UTAH MEDICAID DUR REPORT
AUGUST 2020

BIOLOGICAL TREATMENTS FOR ASTHMA

Benralizumab (Fasenra)
Dupilumab (Dupixent)
Mepolizumab (Nucala)
Omalizumab (Xolair)
Reslizumab (Cinqair)

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Drug Regimen Review Center

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Background

Asthma is a heterogeneous disease typically characterized by chronic inflammation of the respiratory tract. Asthma can range from mild to severe depending on the frequency of respiratory symptoms, expiratory airflow obstruction, and frequency of exacerbations that require oral corticosteroids (OCS). The treatment of asthma follows a stepwise approach that usually includes reliever therapy to quickly alleviate exacerbations and short-term symptoms, and controller therapy to prevent exacerbations and control symptoms. Patients with severe asthma represent approximately 4% of asthmatic cases. These patients have severe symptoms and reduced quality of life that constitute a substantial patient and societal burden. Management of severe asthma usually includes medium or high dose inhaled corticosteroids (ICS) plus long-acting beta 2 agonist (LABA) therapy and may require the addition of OCS, which are associated with serious adverse events. Other add-on therapies may be required, such as biological treatments that are effective at decreasing severe asthma exacerbations and OCS use.

There are different types of asthma phenotypes based on clinical, biological, and physiological characteristics of the disease. Half of patients with severe asthma have type 2 inflammatory phenotype. This phenotype typically involves inflammatory cytokines such as interleukin (IL)-4, IL-5, and IL-13 that are released by type-2 immune cells (T helper 2 [Th2] cells and type-2 innate lymphoid cells [ILC2s]) in response to infections or allergen exposure. Some key manifestations include elevated levels of IgE and eosinophils. Allergic asthma and eosinophilic asthma are type-2 inflammatory phenotypes of severe asthma.

There are currently 5 biological treatments (monoclonal antibodies) indicated as add-on maintenance therapy for patients with asthma and type 2 inflammatory phenotype (allergic asthma or eosinophilic asthma). These include 3 IL-5 antagonists (benralizumab, mepolizumab, and reslizumab), an IL-4 receptor antagonist (dupilumab), and an immunoglobulin E (IgE) antagonist (omalizumab). Based on their mechanism of action, biological treatments target differing type-2 inflammatory signaling pathways (IL-4, IL-5, IgE), improving airway inflammation and allergic response by reducing the levels of inflammatory cytokines, circulating IgE, and eosinophils. There are important differences between the asthma indications of these agents with respect to asthma severity (dupilumab and omalizumab are indicated for moderate-to-severe asthma while benralizumab, mepolizumab, and reslizumab are indicated for severe asthma); covered age (reslizumab is approved in adults only, while the others are approved in adults and pediatric patients of varied ages depending on the product); asthma phenotype (omalizumab is the only product approved for allergic asthma whereas the others are approved for eosinophilic asthma); and dependence on OCS (dupilumab is the only product approved for OCS-dependent moderate-to-severe asthma). Additional FDA-approved indications include atopic dermatitis (AD) and chronic rhinosinusitis with nasal polyposis (CRSwNP) for dupilumab; eosinophilic granulomatosis with polyangiitis (EGPA) for mepolizumab; and chronic idiopathic urticaria (CIU) for omalizumab. These agents will be referred as ‘biological treatments for asthma’ along the report, although some are approved for other indications.
All biological treatments are administered subcutaneously, except reslizumab that is administered intravenously only. Benralizumab, dupilumab, and mepolizumab may be administered by the patient or caregiver. Omalizumab* and reslizumab should be administered by a healthcare professional in a health care setting due to the risk of anaphylaxis that can be fatal.

Maintenance dose frequency is every 2 weeks with dupilumab and omalizumab; every 4 weeks with mepolizumab, omalizumab, and reslizumab; or every 8 weeks with benralizumab.

Prior authorization (PA) criteria is currently in place for benralizumab, dupilumab, and omalizumab. The purpose of this review is to provide evidence to assist the Medicaid Drug Utilization Review (DUR) Board in assuring safe and appropriate use of biologicals for the treatment of asthma and other approved indications. While the focus of this review will be on the asthma-related indications for this group of biologics, some background and guideline information will be provided regarding other additionally approved indications. PA criteria considerations will be proposed for discussion. Relevant utilization data in the Utah Medicaid fee-for-service (FFS) population will be presented.

