Subject: Fasenra (benralizumab)	**Original Effective Date:** 7/10/2018
Policy Number: MCP-319	**Revision Date(s):**
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MCPC Approval Date: 7/10/2018	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Fasenra (benralizumab)** as add-on maintenance treatment of severe asthma in patients 12 years and older with an eosinophilic phenotype when appropriate criteria are met.

The intent of the Fasenra (benralizumab) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies.

- Asthma is a common, chronic respiratory disease in which the lung's airways become inflamed and narrowed. While the majority of patients with asthma can be treated effectively with the proper use of maintenance medications, patients with severe asthma are refractory to current standards of treatment, including oral corticosteroids.
  - Generally, eosinophils circulate in the peripheral blood and are found in peripheral tissue and respiratory mucosa, and levels increase in the presence of acute inflammation. Eosinophils are recruited into the airway in allergic asthma by the action of cytokines and chemokines, such as interleukin-5 (IL-5), a potent eosinophil activator that facilitates recruitment into tissues. **IL-5 antagonists** block IL-5 from binding to eosinophils, resulting in the inhibition of eosinophil growth and differentiation, recruitment, activation, and survival.
  - **Eosinophilic asthma** is a subset of **severe asthma** that is characterized by increased eosinophil counts. Because increased eosinophilia correlates with worse disease, mediators of the eosinophil pathway, such as interleukin-5 (IL-5), are targets for preventing eosinophil-mediated inflammation.
  - **Cinqair (reslizumab), Nucala (mepolizumab), and Fasenra (benralizumab)** are indicated for the add-on maintenance treatment of severe eosinophilic asthma and are indicated for use in severe eosinophilic asthma. Used as maintenance therapy, these agents may benefit individuals with eosinophilic asthma.

- The anti-asthmatic monoclonal antibodies are subdivided into two subclasses: Anti-IgE antibodies and Anti-IL-5 antibodies.
    1) **Anti-IL-5 monoclonal antibodies: Cinqair (reslizumab), Nucala (mepolizumab), Fasenra (benralizumab)**
        - IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils (a cell type associated with inflammation and an important component of the pathogenesis of asthma).
        - Benralizumab, a humanized monoclonal antibody (IgG1, kappa), is an interleukin-5 antagonist. Benralizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of benralizumab action in asthma has not been definitively established.
        - Cinqair (reslizumab), Nucala (mepolizumab), and Fasenra (benralizumab) are indicated for the add-on maintenance treatment of severe eosinophilic asthma. **These agents have been evaluated in combination with other asthma treatments and are <u>not</u> utilized as monotherapy.**
        - Fasenra (benralizumab) and Nucala (mepolizumab) have been shown to be safe and effective for use in **children 12 years of age and older**. Cinqair (reslizumab) is indicated for **adults ages 18 year and older.** There are currently no generic products available for these agents.
        - Due to the associated risks of anaphylaxis and complicated administration, all three agents (benralizumab, mepolizumab, reslizumab) must be **administered by a healthcare professional**.
    2) **Anti-immunoglobulin E (IgE) monoclonal antibodies: Xolair (omalizumab)**
        - Xolair (omalizumab) is the only anti-IgE antibody currently available and is FDA-approved for the treatment of moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen in addition to chronic idiopathic urticaria.

- **Fasenra (benralizumab)**
    - Benralizumab is the third anti-IL-5 antibody to be approved for treatment of severe eosinophilic asthma; mepolizumab (Nucala) and reslizumab (Cinqair), which target IL-5 itself, were approved earlier
    - FDA approved in combination with other asthma medications as add-on maintenance treatment of severe asthma in patients 12 years and older with an eosinophilic phenotype
        - Benralizumab is not approved for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus
        - Administered via **subcutaneous injection** [similar to Nucala (mepolizumab)]; while Cinqair (reslizumab) is administered via **IV infusion only**
        - FDA Approval was based on results obtained from Phase III clinical trials **SIROCCO, CALIMA, and ZONDA** from the WINDWARD program [*which included six phase III trials SIROCCO, CALIMA, ZONDA, BISE, BORA, and GREGALE*]

- The two pivotal trials, **SIROCCO and CALIMA,** are randomized, double-blinded, parallel-group, placebo-controlled trials designed to evaluate the efficacy and safety of subcutaneous administration of Benralizumab (fixed 30-mg dose) for up to 56 weeks in exacerbation-prone adult and adolescent patients 12 years of age and older. [Bleecker ER, et al. (SIROCCO Study); FitzGerald JM, et al. (CALIMA)]
    - The results of the studies demonstrated that Fasenra 30mg was well-tolerated and achieved the primary endpoint.
    - 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
    - Demonstrated up to a 51% reduction in asthma exacerbations, significant improvement in lung function, and a 75% reduction in daily oral steroid use.

- Phase III clinical trial **ZONDA** was conducted to evaluate the effect of a 30mg dose of Fasenra administered in an eight four-week dosing regimen for 28 weeks in adult patients with severe, uncontrolled eosinophilic asthma, who received high-dose ICS or LABA and oral corticosteroids (OCS) with or without additional asthma controllers.
  - The results of the study showed that the addition of Fasenra (30mg) to standard-of-care allowed patients dependent on OCS to significantly decrease or withdraw steroids while maintaining asthma control.
  - Benralizumab significantly reduced the glucocorticoid dose from baseline, but found no significant improvement in FEV1 at 28 weeks. Patients received benralizumab 30 mg every 4 weeks or benralizumab 30 mg every 4 weeks for the first 3 doses and then every 8 weeks and all patients continued background asthma therapy
  - The primary efficacy endpoint of demonstrating statistically significant and clinically relevant reduction in daily maintenance OCS was achieved. The study showed that the patients treated with Fasenra achieved a median reduction in OCS dose of 75%.

- The most common adverse effects associated with benralizumab were headache (8% vs 6% with placebo), pyrexia (3% vs 2%), pharyngitis (5% vs 3%), hypersensitivity reactions (3% vs 3%), and injection-site reactions (2.2% vs 1.9%); for most, incidences were similar to placebo. [Bleecker ER, et al. (SIROCCO Study); FitzGerald JM, et al. (CALIMA)]

- Antidrug antibodies may develop during therapy; however, there was no evidence of an association between antidrug antibodies and changes in efficacy or safety of benralizumab

- **Comparative Efficacy**
  - No head-to-head trials comparing benralizumab with other anti-IL-5 antibodies mepolizumab (Nucala) and reslizumab (Cinqair) are available.
  - Head-to-head trials comparing anti-IL-5 antibodies to omalizumab (Xolair) have not been conducted at this time also; therefore, the comparative efficacy and safety are unknown at this time.
  - **Benralizumab is given about half as often as mepolizumab (Nucala) and reslizumab (Cinqair), however costs about twice as much per dose, so treatment costs are similarly high with all three drugs.**
  - Concurrent use of Fasenra (benralizumab) with Xolair (omalizumab): The efficacy and safety of Fasenra (benralizumab) in combination with Xolair (omalizumab) have not been established.
    Xolair is a recombinant humanized immunoglobulin G (IgG) monoclonal antibody indicated for use in adults and adolescents (aged ≥ 12 years) with moderate to severe persistent asthma and who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.
  - Fasenra (benralizumab) and Xolair (omalizumab) have different indications for use and the two drugs are not interchangeable. While there is a possibility that patients with severe asthma may meet criteria for treatment with both omalizumab (allergic asthma) and benralizumab (eosinophilic asthma), there is currently no clinical trials evaluating combination therapy with two monoclonal antibodies. Therefore, such use is not recommended.
  - **There are no comparative trials among the agents in this class to suggest preference of one agent over another for the treatment of severe asthma.**
  - Mepolizumab (Nucala) and reslizumab (Cinqair) are humanized IL-5 antagonist monoclonal antibodies that reduce eosinophils, while benralizumab (Fasenra) targets IL-5 receptor alpha, resulting in nearly complete depletion of eosinophil**s. It is unknown if the difference in binding sites has a clinically significant impact on efficacy or safety among these 3 drugs.**

CLASSIFICATION: Interleukin-5 Receptor Antagonists; Monoclonal Antibodies (Respiratory)

FDA INDICATIONS

ASTHMA Add-on maintenance treatment of severe asthma in adults and children ≥12 years of age with an eosinophilic phenotype

Limitations of use: Not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus

Available as: 30mg/mL pre-filled syringe solution for injection

FDA Approved: November 2017

Black Box Warning: None at the time of this writing

REMS: None at the time of this writing.
REMS is not required for benralizumab, mepolizumab, or reslizumab

RECOMMENDATIONS/COVERAGE CRITERIA

Fasenra (benralizumab) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

❒ Prescribed by, or in consultation with, a board-certified asthma specialist (allergist, immunologist, pulmonologist) or physician experienced in the management of asthma. Submit consultation notes if applicable.

NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]
Clinical **documented** diagnosis of (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*): [ALL]

❒ Diagnosis of **severe** asthma with an eosinophilic phenotype or predominantly eosinophil-driven disease also described as "airway eosinophilia"
- *Benralizumab is not approved for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.*

❒ Blood eosinophil counts *in the absence of other potential causes associated with elevated peripheral eosinophil counts. Laboratory documentation required: [ONE]

**Clinically important pulmonary disease other than asthma (e.g. active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome)*

❍ Greater than or equal to 150 cells/microliter* at initiation of therapy (within 6 weeks of request)

❍ Greater than or equal to 300 cells/microliter* in the prior 12 months

**1 microliter (µL) is equal to 1 cubic millimeter (mm3)*

Appendix 4: Blood Eosinophil Counts

- *The SIROCCO and CALIMA trials were powered for efficacy analysis in patients with baseline blood eosinophil count (BEC) ≥ 300 cells/µL. In addition, the ZONDA trial found Fasenra to significantly reduce oral corticosteroid dose in patients with baseline BEC ≥ 150 cells/µL.*

❒ Persistent airflow obstruction as indicated a pre-treatment/pre-bronchodilator FEV1 less than 80% predicted

3. Age/Gender/Other restrictions [ALL]

- ❒ 12 years of age or older
  - *Safety and efficacy of benralizumab have not been established in patients younger than 12 years of age*
- ❒ Member is a non-smoker OR smoking cessation has been at least 6 months
- ❒ Underlying conditions or triggers for asthma or pulmonary disease are being maximally managed

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ Exacerbation(s) or hospitalization(s) *within the past 12 months* documented by **ONE (1)** of the following: [ONE]
  - ❍ TWO (2) or more exacerbations requiring treatment with systemic corticosteroid (intramuscular, intravenous, or oral) despite the use of high-dose inhaled corticosteroids in the past 12 months
    OR
  - ❍ Two-fold increase or greater in the dose of systemic corticosteroid treatment for asthma exacerbations
    OR
  - ❍ Asthma worsens upon tapering of oral corticosteroid therapy
    OR
  - ❍ ONE (1) or more asthma-related urgent treatment (such as hospitalization, emergency room visit, unscheduled physician's office visit) within the previous 12 months
    OR
  - ❍ Mechanical ventilation in the past 12 months
    OR
  - ❍ Poor symptom control indicated by ACQ score consistently greater than 1.5 or ACT score consistently less than 20)
    OR
  - ❍ Forced expiratory volume in 1 second (FEV1) < 80% predicted **OR** FEV1/forced vital capacity (FVC) < 0.80

❒ Symptoms inadequately controlled (as documented in criteria above) after an **adherent** regimen of at **least 3 months** of the following COMBINATION THERAPY: **[A OR B]**

A. High-dose Inhaled Corticosteroid (appropriately adjusted for age) **AND** a second controller drug (i.e. long-acting beta agonist, leukotriene receptor antagonist) with or without oral corticosteroid **[ONE: 1 OR 2]**

1) High-dose inhaled corticosteroid* (or maximally tolerated dose) [*e.g. Aerospan (flunisolide), Alvesco (ciclesodine), Asmanex (mometasone furoate), Flovent HFA (fluticasone propionate), Pulmicort (budesonide), QVAR (beclomethasone dipropionate HFA)*]

[Appendix 2: Estimated Comparative Daily Dosages for ICS in ≥ 12 years of age and Adults]

AND

ONE (1) ADDITIONAL ASTHMA CONTROLLER MEDICATION

- Long-acting beta-agonists (LABA) [e.g., salmeterol products (Serevent)]
- Leukotriene Receptor Antagonists (LTRAs) [e.g., montelukast tablets/granules (Singulair, generics), zafirlukast tablets (Accolate)]
- Inhaled long-acting muscarinic antagonist (LAMA) [e.g. tiotropium bromide inhalation spray (Spiriva, Respimat)]
- Theophylline (Theo-24, Uniphyl, TheoChron ER, generics)

OR

2) Combination inhaled corticosteroid/long-acting beta2-agonist product* at maximum recommended doses of ICS/LABA combinations (or maximally tolerated dose) [i.e. fluticasone propionate/salmeterol (Advair), mometasone/formoterol (Dulera), budesonide/formoterol (Symbicort)]
**Maximum recommended doses of ICS/LABA combinations (not an all-inclusive list):*

- *Fluticasone/salmeterol (Advair): Advair Diskus 500 mcg/50 mcg twice daily, or 2 inhalations of Advair HFA 230 mcg/21 mcg twice daily*
- *Budesonide/formoterol (Symbicort): 160 mcg/4.5 mcg twice daily*
- *Mometasone/formoterol (Dulera): 200 mcg/5 mcg twice daily*

NOTE: Use of a combination inhaler containing both an ICS and a LABA (#2) fulfills the requirement for both criteria (in #1)

MOLINA STAFF: Verify pharmacy claims data for **compliance** with the combination therapy above (member is currently receiving this regimen) AND **for rescue medication** use within the last 90 days. For new members to Molina Healthcare, confirm rescue medications use in medical chart history. **Non-compliance, which can be documented by review of the prescription fill history, would not constitute therapeutic failure.**

B. Labeled contraindication(s) or clinical intolerance(s) to the agent(s) in the above criterion [i.e. adverse effects from high-dose inhaled corticosteroid or long-term risks of adverse effects from high dose ICS or oral corticosteroids *(i.e. Cataracts in patients > 40 years of age; Glaucoma; Recurrent thrush; Dysphonia; Growth inhibition, after evaluation by Endocrine Consult; Diagnosis of osteoporosis, treatment resistant to FDA approved osteoporosis treatment)*]

NOTE

- *The pivotal trials defined severe asthma as 2 or more exacerbations of asthma despite regular use of high-dose ICS plus an additional controller (e.g., LABA or LTRA) with or without oral corticosteroids. Although the CALIMA trial included patients receiving medium-dose ICS, Fasenra was not shown to have an effect on annual exacerbation rate, pre-bronchodilator forced expiratory volume in 1 second, or total asthma symptom score in those patients.*
- *Inhaled corticosteroids (ICS) are the preferred treatment option for all severities according to current clinical guidelines for the treatment of persistent asthma,*
- *The 2014 International European Respiratory Society (ERS)/American Thoracic Society (ATS) Guidelines on Definition, Evaluation, and Treatment of Severe Asthma define severe asthma as patients with a confirmed asthma diagnosis which requires treatments with ICS plus long-acting beta-2 agonist (LABA) or leukotriene modifier/theophylline therapy to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy.*
- *As with other severe forms of asthma, the International Guidelines treatment for severe asthma, including eosinophilic asthma, is high dose ICS plus a LABA, leukotriene modifier or theophylline and/or continuous systemic corticosteroids as background therapy.*

❒ Fasenra (benralizumab) is **not** being prescribed as: [ANY]

❍ Monotherapy for asthma [*Fasenra (benralizumab) must be prescribed as add-on maintenance to be used in combination with other medications for long-term control of asthma*]

❍ Concurrent therapy use with other monoclonal antibodies typically used to treat asthma: Xolair (omalizumab) **OR** other IL-5 inhibitors [Cinqair (reslizumab), Nucala (mepolizumab)]

