary coverage criteria. No new references added; other(s) updated.
07/01/2023	Reviewed. No changes.
12/01/2022	Document updated with literature review. The following change was made to Coverage: Added tezepelumab-ekko [Tezspire] and dupilumab [Dupixent]) to this statement: Will not be used in combination with another antiasthmatic monoclonal antibody agent (e.g., reslizumab [Cinqair], omalizumab [Xolair], mepolizumab [Nucala]. References revised; none added.
09/01/2021	Reviewed. No changes.
10/01/2020	Document updated with literature review. The following changes were made to Coverage: 1) Modified medically necessary conditional criteria; 2) Removed documentation requirements; and 3) Modified NOTE 1 to read: "Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering off corticosteroids, will also meet this definition of severe asthma. For definition of uncontrolled asthma see Description section." The following references were added/updated: 1-4. Title changed from "Benralizumab (Fasenra)".
12/01/2018	New medical document. Benralizumab (Fasenra™) may be considered medically necessary for the add-on maintenance treatment of eosinophilic phenotype (severe) asthma when the patient meets ALL of the following criteria (see NOTE 1 for documentation required): 12 years of age or older; and Blood eosinophilic count is 150 cells/µL or higher prior to initiation of this therapy; and Reduced lung function at baseline (pre-bronchodilator FEV_1 below 80% for all age groups); and History of 2 or more severe asthmatic exacerbations requiring systemic corticosteroid treatment within the past 12 months; and History of current and regular treatments with high-dose inhaled corticosteroids AND long-acting ß- (beta-) agonists, with or without

	oral corticosteroid therapy and additional asthma-controlled medications. NOTE 1: Documentation should include ALL of the following information: Eosinophil count, and Lung function (FEV_1), and History of asthmatic exacerbations, and Current medications (specifically inhaled corticosteroids and long-acting ß- [beta-] agonists). Benralizumab (Fasenra™) is considered experimental, investigational and/or unproven when the above criteria are not met, and for all other indications, including but not limited to: Treatment of other eosinophilic conditions, or Relief of acute bronchospasm or status asthmaticus.