Methods

A literature search for systematic reviews and meta-analyses published in the last year and addressing the efficacy and safety of the 5 biologicals for asthma was conducted in Ovid Medline. Reference lists of relevant systematic reviews were additionally screened. The complete search strategy are provided in Appendix A.

Information concerning product labeling was obtained from the FDA or manufacturer’s website. Additional product information was found in Micromedex and Lexicomp. Treatment guidelines for the management of asthma were searched for in the Global Initiative for Asthma (GINA) and the National Heart, Lung, and Blood Institute (NHLBI) websites. Regarding other FDA approved indications for this group of biologics, treatment guidelines for the management of atopic dermatitis (AD), chronic rhinosinusitis with nasal polyposis (CRSwNP), eosinophilic granulomatosis with polyangiitis (EGPA), and chronic idiopathic urticaria (CIU) were searched for in the American Academy of Dermatology (AAD), the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF), the EGPA Consensus Task Force, and the American Academy of Allergy, Asthma, and Immunology (AAAAI) websites, respectively. In addition, searches were performed in other relevant American and European organization websites.

* During the Covid-19 pandemic, an exception is made to allow certain patients to self-administer omalizumab; further information can be found at https://www.gene.com/download/pdf/Xolair_DHCP_important-prescribing-information_04-16-20.pdf
**Biological Treatments for Asthma**

Table 1 provides the formulations, indications, and dosing recommendations for the use of biological treatments for asthma. Appendix B includes special population considerations for these agents.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name (ROA) (Approval Date)</th>
<th>FDA-Approved Indication Regarding Asthma</th>
<th>Preparation</th>
<th>Age (per Labeled Indication)</th>
<th>Recommended Dosage for Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Fasenra (SQ) (2017)</td>
<td>Add-on maintenance treatment for patients with severe asthma and an eosinophilic phenotype</td>
<td>Pre-filled syringe: 30mg/mL, Autoinjector: 30mg/mL</td>
<td>≥ 12 years</td>
<td>30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limitation of use: Not for treatment of other eosinophilic conditions; not for the relief of acute bronchospasm or status asthmaticus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dupilumab&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Dupixent (SQ)&lt;sup&gt;a&lt;/sup&gt; (2017)</td>
<td>Add-on maintenance treatment for patients with moderate-to-severe asthma and an eosinophilic phenotype or oral corticosteroid dependent asthma</td>
<td>Pre-filled syringe: 300mg/2mL, 200mg/1.14mL</td>
<td>≥ 12 years</td>
<td>Initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week OR Initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week (dosage also recommended for patients with oral CS-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limitation of use: Not for the relief of acute bronchospasm or status asthmaticus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepolizumab&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Nucala (SQ)&lt;sup&gt;b&lt;/sup&gt; (2015)</td>
<td>Add-on maintenance treatment for patients with severe asthma and an eosinophilic phenotype</td>
<td>Single-dose vial: 100mg</td>
<td>≥ 6 years</td>
<td>≥ 12 years: 100 mg once every 4 weeks 6 to 11 years: 40 mg once every 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limitation of use: Not for the relief of acute bronchospasm or status asthmaticus</td>
<td>Pre-filled syringe: 100mg/mL, Autoinjector: 100mg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Name</td>
<td>FDA-Approved Indication Regarding Asthma</td>
<td>Preparation</td>
<td>Age (per Labeled Indication)</td>
<td>Recommended Dosage for Asthma</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------</td>
<td>-------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| **Omalizumab**<sup>7</sup>  
Xolair (SQ)<sup>c</sup>  
(2003) | Moderate to severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids  
Limitation of use: Not for the relief of acute bronchospasm or status asthmaticus | Pre-filled syringe: 75mg, 150mg | ≥ 6 years | 75 to 375 mg every 2 or 4 weeks. Determine dose and dosing frequency by pretreatment serum total IgE level (IU/mL) and body weight. See dose recommendations in Tables 1 and 2 of the PI |
| **Reslizumab**<sup>10</sup>  
Cinqair (IV)  
(2016) | Add-on maintenance treatment for patients with severe asthma and an eosinophilic phenotype  
Limitation of use: Not for treatment of other eosinophilic conditions; not for the relief of acute bronchospasm or status asthmaticus | Single-use vial: 100mg/10mL | Adults | 3 mg/kg once every 4 weeks over 20-50 minutes |