- *Member with severe asthma may meet criteria for treatment with both omalizumab (allergic asthma) and benralizumab (eosinophilic asthma); however, there is currently no clinical trials evaluating combination therapy with two monoclonal antibodies and this combination has not been studied and no evidence or relevant clinical data supporting the concurrent use of both agents are available thus such use cannot be recommended and will not be authorized.*

5. Contraindications*/Exclusions/Discontinuations

**No formal drug interaction studies have been conducted and none are anticipated based on benlizumab's mechanism of action. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the clearance of benralizumab.*

Authorization will not be granted if ANY of the following conditions apply [ANY]

❒ Non-FDA approved indications [such as: urticaria and other eosinophilic conditions; severe allergic asthma without documentation of severe eosinophilia]
- ❍ Aspirin-exacerbated respiratory disease (AERD)
- ❍ Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome)
- ❍ Hypereosinophilic syndromes (other than severe eosinophilic asthma as indicated), including:
- ❍ Angiolymphoid hyperplasia
- ❍ Atopic dermatitis
- ❍ Eosinophilic esophagitis
- ❍ Nasal polyposis
- ❍ Acute bronchospasm and/or status asthmaticus

❒ Non-FDA approved dosing regimen or route of administration (Subcutaneous injection on upper arm, thigh, or abdomen)

❒ Severe hypersensitivity reaction to benralizumab (Fasenra) or any of its excipients (i.e., L-histidine; L-histidine hydrochloride monohydrate; polysorbate 20; alpha, alpha-trehalose dihydrate)

❒ Known or suspected infection

❒ Helminth infections: Members with pre-existing helminth infections should undergo treatment of the infection prior to initiation of reslizumab therapy

Exclusions [ANY]

- ❒ Concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma.
- ❒ Fasenra (benralizumab) therapy initiated with samples AND member does not meet policy criteria for coverage prior to the start of therapy. Coverage will not be authorized upon completion of samples.
- ❒ Concurrent use with Xolair (omalizumab) [If currently treated with Xolair (omalizumab), then Xolair (omalizumab) must be discontinued when starting Fasenra (benralizumab)]
- ❒ Concurrent use with any other IL-5 inhibitor [Nucala (mepolizumab), Cinqair (reslizumab)]

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Fasenra (benralizumab) may be authorized for continuation of therapy if meet ALL of the following criteria are met: [ALL]

1. Initial Coverage Criteria

- ❒ Member currently meets ALL initial coverage criteria

- ❒ Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually. The prescribing physician should periodically reassess the need for continuation of therapy based on the member's disease severity and level of asthma control. Continuation of therapy requires submission of relevant medical records or chart notes documenting continued efficacy.

2. Compliance

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including:
  - ❍ Adherent to the prescribed medication regimen
  - ❍ Tolerance to therapy
  - ❍ No severe adverse reactions or drug toxicity

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

  NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

3. Labs/Reports/Documentation required [ALL]

Documentation of significant reduction in corticosteroid dosage or asthma exacerbations as demonstrated by:

- ❒ Fasenra (benralizumab) has resulted in clinical improvement as documented by ONE (1) or more of the following from baseline [ONE]
  - ❍ Improvement in lung function (increase in percent predicted FEV1 or PEF) from pre-treatment baseline
  - ❍ Decreased utilization of rescue medications
  - ❍ Decreased frequency of exacerbations (defined as worsening of asthma that requires increase in inhaled corticosteroid dose or treatment with systemic corticosteroids)
  - ❍ Decreased frequency of unscheduled clinic, urgent care or emergency department visits
  - ❍ Reduction in reported symptoms: chest tightness, coughing, shortness of breath, nocturnal wakening wheezing, sustained improvement in Asthma Control Test (ACT) scores
  - ❍ Reduction use of ICS, leukotriene or beta agonist therapy
  - ❍ Reduction in reported symptoms (decrease in asthma symptom score), as evidenced by decreases in frequency or magnitude of ONE (1) or more of the following symptoms: [ONE]
    - o Asthma attacks
    - o Chest tightness or heaviness
    - o Coughing or clearing throat
    - o Shortness of breath; Difficulty taking deep breath or difficulty breathing out
    - o Wheezing/heavy breathing
    - o Sleep disturbance, night wakening, or symptoms upon awakening

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or absence of unacceptable toxicity from the drug
  **Unacceptable toxicity may include (but not limited to) symptoms of anaphylaxis or severe hypersensitivity reactions (bronchospasm, hypotension, syncope, urticara, and/or angioedema), parasitic (helminth) infection, etc.*
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❒ Non-FDA approved indications [such as: urticaria and other eosinophilic conditions; severe allergic asthma without documentation of severe eosinophilia]
  - ❍ Aspirin-exacerbated respiratory disease (AERD)
  - ❍ Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome)
  - ❍ Hypereosinophilic syndromes (other than severe eosinophilic asthma as indicated), including:
  - ❍ Angiolymphoid hyperplasia
  - ❍ Atopic dermatitis
  - ❍ Eosinophilic esophagitis
  - ❍ Nasal polyposis
  - ❍ Acute bronchospasm and/or status asthmaticus
- ❒ Non-FDA approved dosing regimen or route of administration (Subcutaneous injection on upper arm, thigh, or abdomen)
- ❒ Severe hypersensitivity reaction to benralizumab (Fasenra) or any of its excipients (i.e., L-histidine; L-histidine hydrochloride monohydrate; polysorbate 20; alpha, alpha-trehalose dihydrate)
- ❑ Known or suspected infection
- ❑ Helminth infections: Pre-existing helminth infections should undergo treatment of the infection prior to initiation of reslizumab therapy

Exclusions [ANY]

- ❒ Concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma.
- ❒ Fasenra (benralizumab) therapy initiated with samples AND member does not meet policy criteria for coverage prior to the start of therapy. Coverage will not be authorized upon completion of samples.
- ❒ Concurrent use with Xolair (omalizumab) [If currently treated with Xolair (omalizumab), then Xolair (omalizumab) must be discontinued when starting Fasenra (benralizumab)]
- ❒ Concurrent use with any other IL-5 inhibitor [Nucala (mepolizumab), Cinqair (reslizumab)]

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. **Recommended Dosage [ALL]**

- ❒ Severe asthma, Add-on maintenance in patients with eosinophilic phenotype [Ages 12 and older]: 30 mg SC every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter
  - Pediatric: Safety and efficacy of benralizumab have not been established in patients younger than 12 years of age

2. Authorization Limit [ALL]

- ❒ Quantity limit [ALL]
  30 mg single dose prefilled syringe
  - ❍ Load: 30 mg (1 syringe) every 28 days for 3 doses
  - ❍ Maintenance: 30 mg (1 syringe) every 56 days
  - ❍ Max quantity: 30 mg every 8 weeks
- ❒ Duration of initial authorization: **3 months**
- ❒ Continuation of treatment: Re-authorization is required every **6 months** to determine effectiveness of therapy and continued need based on documented positive clinical response such as improvement in selected markers of asthma control, such as symptoms severity, frequency of rescue treatments, oral steroid requirements, and frequency of urgent outpatient visits and/or hospitalization. Refer to 'Continuation of Therapy' section.

3. Route of Administration [ALL]

- ❒ Fasenra (benralizumab) is considered a **provider-administered** medication and the prescribing information for benralizumab states the drug should be administered by a health care professional in line with clinical practice. However, one trial found that most patients and caregivers could administer benralizumab using the prefilled syringe in their home environment (Ferguson GT, et al 2017)
- ❒ Fasenra (benralizumab) should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis. Patients should be monitored for hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, and rash. Most hypersensitivity reactions occurred within hours of administration, but in some cases onset was delayed (i.e., days). If hypersensitivity occurs, benralizumab should be discontinued.
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

COVERAGE EXCLUSIONS

This policy only addresses the indication of Fasenra (benralizumab) as add-on maintenance treatment of severe asthma in patients 12 years and older with an eosinophilic phenotype when appropriate criteria are met.

All other uses of Fasenra (benralizumab) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- ❒ Non-FDA approved indication [i.e. urticaria and other eosinophilic conditions; severe allergic asthma without documentation of severe eosinophilia]

- ❒ Younger than 12 years of age
  - *Fasenra (benralizumab) is not indicated for use in children younger than 12 years of age. Safety and efficacy of benralizumab have not been established in this age group.*

- ❒ Non-FDA approved dosing regimen(s)

- ❒ Individuals who have had previous anaphylactic reaction to Fasenra (benralizumab)

- ❒ Fasenra (benralizumab) therapy initiated with samples and the member does not meet policy criteria for coverage (as outlined above) prior to the start of therapy. Coverage will not be authorized upon completion of samples.

- ❒ Concurrent use with omalizumab (Xolair)
  - *In the clinical trials, patients who had previously received omalizumab were eligible for inclusion into the study if they had not received omalizumab for at least 6 months. The washout period was to avoid any potential carry over from omalizumab which has a long half-life. There are no recommendations in the labeling requiring a waiting period before starting reslizumab; however, providers should be aware of any potential adverse drug events.*

- ❒ Concurrent use with other IL-5 inhibitors [*Cinqair (reslizumab), Nucala (mepolizumab)*]

- ❒ Administration in any manner other that which is FDA-approved (subcutaneous) will not be authorized

SUMMARY OF CLINICAL EVIDENCE

Severe asthma is defined as Global Initiative for Asthma (GINA) steps 4-5 asthma requiring treatment with guideline-suggested medications (such as high-dose inhaled corticosteroids and long-acting beta agonists, a leukotriene modifier, or theophylline for the preceding year, or systemic corticosteroids for ≥ 50% of the previous year) to prevent it from becoming uncontrolled, or which remains uncontrolled despite therapy. *Dynamed 2018*

Prevalence of asthma in the United States (U.S.) continues to rise. An estimated 7.8% (24.6 million) Americans have asthma with approximately 10% to 20% in poor control (CDC: Asthma Data, Statistics, and Surveillance; Wakford HH et al.)

Severe asthma is reported to account for about 5%-10% of the total asthma population, but the exact prevalence is unknown due to heterogeneity in presentation of severe asthma and prior lack of a standardized definition.

PIVOTAL TRIALS

The efficacy and safety of benralizumab, given in combination with high-dose inhaled corticosteroids (ICSs) and long-acting beta2-agonists (LABAs), was evaluated in three multi-center, randomized, double-blind, parallel-group, placebo-controlled, phase III clinical trials: CALIMA (NCT01914757) (FitzGerald, 2016), SIROCCO (NCT01928771) (Bleecker, 2016), and ZONDO (NCT02075255) (Nair, 2017).

The two pivotal trials, SIROCCO and CALIMA, are randomized, double-blinded, parallel-group, placebo-controlled trials designed to evaluate the efficacy and safety of subcutaneous administration of Benralizumab (fixed 30-mg dose) for up to 56 weeks in exacerbation-prone adult and adolescent patients 12 years of age and older. The patients were dependent on high-dose inhaled corticosteroids (ICS) plus long-acting β2-agonist (LABA) with a baseline blood eosinophil count of more than or equal to 300 cells/microliter.

A total of 2,510 patients (1,204 in SIROCCO and 1,306 in CALIMA) received standard-of-care medicine (including high-dosage inhaled corticosteroids and long-acting beta2-agonists) and were randomized globally to receive either Benralizumab 30 mg every four weeks; Benralizumab 30 mg every four weeks for the first three doses followed by 30 mg every eight weeks; or placebo administered via subcutaneous injection using an accessorized pre-filled syringe.

SIROCCO (48 weeks) and **CALIMA (56 weeks)** are randomized, double-blind, placebo-controlled, phase 3 trials, evaluated the efficacy of add-on therapy with benralizumab 30 mg SC every 4 weeks or every 4 weeks for the first 3 doses and then every 8 weeks in patients 12-75 years old with severe uncontrolled asthma and baseline blood eosinophil counts ≥300 cells/μL who were taking a high-dose inhaled corticosteroid and a long-acting $beta_2$-agonist (LABA), with or without additional asthma-controller medications. Patients in both trials must have had ≥2 asthma exacerbations requiring either systemic corticosteroid treatment or a temporary increase in their usual maintenance oral corticosteroid dosage within one year before enrollment. In both trials, benralizumab significantly reduced annual asthma exacerbation rates and improved forced expiratory volume in one second (FEV_1). It also modestly improved patient-reported asthma symptom scores. [SIROCCO trial (Bleecker ER, et al, 2016); CALIMA trial (FitzGerald JM, et al, 2016)]

Benralizumab vs Placebo

Efficacy and Safety Study of Benralizumab Added to High-dose Inhaled Corticosteroid plus LABA in Patients with Uncontrolled Asthma

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase III Efficacy and Safety Study of Benralizumab Added to High-dose Inhaled Corticosteroid Plus Long-acting β2 Agonist in Patients With Uncontrolled Asthma **(SIROCCO)** (Bleecker ER, et al, 2016)

Summary:

ADULTS: Benralizumab 30 mg once every 4 weeks (n=399), or benralizumab 30 mg once every 4 weeks for the first 3 doses followed by once every 8 weeks (n=398) significantly reduced the annual exacerbation rate ratio by 45% and 51% compared with placebo (n=407) in the 48-week randomized SIROCCO trial in adults and adolescents (12 years or older) with blood eosinophils 300 cells/mcL or greater and uncontrolled severe asthma receiving inhaled corticosteroids plus long-acting beta agonist therapy with or without oral corticosteroids. Benralizumab also significantly increased the mean change in prebronchodilatory FEV1 (0.345 and 0.398 L vs 0.239 L). Total asthma symptom score was significantly improved with benralizumab every 8 weeks compared with placebo (-1.3 vs -1.04), but was not significant in the benralizumab every 4 week group. All patients continued background asthma therapy

Limitations: Long-term efficacy and safety (greater than 1 year) remains to be proven.

Subjects

1,205 subjects (12 to 75 years of age) with asthma requiring treatment with medium- or high-dosage ICS plus LABA for at least 1 year prior to enrollment

- At least 2 documented asthma exacerbations requiring systemic corticosteroid treatment or a temporary increase in the usual maintenance dosages of oral corticosteroids within 1 year of enrollment; treatment with ICS plus LABA with or without oral corticosteroids and additional asthma controllers for at least 3 months;
- Pre-bronchodilator forced expiratory volume in the first second of expiration (FEV_1) less than 80% predicted (less than 90% predicted for patients 12 to 17 years of age) at screening;
- Documented post-bronchodilator reversibility of at least 12% and at least 200 mL in FEV_1 within 12 months; and an Asthma Control Questionnaire, 6-question version (ACQ-6) score of at least 1.5
- Patients 12 to 17 years of age could have been treated with medium- or high-dosage ICSs, while patients 18 years or older had to be treated with high-dosage ICS.
- Exclusion criteria included history of anaphylaxis with any biologic drug; clinically important pulmonary disease other than asthma; and helminthic parasitic infection diagnosed within 24 weeks of enrollment that had either not been treated or did not respond to standard-of-care treatment. Mean age was 49 years; 95% were 18 years or older; 66% were female; 73% were white, 13% were Asian, 4% were black, and 19% were Hispanic or Latino; mean eosinophil count was 472 cells/mcL, mean pre-bronchodilator FEV_1 was 1.67 L, and ACQ-6 score was 2.77 to 2.87.

Study Design

- Subjects were randomized 1:1:1 to subcutaneous benralizumab 30 mg either:
  - every 4 weeks (Q4W group),
  - every 8 weeks (first 3 doses given 4 weeks apart) (Q8W group), or
  - placebo using a prefilled syringe for 48 weeks
- Adolescent patients enrolled at sites in the European Union (EU) were randomly assigned to subcutaneous benralizumab 30 mg every 8 weeks (first 3 doses given every 4 weeks) or placebo.
- Randomization was stratified by age group (adult or adolescent), country (in adults) or region (within the EU and outside the EU for adolescents), and blood eosinophil counts.
- Patients maintained their background asthma control regimen at a stable dosage throughout the study. SABAs were allowed as rescue drugs to control worsening asthma symptoms.