Abbreviations: CS, corticosteroid; FDA, U.S. Food and Drug Administration; IV, intravenous; PI, prescribing information; ROA, route of administration; SQ, subcutaneous

<sup>a</sup>Other FDA-approved indications for dupilumab:
- Moderate-to-severe atopic dermatitis in patients aged 6 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
- Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)

<sup>b</sup>Other FDA-approved indications for mepolizumab:
- Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)

<sup>c</sup>Other FDA-approved indications for omalizumab:
- Chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment

All biological treatments for asthma are monoclonal antibodies generated by recombinant DNA technology.<sup>6-10</sup> Omalizumab inhibits interaction of IgE and IgE receptor (FcεR1), depleting free IgE and downregulating the expression of IgE receptors.<sup>1,7</sup> Mepolizumab and reslizumab bind to free IL-5 and benralizumab binds to the alpha subunit of the IL-5 receptor, which blocks the interaction of IL-5 to its receptor and leads to “inhibition of eosinophil differentiation and maturation in bone marrow.”<sup>1,2</sup> In addition, benralizumab induces eosinophil cell death.<sup>1</sup> Dupilumab inhibits IL-4 receptor alpha, blocking inflammatory responses induced by the cytokines IL-4 and IL-13.<sup>1,9</sup> Eosinophils, pro-inflammatory cytokines, nitric oxide, and IgE are associated with inflammation in asthma and other conditions such as EGPA.<sup>6-10</sup>

Table 2 includes the description and mechanism of action of biological treatments for asthma.
### Table 2. Description and Mechanism of Action of Biological Treatments for Asthma

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Description</th>
<th>Mechanism of Action</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab</td>
<td>Recombinant humanized afucosylated mAb of the IgG1 kappa produced in Chinese hamster ovary cells</td>
<td>Anti-IL-5Rα</td>
<td>Inhibits IL-5 signaling and induces apoptosis of eosinophils that leads to a reduction in peripheral blood eosinophils (cells involved in inflammation)(^5,6)</td>
</tr>
<tr>
<td>Fasenra</td>
<td>Anti-IL-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Recombinant humanized mAb of the IgG_4 produced in Chinese hamster ovary cells</td>
<td>Anti-IL-4Rα</td>
<td>Inhibits IL-4Rα, blocking inflammatory responses induced by IL-4 and IL-13(^9)</td>
</tr>
<tr>
<td>Dupixent</td>
<td>Anti-IL-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Recombinant humanized mAb produced in Chinese hamster ovary cells</td>
<td>Anti-IL-5</td>
<td>Inhibits IL-5 signaling, reducing production and survival of eosinophils (cells involved in inflammation)(^8)</td>
</tr>
<tr>
<td>Nucala</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Recombinant humanized mAb of the IgG1 kappa produced in Chinese hamster ovary cells</td>
<td>Anti-IgE</td>
<td>Blocks binding of IgE to IgE receptor of mast cells and basophils, reducing the secretion of allergic response mediators (eg, IgE) and the number of IgE receptors(^7)</td>
</tr>
<tr>
<td>Xolair</td>
<td>Anti-IgE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Recombinant humanized mAb of the IgG4 kappa produced in murine myeloma non-secreting 0 (NS0) cells</td>
<td>Anti-IL-5</td>
<td>Inhibits binding of IL-5 to the IL-5 receptor, reducing production and survival of eosinophils (cells involved in inflammation)(^10)</td>
</tr>
<tr>
<td>Cinqair</td>
<td>Anti-IL-5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IL, interleukin; IL-4Rα, interleukin-4 receptor alpha; IL-5Rα, interleukin-5 receptor alpha; mAb, monoclonal antibody; IgE, immunoglobulin E; IgG, immunoglobulin G