- The intention-to-treat cohort was used for the efficacy evaluation. The study was conducted at 374 centers in Australia, Brazil, Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russia, South Africa, South Korea, Spain, Turkey, United Kingdom, United States, and Vietnam.

Results

Primary End Point(s)

- Patients with baseline blood eosinophil counts at least 300 cells/mcL receiving benralizumab had a decreased annual asthma exacerbation rate compared with placebo at week 48. The rate ratio (RR) versus placebo was 0.55 (95% confidence interval [CI], 0.42 to 0.71; *P*<0.0001) for the Q4W cohort and 0.49 (95% CI, 0.37 to 0.64; *P*<0.0001) for the Q8W cohort.
- Patients with baseline blood eosinophil counts less than 300 cells/mcL receiving benralizumab also had a decreased annual asthma exacerbation rate compared with placebo at week 48. The RR versus placebo was 0.7 (95% CI, 0.5 to 1; *P*=0.0471) for the Q4W cohort and 0.83 (95% CI, 0.59 to 1.16; *P*=0.2685) for the Q8W cohort.

Secondary End Point(s)

- The benralizumab Q8W cohort had reduced asthma exacerbations leading to emergency department visits or hospital admissions compared with placebo treatment (RR, 0.37; 95% CI, 0.2 to 0.67; *P*=0.001); in the Q4W cohort, the RR was 0.61 (95% CI, 0.37 to 1.01; *P*=0.0529).
- Difference (least squares [LS] mean change from baseline) versus placebo in prebronchodilator FEV_1 at week 48 in patients with baseline blood eosinophil counts at least 300 cells/mcL was 0.106 L (95% CI, 0.016 to 0.196; *P*=0.0215) with benralizumab Q4W and 0.159 L (95% CI, 0.068 to 0.249; *P*=0.0006) with benralizumab Q8W. In patients with baseline blood eosinophil counts less than 300 cells/mcL, the difference was –0.025 L (95% CI, –0.134 to 0.083; *P*=0.6438) with benralizumab Q4W and 0.102 L (95% CI, 0.003 to 0.208; *P*=0.568) with benralizumab Q8W.
- Difference (LS mean change from baseline) versus placebo in total asthma symptom score at week 48 in patients with baseline blood eosinophil counts at least 300 cells/mcL was –0.08 (95% CI, –0.27 to 0.12; *P*=0.442) with benralizumab Q4W and –0.25 (95% CI, –0.45 to –0.06; *P*=0.0118) with benralizumab Q8W. In patients with baseline blood eosinophil counts less than 300 cells/mcL, the difference was –0.2 (95% CI, –0.48 to 0.08; *P*=0.1688) with benralizumab Q4W and –0.29 (95% CI, –0.57 to –0.01; *P*=0.0431) with benralizumab Q8W.
- Difference (LS mean change from baseline) versus placebo in ACQ-6 score at week 48 in patients with baseline blood eosinophil counts at least 300 cells/mcL was –0.15 (95% CI, –0.34 to 0.04; *P*=0.1107) with benralizumab Q4W and –0.29 (95% CI, –0.48 to –0.1; *P*=0.0028) with benralizumab Q8W. In patients with baseline blood eosinophil counts less than 300 cells/mcL, the difference was 0 (95% CI, –0.27 to 0.27; *P*=0.9903) with benralizumab Q4W and –0.22 (95% CI, –0.48 to 0.05; *P*=0.1066) with benralizumab Q8W.

Adverse Events

The most common adverse events were worsening asthma (105 [13%] in 797 benralizumab-treated participants vs. 78 [19%] of 407 placebo-treated participants) and nasopharyngitis (93 [12%] vs. 47 [12%]).

Reference: ClinicalTrials.gov Identifier: NCT01928771 at https://clinicaltrials.gov/ct2/show/NCT01928771

Efficacy and Safety Study of Benralizumab in Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist **(CALIMA)** (FitzGerald JM, et al, 2016)

Summary: Benralizumab 30 mg once every 4 weeks (n=241), or benralizumab 30 mg once every 4 weeks for the first 3 doses followed by once every 8 weeks (n=239) significantly reduced the annual exacerbation rate ratio by 36% and 28% compared with placebo (n=248) in the 56-week randomized CALIMA trial in adults and adolescents (12 years or older) with blood eosinophils 300 cells/mcL or greater and uncontrolled severe asthma receiving high-dose inhaled corticosteroids plus long-acting beta agonist therapy with or without oral corticosteroids. Benralizumab also significantly increased the mean change in prebronchodilatory FEV1 (0.34 and 0.33 vs 0.215 L). Total asthma symptom score was significantly improved with benralizumab every 8 weeks compared with placebo (-1.4 vs -1.16), but was not significant in the benralizumab every 4 week group. All patients continued background asthma therapy

Limitations: Long-term efficacy and safety (greater than 1 year) remains to be proven.

Subjects

- 1,306 subjects (12 to 75 years of age) with severe asthma requiring treatment with medium- to high-dosage ICS plus LABA for at least 12 months prior to enrollment; at least 2 asthma exacerbations in the last 12 months that required use of a systemic corticosteroid or temporary increase in the usual maintenance dosage of oral corticosteroids; treatment with ICS (at least 500 mcg/day of fluticasone propionate dry powder formulation or equivalent total daily dosage) plus LABA for 3 months or more prior to enrollment, with or without oral corticosteroids and additional asthma controllers; a prebronchodilator FEV_1 less than 80% predicted (less than 90% predicted for patients 12 to 17 years of age)
- ACQ-6 score of 1.5 or greater; and postbronchodilator reversibility in FEV_1 of 12% or greater and 200 mL or greater in FEV_1 within 12 months
- Mean age was 49 years; 96% were 18 years and older; 62% were female; 84% were white, 3% were black, 12% were Asian, and 23% were Hispanic or Latino; mean eosinophil count was 472 cells/mcL, local eosinophil count was 370 to 400 cells/mcL, mean prebronchodilator FEV_1 was 1.76 L, and ACQ-6 score was 2.69 to 2.75.

Study Design

- The study consisted of a 4-week screening and run-in phase, randomization at week 0, treatment period (weeks 0 to 56), and a final follow-up visit at week 60.
- Randomization was stratified by ICS dosage at baseline (medium or high), age group (adult or adolescent), country (in adults) or region (within the EU and outside the EU for adolescents), and blood eosinophil counts (less than 300 cells/mcL and 300 cells/mcL or greater).
- Patients were randomized 1:1:1 to benralizumab 30 mg once every 4 weeks (Q4W group), benralizumab 30 mg once every 8 weeks (first 3 doses were given every 4 weeks) (Q8W group), or placebo.
- Patients 12 to 17 years of age enrolled in the EU were randomly assigned (1:1) to receive benralizumab 30 mg every 8 weeks or placebo.
- All study medication was given by subcutaneous injection at rotating administration sites using a prefilled syringe.
- Patients continued to receive their background asthma controller medications at a stable dosage throughout the study. SABAs could be used as rescue medications.
- The intention-to-treat cohort was used for the efficacy evaluation. The study was conducted at 303 sites in the United States, Canada, Germany, Sweden, Poland, Romania, Ukraine, Argentina, Chile, Japan, and the Philippines.

Results

Primary End Point(s)

- Patients with baseline blood eosinophil counts at least 300 cells/mcL receiving benralizumab had a decreased annual asthma exacerbation rate compared with placebo at week 56. The RR versus placebo was 0.64 (95% CI, 0.49 to 0.85; *P*=0.0018) for the Q4W cohort and 0.72 (95% CI, 0.54 to 0.95; *P*=0.0188) for the Q8W cohort.
- Patients with baseline blood eosinophil counts less than 300 cells/mcL receiving benralizumab also had a decreased annual asthma exacerbation rate compared with placebo at week 56. The RR versus placebo was 0.64 (95% CI, 0.45 to 0.92; *P*=0.015) for the Q4W cohort and 0.6 (95% CI, 0.42 to 0.86; *P*=0.0048) for the Q8W cohort.