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### Asthma Overview

According to data reported by the Centers for Disease Control and Prevention (CDC) in 2018, the current asthma prevalence in American children and adults is approximately 7.7% (24.8 million).\(^11\) The prevalence was similar in adults (7.7%) and children (7.5%) and higher in females (9.1% in females vs. 6.2% in males) and those living below 100% of federal poverty threshold.\(^11\) Asthma resulted in 1.6 million emergency department visits for asthma-related concerns and 10.5 deaths per million in 2017.\(^12,13\) In Utah, 2018 data from the CDC reported an adult asthma prevalence of 9.3%, with an asthma-related death rate of 10.9 per million.\(^14\)

Asthma is defined by the 2020 Global Initiative for Asthma (GINA) guideline as a heterogeneous disease typically characterized by chronic inflammation of the respiratory tract.\(^1\) The inflammatory pathogenesis of asthma results in variable respiratory symptoms including shortness of breath, wheezing, chest tightness, and cough, and variable expiratory airflow obstruction due to bronchoconstriction, thickness of airway walls, and increased mucus.\(^1,15\) Resolution of symptoms and airflow obstruction may occur either spontaneously or with treatment; however, some patients may experience life-threatening exacerbations that are associated with a substantial burden to patients and society.\(^1\) Asthma is a disease with a broad spectrum of various underlying mechanisms, but somewhat consistent characteristics (eg, demographic, pathophysiological, and/or clinical features) have led to categorization into "asthma phenotypes."\(^11,16\) However, there is not strong correlation between asthma phenotypes and clinical presentations or treatment responses. Common phenotypes include allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airflow limitation, and asthma with obesity.\(^1\)
The causes and risk factors that may trigger asthma symptoms or increase the risk of exacerbations vary widely due to the diverse pathophysiology of asthma. These include viral infections, allergen exposure, tobacco smoke exposure, comorbidities (eg, obesity, food allergy, chronic rhinosinusitis), exercise, psychological or socioeconomic problems, low lung function, blood eosinophilia, poor adherence to asthma medication, inappropriate inhaler technique, and some drugs such as beta-blockers and non-steroidal anti-inflammatory drugs (NSAIDs).1,15

Diagnosis of asthma is based on the history of respiratory symptoms typical for asthma (eg, shortness of breath, wheezing) and evidence of variability in expiratory airflow obstruction.1 Pulmonary function testing using spirometry is needed to confirm a diagnosis of asthma.1 Spirometry parameters include measured force of the exhalation, known as the forced expiratory volume in 1 second (FEV1), and the amount of air exhaled is known as the forced vital capacity (FVC).17 A ratio of FEV1 to FVC (FEV1/FVC) of <0.75 in adults and <0.90 in children is indicative of expiratory airflow limitation. Extreme variability in lung function as determined by one of the various tests specified by GINA guidelines (eg, bronchodilator reversibility test, positive exercise challenge test) will finalize a diagnosis of asthma.1

The goals of long-term asthma management are to achieve optimal control of asthma symptoms and reduce the risk of exacerbations, asthma-related mortality, persistent airflow obstruction, and adverse effects from medications. Management of asthma encompasses a continuous cycle to “assess, adjust treatment, and review response.” Evaluation of symptom control, comorbidities, inhaler technique, adherence, and patient/family preferences and goals should be carried out in each asthma patient.1,15,18 Treatment strategies include asthma medications, management of modifiable risk factors and comorbidities, and non-pharmacological interventions (eg, smoking cessation, regular physical exercise, and avoiding exposure to known allergens). Skills training for an appropriate use of inhaler devices and education on self-management and adherence should be part of the asthma management.5,6

The main guideline for the management of asthma is provided by GINA, which includes a stepwise plan for therapy based on 3 main asthma severity categories: mild asthma (ie, asthma well-controlled with Step 1 or 2 therapy), moderate asthma (ie, asthma well-controlled with Step 3 therapy), and severe asthma (ie, asthma requiring Step 4 or 5 therapy).1 Pharmacotherapies for asthma include inhaled corticosteroids (ICS), short- and long-acting inhaled β2-agonists (SABA and LABA), leukotriene receptor antagonists (LTRA), short- and long-acting muscarinic antagonists, monoclonal antibodies, and oral corticosteroids (OCS).1,18 There are 2 important distinctions of therapy: relievers and controllers. All patients should have an as-needed (PRN) reliever inhaler (low dose ICS-formoterol or SABA) to quickly alleviate exacerbations and short-term symptoms. Controller treatment is administered on a regular, scheduled basis to prevent exacerbations and control symptoms.1