Secondary End Point(s)

- Annual rate of asthma exacerbations requiring emergency department visit or hospital admission did not differ between benralizumab and placebo; RR was 1.23 (95% CI, 0.64 to 2.35; *P*=0.5381) for the Q8W cohort and 0.93 (95% CI, 0.48 to 1.82; *P*=0.8366) for the Q8W cohort.
- Difference (LS mean change from baseline) versus placebo in prebronchodilator FEV_1 at week 56 in patients with baseline blood eosinophil counts at least 300 cells/mcL was 0.125 L (95% CI, 0.037 to 0.213; *P*=0.0054) for benralizumab Q4W and 0.116 L (95% CI, 0.028 to 0.204; *P*=0.0102) for benralizumab Q8W. In patients with baseline blood eosinophil counts less than 300 cells/mcL, the difference was 0.064 L (95% CI, –0.049 to 0.176; *P*=0.2676) with benralizumab Q4W and –0.015 L (95% CI, –0.127 to 0.096; *P*=0.7863) with benralizumab Q8W.
- Difference (LS mean change from baseline) versus placebo in total asthma symptom score at week 56 in patients with baseline blood eosinophil counts at least 300 cells/mcL was –0.12 (95% CI, –0.32 to 0.07; *P*=0.2241) with benralizumab Q4W and –0.23 (95% CI, –0.43 to –0.04; *P*=0.0186) with benralizumab Q8W. In patients with baseline blood eosinophil counts less than 300 cells/mcL, the difference was –0.16 (95% CI, –0.44 to 0.13; *P*=0.2868) with benralizumab Q4W and 0.01 (95% CI, –0.28 to 0.29; *P*=0.9663) with benralizumab Q8W.
- Difference (LS mean change from baseline) versus placebo in ACQ-6 score at week 56 in patients with baseline blood eosinophil counts at least 300 cells/mcL was –0.19 (95% CI, –0.38 to –0.01; *P*=0.0425) with benralizumab Q4W and –0.25 (95% CI, –0.44 to –0.07; *P*=0.0082) with benralizumab Q8W. In patients with baseline blood eosinophil counts less than 300 cells/mcL, the difference was –0.24 (95% CI, –0.51 to 0.03; *P*=0.0776) with benralizumab Q4W and –0.1 (95% CI, –0.37 to 0.16; *P*=0.4488) with benralizumab Q8W.

Adverse Events

The most common adverse events were nasopharyngitis (n= 90 [21%] in the Q4W group; n=79 [18%] in the Q8W group; and, n=92 [21%] in the placebo group) and worsening asthma (n=61 [14%] in the Q4W group; n=47 [11%] in the Q8W group; and, n=68 [15%] in the placebo group).

Reference: ClinicalTrials.gov Identifier: NCT01914757 at https://clinicaltrials.gov/ct2/show/NCT01914757

Efficacy and Safety Study of Benralizumab to Reduce OCS Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus LABA and Chronic OCS Therapy

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients With Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy **(ZONDA)** (Nair P, et al, 2017)

Nair and colleagues (2017) performed a 28-week clinical trial (ZONDO) evaluating if benralizumab was effective as an oral glucocorticoid-sparing therapy in individuals with severe uncontrolled asthma requiring treatment with high-dosage ICS plus a LABA, chronic oral corticosteroid use, and blood eosinophil counts of at least 150 cells/μL.

Summary

ADULTS: Benralizumab significantly decreased the glucocorticoid dose from baseline by 75% compared with 25% with placebo while maintaining asthma control in the 28-week randomized ZONDA trial (N=220) in adults with severe asthma with persistent blood eosinophilia despite treatment with high-dose inhaled glucocorticoids, long-acting beta-2 agonists,

and oral glucocorticoids. Patients received benralizumab 30 mg every 4 weeks or benralizumab 30 mg every 4 weeks for the first 3 doses and then every 8 weeks and all patients continued background asthma therapy. Benralizumab was also associated with a greater percentage of patients discontinuing glucocorticoid therapy (56% and 52% vs 19%), however at 28 weeks, there was no significant difference between either benralizumab group and placebo in the FEV1 before bronchodilation.

Comments: Unlike the previous studies, the ZONDA trial was designed to compare benralizumab with placebo for maintenance of asthma control and ability to allow for a reduction in the oral glucocorticoid dose in adult patients who had severe asthma with persistent blood eosinophilia despite treatment with high-dose inhaled glucocorticoids, LABAs, and oral glucocorticoids.

Limitations: Study duration was only 28 weeks and did not assess whether the reduction in oral glucocorticoid dose could remain unchanged over the course of several years without an increase in asthma exacerbations.

Patients

- 220 asthma patients; 28-week oral corticosteroid reduction trial
- Blood eosinophil counts greater than or equal to 150 cells/mcL and a history of at least one exacerbation in the past 12 months
- Asthma that had been treated with medium- to high-dose inhaled glucocorticoid and LABA for at least 12 months before enrollment and with high-dose inhaled glucocorticoid and LABA for at least 6 months before enrollment
- Received oral glucocorticoid therapy for at least 6 continuous months directly before enrollment (7.5 to 40 mg per day) --in addition to regular use of high-dose ICS and LABA with or without additional controller(s) to maintain asthma control
- Mean age was 51 years, 61% were female, median oral glucocorticoid dose at trial entry and at the end of the run-in phase was 10 mg/day, mean inhaled glucocorticoid dose was approximately 1,000 to 1,200 mcg/day, leukotriene receptor antagonists were used by about 37%, mean number of exacerbations in the previous year was 3, and mean blood eosinophil count at baseline was 575 cells/mcL

Intervention

- The study consisted of a run-in phase that included stabilization of the oral glucocorticoid dose, a randomized intervention period, and a follow-up visit.
- Any patient receiving an oral glucocorticoid other than prednisone or prednisolone was switched to an equivalent dose of oral prednisone or prednisolone.
- During the run-in phase (week –8 to –1), the oral glucocorticoid dose was adjusted to the minimum dose that could be received without loss of asthma control. After the run-in phase, patients were randomized 1:1:1 to receive subcutaneous injections of benralizumab 30 mg every 4 weeks (Q4W group), benralizumab 30 mg every 4 weeks for 3 doses and then every 8 weeks (Q8W group), or placebo every 4 weeks.
- During the intervention period from week 0 to 4 (i.e., induction phase), patients continued receiving the oral glucocorticoid dose established during the run-in phase. From week 4 to 24 (i.e., dose-reduction phase), the dose of the oral glucocorticoid was reduced every 4 weeks by 2.5 to 5 mg. Patients receiving an oral glucocorticoid dose of 12.5 mg/day or less at the end of the run-in phase (baseline) were eligible for a 100% dose reduction (discontinuation of oral glucocorticoid therapy). If a patient's asthma worsened during the maintenance phase (week 24 to 28), the final dose was deemed to be 1 adjustment increment greater than the dose at which the worsening started.
- Except for the oral glucocorticoid therapy, patients continued their original background asthma therapy of high-dose inhaled glucocorticoid and LABA plus any other asthma controller medications (e.g., leukotriene modifiers, long-acting muscarinic antagonists, theophylline) unchanged throughout the trial. SABAs were permitted as rescue medications. No additional asthma controller drug was initiated during the study unless it was used as a rescue drug to treat an exacerbation.

Results

Primary End Point(s)

- Median reduction from baseline in the final oral glucocorticoid dose was 75% in patients who received either of the benralizumab regimens and 25% in patients who received placebo (P<0.001 for both comparisons). A 90% or more reduction from baseline in final oral glucocorticoid dose occurred in 33% of the benralizumab Q4W group, 37% of the benralizumab Q8W group, and 12% of the placebo group.
- A 75% or more reduction from baseline in final oral glucocorticoid dose occurred in 53% of the benralizumab Q4W group, 51% of the benralizumab Q8W group, and 20% of the placebo group. A 50% or more reduction from baseline in final oral glucocorticoid dose occurred in 67% of the benralizumab Q4W group, 66% of the benralizumab Q8W group, and 37% of the placebo group.
- A greater than 0% reduction from baseline in final oral glucocorticoid dose occurred in 76% of the benralizumab Q4W group, 79% of the benralizumab Q8W group, and 53% in the placebo group.
- The odds ratio (OR) for reduction in the oral glucocorticoid dose compared to placebo was 4.09 (95% CI, 2.22 to 7.57; P<0.001) with benralizumab Q4W and 4.12 (95% CI, 2.22 to 7.63; P<0.001) with benralizumab Q8W.