According to the GINA guideline, monoclonal antibodies are options for add-on therapy in the management of severe asthma,1 which will be discussed in further detail in the following section. Recall though that dupilumab and omalizumab are approved for moderate-to-severe asthma (dupilumab for eosinophilic phenotype or OCS-dependent asthma; and omalizumab for allergic phenotype) while the other biologics are approved for severe eosinophilic asthma.6-10
Table 3 summarizes the stepwise treatment approach for initial asthma management according to the 2020 GINA guideline. Appendix C includes the low, medium, and high daily doses of ICS (per GINA guideline).

<table>
<thead>
<tr>
<th>Steps and Asthma Severity</th>
<th>Preferred Reliever</th>
<th>Alternative Reliever Option</th>
<th>Preferred Controller Choice</th>
<th>Alternative Controller Option</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 1 Mild Asthma</strong></td>
<td></td>
<td></td>
<td>Age ≥12: PRN low-dose ICS-FM (data available for BUD-FM only)</td>
<td>Age ≥12: Low dose ICS whenever SABA is taken</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age 6-11: None</td>
<td>Age 6-11: None</td>
<td>Age 6-11: Low dose ICS whenever SABA is taken</td>
</tr>
<tr>
<td><strong>STEP 2 Mild Asthma</strong></td>
<td></td>
<td>Age ≥12: Daily low dose ICS-FM (data available for BUD-FM only)</td>
<td>Age ≥12: Daily low dose ICS</td>
<td>All ages: LTRA or low dose ICS whenever SABA is taken</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age 6-11: Daily low dose ICS</td>
<td>Age ≥12: Medium dose ICS or low dose ICS</td>
<td>Age 6-11: Low dose ICS+LTRA</td>
</tr>
<tr>
<td><strong>STEP 3 Moderate Asthma</strong></td>
<td></td>
<td>Age ≥12: Low-dose ICS-LABA or Low dose ICS-FM (as maintenance and reliever)</td>
<td>Age ≥12: Medium dose ICS or low dose ICS</td>
<td>Age 6-11: Low dose ICS+LTRA</td>
</tr>
<tr>
<td></td>
<td>Age ≥12: PRN low-dose ICS-FM</td>
<td>Age 6-11: PRN SABA</td>
<td>Age ≥12: - Low-dose ICS-LABA or - Medium dose ICS</td>
<td>Age ≥12: High dose ICS, add-on tiotropium, or add-on LTRA</td>
</tr>
<tr>
<td></td>
<td><strong>Age 6-11:</strong> PRN SABA</td>
<td>All ages: LTRA or low dose ICS whenever SABA is taken</td>
<td>Age 6-11: - Medium dose ICS-LABA plus PRN SABA or - Low dose ICS-FM (as maintenance and reliever)</td>
<td>Age 6-11: High dose ICS-LABA, or add-on tiotropium, or add-on LTRA</td>
</tr>
<tr>
<td><strong>STEP 4 Severe Asthma</strong></td>
<td></td>
<td>Age ≥12: High dose ICS-LABA</td>
<td>Age ≥12: High dose ICS-LABA or - Refer for phenotypic assessment and consider add-on therapy (eg, tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R)</td>
<td>Age ≥12: Add low dose OCS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age 6-11: Refer for phenotypic assessment and consider add-on therapy (eg, anti-IgE)</td>
<td>Age 6-11: Add-on anti-IL5 or low dose OCS</td>
<td>Age 6-11: Add-on anti-IL5 or low dose OCS</td>
</tr>
<tr>
<td><strong>STEP 5 Severe Asthma</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: anti-IgE, anti-immunoglobulin E; anti-IL4R, anti-interleukin 4 receptor treatment; anti-IL5/5R, anti-interleukin 5/5 receptor treatment; BUD, budesonide; FM, formoterol; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; ICS-LABA, fixed-dose combination of inhaled corticosteroids and long acting beta-agonists; IL, interleukin; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroid; PRN, pro re nata or as needed; SABA, short-acting β2 agonists
Severe Asthma Overview

There are several concepts related to severe asthma, including uncontrolled asthma and difficult-to-treat asthma. **Uncontrolled asthma** is characterized by poor symptom control and/or ≥2 exacerbations within 1 year requiring OCS or ≥1 serious exacerbations requiring hospitalization. **Difficult-to-treat asthma** is uncontrolled asthma refractory to GINA Step 4 or 5 treatment, or asthma that needs such therapies to control symptoms and minimize the risk of exacerbations. **Severe asthma** is a subcategory of difficult-to-treat asthma in which patients have uncontrolled asthma despite good adherence with fully optimized Step 4 or 5 therapy and management of contributing factors (eg, comorbidities, modifiable risk factors such as smoking, and incorrect inhaler technique). 1 Severe asthma may also refer to asthma that deteriorates when decreasing high-dose treatment. 1 It is estimated that approximately 17% of patients with asthma experience difficult-to-treat asthma and 3.7% of patients experience severe asthma. 1

The 2020 European Respiratory Society/American Thoracic Society (ERS/ATS) guideline for the management of severe asthma in adults and school-aged children defines severe asthma (once the diagnosis of asthma is confirmed and comorbidities managed) as “…asthma that requires treatment with high dose inhaled corticosteroids […] plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy.” 19

Severe asthma results in a significant burden on the patient and healthcare spending. Frequent symptoms and exacerbations greatly interfere with a patient’s daily needs, social needs, ability to work, and emotional and mental health. In addition, frequent clinic visits, hospitalizations, complex medication regimens and adverse effects of OCS yield a great cost to the healthcare system. 1 One study has demonstrated that healthcare costs associated with this population exceeded those of type-2 diabetes, stroke, or chronic obstructive pulmonary disease (COPD). 20

Severe Asthma Phenotypes

Severe asthma phenotypes can be divided into 2 categories: type 2 and non-type 2 inflammation. Following diagnosis of severe asthma, a specialist or severe asthma clinic needs to determine which of the 2 severe asthma phenotypes the patient has during high dose ICS therapy or the lowest possible dose of OCS. Factors triggering symptoms, exacerbations, and reduced quality of life should be adequately assessed.

Type 2 inflammation phenotype affects approximately half of patients with severe asthma. 1 It typically involves immune cells (eg, T helper cell type 2) that release cytokines (eg, IL-4, IL-5, and IL-13) in response to allergens and activate type 2 immunity in the airway, producing high levels of IgE and eosinophilia. 1,3,21 Type 2 inflammation can additionally be induced by viruses, bacteria, and irritants that activate the immune system through the production of alarmins (eg, IL-33, IL-25, and thymic stromal lymphopoietin) by the airway epithelial cells. 1,3,21 IL-5 stimulates the differentiation, maturation, activation, and survival of eosinophils. 2,3,5 IL-4 and IL-13 induce the synthesis of allergen-specific IgE, promoting “airway hyperresponsiveness, smooth muscle hypertrophy, and airway remodeling.” 3 IL-13 also increases the production of airway nitric oxide (NO), mucus, and smooth muscle contractility. 5 Blood eosinophils at a concentration of ≥150/µL, fractional exhaled nitric oxide fraction (FeNO) at ≥20 ppb, sputum eosinophils at ≥2%, and asthma that is clinically allergen-driven or requires maintenance...
OCS can all indicate type 2 inflammation on their own or in combination with each other. Non-type 2 inflammation phenotype is typically characterized by an increase in neutrophils.

Type 2 inflammatory asthma phenotype may not respond to high dose ICS but may respond to OCS. However, OCS-related serious adverse events make alternative treatments necessary. With increasing knowledge of type 2 inflammatory pathways, IgE, IL-5, IL-4, and IL-13 have been identified as therapeutic targets. The biological agents benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab interfere with the type 2 inflammatory pathway through the inhibition of IgE and type-2 cytokine (IL-5, IL-4, and IL-13) effects.

Some examples of type 2 inflammation phenotypes include early-onset allergic asthma, late-onset eosinophilic asthma, and aspirin-exacerbated respiratory disease (AERD):

- **Early onset allergic asthma** phenotype affects 40-50% of asthma patients and is characterized by its presentation during childhood, atopy, positive allergy skin testing, and increased levels of serum specific IgE, FeNO, and sputum/blood eosinophils.