Secondary End Point(s)

- Cessation of oral glucocorticoid therapy occurred in 56% of the benralizumab Q4W group, 52% of the benralizumab Q8W group, and 19% of the placebo group. The OR for cessation of oral glucocorticoid therapy compared to placebo was 5.23 (95% CI, 1.92 to 14.21; P<0.001) with benralizumab Q4W and 4.19 (95% CI, 1.58 to 11.12; P=0.002) with benralizumab Q8W.
- A 50% or more reduction from baseline in final oral glucocorticoid dose occurred in 67% (OR, 3.59; 95% CI, 1.79 to 7.22; P<0.001) of the benralizumab Q4W group, 66% (OR, 3.03; 95% CI, 1.57 to 5.86; P<0.001) of the benralizumab Q8W group, and 37% of the placebo group.
- A 25% or more reduction from baseline in final oral glucocorticoid dose occurred in 75% (OR, 2.89; 95% CI, 1.45 to 5.79; P=0.002) of the benralizumab Q4W group, 78% (OR, 3.25; 95% CI, 1.62 to 6.52; P<0.001) of the benralizumab Q8W group, and 51% of the placebo group.
- Final oral glucocorticoid dose of 5 mg/day or less was achieved in 61% (OR, 3.16; 95% CI, 1.6 to 6.23; P<0.001) of the benralizumab Q4W group, 59% (OR, 2.74; 95% CI, 1.41 to 5.31; P=0.002) of the benralizumab Q8W group, and 33% of the placebo group.

Adverse Events

The most frequent reported adverse events were nasopharyngitis (17% of participants), worsening asthma (13% of participants), and bronchitis (10% of participants). Frequencies of adverse events were similar between each benralizumab group and the placebo group.

Reference: ClinicalTrials.gov Identifier: NCT02075255 at https://clinicaltrials.gov/ct2/show/NCT02075255

CLINICAL PRACTICE GUIDELINES

Global Initiative for Asthma (GINA, 2018)

- Provides a stepwise approach to asthma management, adjusting treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects
- Step 5 treatment: Benralizumab (monoclonal anti-IL5 receptor) has been added to the existing Type 2-targeted biologics for severe eosinophilic asthma. The age ranges approved for Type 2-targeted biologics have also been clarified since GINA 2017
- Phenotype-guided add-on treatment:
  - Patients with severe asthma, uncontrolled on Step 4 treatment, may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma
  - Patients ≥ 6 years with severe allergic asthma with elevated IgE levels may benefit from omalizumab (anti-IgE) therapy (Evidence A)
  - Those with severe eosinophilic asthma may benefit from anti-IL5 therapy (subcutaneous mepolizumab (Nucala) ≥ 12 years; intravenous reslizumab (Cinqair) > 18 years) or anti-IL receptor therapy (subcutaneous benralizumab (Fasenra) ≥ 12 years) (Evidence A)
  - LTRAs may be helpful of patients found to be aspirin sensitive (Evidence A)

European Respiratory Society (ERS)/American Thoracic Society (ATS)

- The guidelines recommend "While the anti-IL5 antibody, mepolizumab, was not beneficial in unselected adult patients with moderate asthma, when studied in severe asthma patients with persistent sputum eosinophilia, two anti- IL-5 antibodies, mepolizumab and reslizumab, have been shown to decrease exacerbations and oral corticosteroid use, as well as improve symptoms and lung function to varying degrees."
- Asthma is classified as severe when it requires treatment with high-dose inhaled corticosteroids plus a second asthma controller therapy (e.g., long-acting β2-agonist), and/or systemic corticosteroids to prevent asthma from becoming or remaining uncontrolled despite this therapy.
  - Although there are no widely accepted definitions for specific asthma phenotypes, an eosinophilic phenotype (i.e., eosinophilic asthma) is generally characterized by blood and sputum eosinophilia and eosinophilic inflammation, recurrent exacerbations, and, frequently, responsiveness to corticosteroids.
  - Sputum eosinophil counts are used as a reliable biomarker for eosinophilic lung inflammation; ATS and ERS currently recommend treatment of severe asthma guided by sputum eosinophil counts in addition to clinical criteria in adults, and treatment guided by clinical criteria alone in pediatric patients. However, sputum eosinophil counts are difficult to use in routine practice because testing must be performed in specialized centers experienced in using the technique.

DEFINITIONS

- Controller medications: suppress the inflammatory causes of asthma to provide clinical control over the long term, whereas reliever medications relieve bronchoconstriction quickly.

  Controller medications include inhaled glucocorticoids (Flovent, Pulmicort, Qvar, Asmanex), long-acting beta-agonists (LABAs) such as salmeterol, formoterol, or vilanterol, and antileukotriene agents (montelukast [Singulair®], zafirlukast [Accolate®] or Zyflo® [zileuton]). Theophylline is also a controller agent, however, it is not as efficacious as LABAs.

- Inhaled corticosteroid(s) (ICS or ICSs): A class of medications also referred to as inhaled steroids; used for the treatment of asthma and COPD. A potent anti-inflammatory medication that improves asthma control more effectively than any other agent used as a single treatment; helps to prevent chronic asthma symptoms such as wheezing, chest tightness, shortness of breath, and chronic cough.

- Long-acting beta-agonist(s) (LABA or LABAs): Also referred to as long-acting $beta_2$-adrenergic agonists. A type of bronchodilator whose effects last for 12 hours or more when used as adjunctive treatment for the prevention of asthma symptoms such as wheezing, chest tightness, shortness of breath, and cough; improves asthma symptoms by increasing airflow through the lungs.

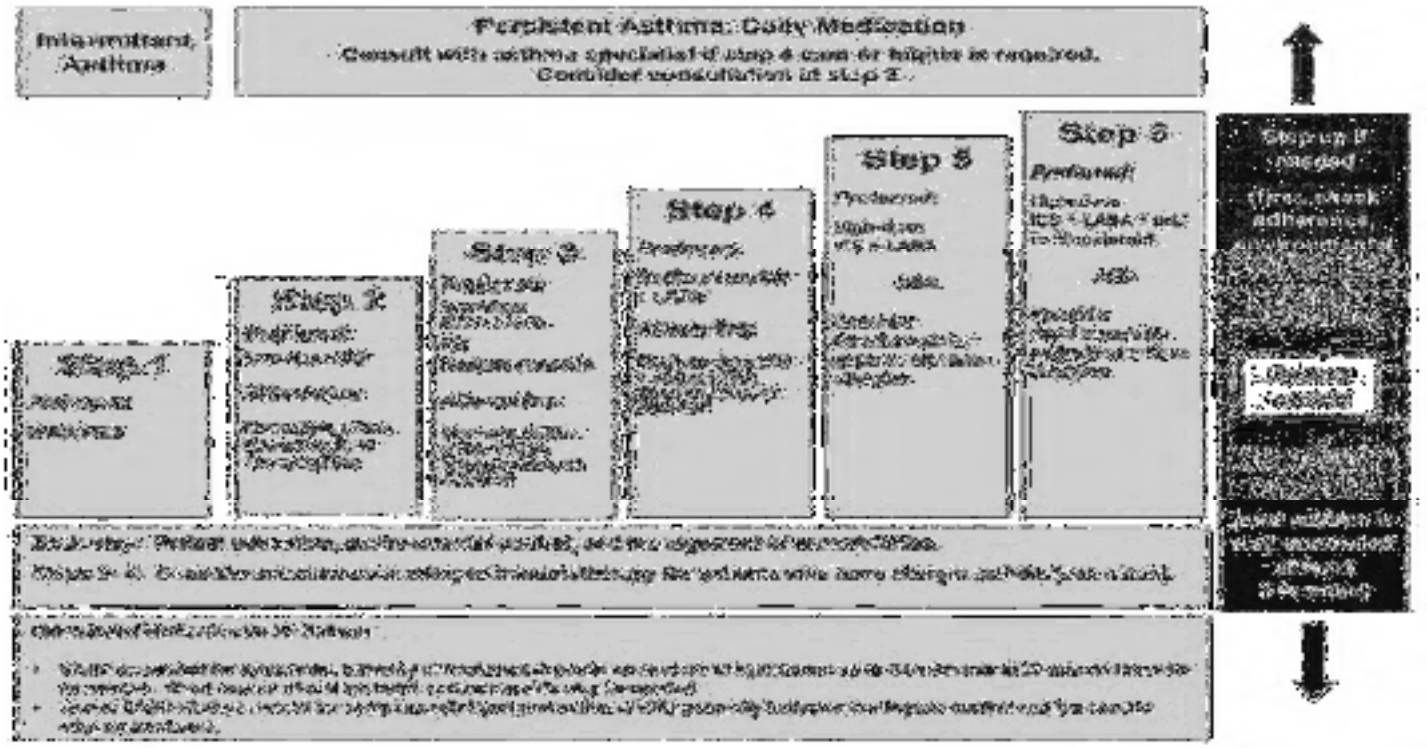
- Hypereosinophilia (HE): An absolute eosinophil count (AEC) in the peripheral blood of greater than 1.5×10^9/L (or greater than 1500 cells/microL) on 2 examinations separated in time by at least 1 month and/or pathologic confirmation of tissue HE.

- FEV_1 (forced expiratory volume in 1 second): A measure of airway obstruction determined using spirometry. Individual FEV_1 values are compared to predicted values based on age, height, sex and race.

- PEF (peak expiratory flow): PEF is often described as a percent of personal best measurement. Personal best PEF is the highest PEF value attained after 2 to 3 weeks of testing when asthma is in good control.

APPENDIX

APPENDIX 1: NAEPP Expert Panel Guidelines: Managing Asthma in Youths ≥ 12 years of age and Adults



NOTE: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting beta2-agonist; Leukotriene Receptor Antagonists (LTRAs), SABA, inhaled short-acting beta2-agonist

Reference: *NIH, National Heart Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3 2007)* http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf

National Asthma Education and Prevention Program (NAEPP). Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication Number 08-5846. October 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf.

APPENDIX 2: ESTIMATED COMPARATIVE DAILY DOSAGES for INHALED CORTICOSTEROIDS (ICS) in YOUTH ≥12 YEARS of AGE and ADULTS

Estimated Comparative Daily Dosages for Inhaled Corticosteroids (ICS) in Youths ≥ 12 years of age and Adults
The values listed below were obtained from the National Institutes of Health.

Drug	Low Daily Dose Adult	Medium Daily Dose Adult	High Daily Dose Adult
Beclomethasone HFA 40 or 80 mcg/puff	80–240 mcg	>240–480 mcg	>480 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	180–600 mcg	>600–1,200 mcg	>1,200 mcg
Flunisolide 250 mcg/puff	500–1,000 mcg	>1,000–2,000 mcg	>2,000 mcg
Flunisolide HFA 80 mcg/puff	320 mcg	>320–640 mcg	>640 mcg
Fluticasone			
HFA/MDI: 44, 110, or 220 mcg/puff	88–264 mcg	>264–440 mcg	>440 mcg
DPI: 50, 100, or 250 mcg/inhalation	100–300 mcg	>300–500 mcg	>500 mcg
Mometasone DPI 200 mcg/inhalation	200 mcg	400 mcg	>400 mcg
Triamcinolone acetonide 75 mcg/puff	300–750 mcg	>750–1,500 mcg	>1,500 mcg

Key: DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler

Reference: Section 4, Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults
Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug.

APPENDIX 3: Clinically Relevant Outcomes for Severe Asthma

- Clinically relevant outcomes for severe asthma include reduction in asthma exacerbations that result in:
  - Decreased emergency department (ED) visits or hospitalizations;
  - Decreased chronic use of OCS;
  - Improved quality of life; and
  - Improved symptom management.

- These tests are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma and is self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users.
  1) **Asthma Control Questionnaire-7 (ACQ-7):** A 7-item questionnaire (1 week recall for items on symptoms and rescue inhaler use) that measures the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. The ACQ-7 assesses symptoms (5 items, self-administered), rescue in-bronchodilator use (1 item, self-administered), and FEV1% (1 item) completed by a healthcare professional. The 7-point scale reports symptoms as: 0 = no impairment; 6 = maximum impairment for symptoms and rescue use; and, 7 categories for FEV1%. The ACQ is 7-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.5 Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 the minimally clinical important difference.[1]
  2) **Asthma Quality of Life Questionnaire (AQLQ):** A 32-item disease-specific questionnaire assesses both physical and emotional impact of disease and used to reflect areas of function important to individuals with asthma; available in both interviewer- and self-administered forms. The 4 domains measured by the AQLQ include activity limitations, emotional function, exposure to environmental stimuli, and symptoms.[2] Scores range from 1 (severely impaired) to 7 (not impaired at all), with higher scores indicating better quality of life.[2] A difference of 0.5 overall and for each item is the minimally clinical important difference for this instrument.[2]
  3) **St. George's Respiratory Questionnaire (SGRQ):** A 50-item quality-of-life tool for patients with obstructive airway disease is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. The questionnaire is composed of 2 parts. Part 1 assesses symptoms and part 2 assesses limitation of activities and its social and psychological impact.[3] Scores range from 0 to 100, with lower scores indicate better functioning and higher scores indicating more limitations. A change of 4 units is considered to be clinically meaningful, 8 points for moderately efficacious treatment, and 12 points for very efficacious treatment.[3]
  4) **Asthma Control Test (ACT):** A score is a tool used to identify patients with poorly controlled asthma.[4] The test contains 5 items that assess the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. 8 Scores range from 5 (poor control of asthma) to 25 (complete control of asthma).[4] An ACT score greater than 19 indicates well-controlled asthma, with a change of 3 points the minimally clinical important difference over time.[4]
  5) **Asthma Symptom Utility Index (ASUI)** is an 11 item questionnaire with scores range from 0 (worst possible symptoms) to 1 (no symptoms). This instrument assesses frequency and severity of cough, wheezing, dyspenia, and nighttime awakening, and medication side effects.

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1) *American Thoracic Society - Asthma Control Questionnaire (ACQ). http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/acq.php#. Accessed April 2018.*
2) *American Thoracic Society - Asthma Quality of Life Questionnaire (AQLQ). http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/aqlq.php. Accessed April 2018.*
3) *American Thoracic Society - St. George's Respiratory Questionnaire (SGRQ). https://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/sgrq.php. Accessed April 2018.*
4) *American Thoracic Society - Asthma Control Test (ACT). http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/act.php. Accessed April 2018.*

APPENDIX 4: Blood Eosinophil Levels

Earlier studies with reslizumab indicate that eosinophilic asthma can be characterized by a sputum eosinophil count of ≥3% and that reslizumab is expected to benefit patients with asthma with sputum eosinophil count of ≥3%. The sponsor chose blood eosinophil as a surrogate of sputum eosinophilia because of the ease of obtaining in clinical practice. The sponsor selected ≥400 cells/μL as the threshold based on a secondary analysis of datasets from asthma patients that indicated blood eosinophil count of ≥400 cells/μL had a high positive predictive value for the presence of sputum eosinophils of ≥3%, and a count of <400 cells/μL identified the majority of patients without sputum eosinophilia. It should be noted that a definitive threshold value of eosinophilia has not been defined.

CODING INFORMATION

The codes listed in the policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

HCPCS	Description
C9466	Injection, benralizumab, 1 mg [Fasenra]
J3490	Unclassified drugs [when specified as benralizumab (Fasenra)]
J3590	Unclassified drugs [when specified as benralizumab (Fasenra)]

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