- **Late-onset eosinophilic asthma** affects approximately 25% of patients with severe asthma and is mainly characterized by its presentation in adulthood, a significant blood/sputum eosinophilia unresponsive to ICS or OCS therapy, elevated FeNO, and increased production of IL-5 and IL-13. This phenotype is occasionally associated with “chronic sinusitis and nasal polyps in patients without a clear history of atopy.”

- **AERD** is a subgroup of the late-onset eosinophilic asthma phenotype characterized by asthma, CRSwNP, and respiratory reactions induced by cyclooxygenase-1 (COX-1) inhibitors.

The 2020 European Academy of Allergy and Clinical Immunology (EAACI) guideline for severe asthma provides the following definitions:

- **Eosinophilic asthma patients** are those with “a sputum eosinophil count of >1% or an asthma-related peripheral blood eosinophil count of ≥150 cells/μL, or a fractional exhaled nitric oxide (FeNO) of ≥20 ppb”

- **Allergic asthma patients** are those “diagnosed with moderate to severe allergic asthma with asthma symptoms due to exposure to a perennial aeroallergen and serum total IgE levels 30-1300 IU/mL not adequately controlled on ICS and/or other background controllers”

- **Severe T2 asthma patients** have “confirmed diagnosis of asthma inadequately controlled on ICS and additional controllers”
Treatment of Severe Asthma and Guideline Recommendations

The 2020 GINA guidelines and the 2007 National Asthma Education and Prevention Program (NAEPP) guidelines include guidance for the management of severe asthma. Additional up-to-date guidelines, which are specific to severe asthma treatment, are provided by the European Respiratory Society/American Thoracic Society (ERS/ATS) and the European Academy of Allergy and Clinical Immunology (EAACI)—both published in 2020.

Table 4 summarizes the treatment guideline recommendations for severe asthma, with focus on biologic agents.

<table>
<thead>
<tr>
<th>Professional Organization and Guideline</th>
<th>Recommendations for Biological Therapy in Severe Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Initiative for Asthma (GINA)</strong></td>
<td>Step 5 (severe asthma) preferred controller options:</td>
</tr>
<tr>
<td>Global Strategy for Asthma Management and Prevention, 2020</td>
<td>- Adults and adolescents 12 years and older:</td>
</tr>
<tr>
<td></td>
<td>o High dose ICS plusLABA</td>
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<tr>
<td></td>
<td>o Refer for phenotypic assessment and consider add-on therapy (eg, tiotropium, <em>anti-IgE</em>, <em>anti-IL-5/5R</em>, <em>anti-IL-4R</em>)</td>
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<tr>
<td></td>
<td>- Children 6-11 years: refer for phenotypic assessment and consideration of add-on treatment (e.g. tiotropium, <em>anti-IgE</em>, <em>anti-IL5/5R</em>, <em>anti-IL4R</em>)</td>
</tr>
<tr>
<td><strong>European Respiratory Society/American Thoracic Society (ERS/ATS)</strong></td>
<td>- Anti-IL 5 strategy is recommended “as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma” (Conditional recommendation, low quality of evidence)</td>
</tr>
<tr>
<td>Management of Severe Asthma: A European Respiratory Society/American Thoracic Society Guidelines, 2020</td>
<td>- Dupilumab is recommended “as add-on therapy for adult patients with severe eosinophilic asthma and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels” (Conditional recommendation, low quality of evidence)</td>
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<tr>
<td></td>
<td>- Blood eosinophil cut-off ≥150 μL⁻¹ can be utilized “to guide anti-IL-5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations” (Conditional recommendation, low quality of evidence)</td>
</tr>
<tr>
<td></td>
<td>- Blood eosinophil cut-off ≥260 μL⁻¹ and FeNO cut-off ≥19.5 ppb are suggested to “identify adolescents (&gt;12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment” (Conditional recommendation, low quality of evidence)</td>
</tr>
<tr>
<td></td>
<td>- For children, adolescents and adults with severe asthma uncontrolled despite GINA step 4–5 or NAEPP step 5 therapies, the addition of tiotropium is recommended (Strong recommendation, moderate quality of evidence)</td>
</tr>
<tr>
<td><strong>European Academy of Allergy and Clinical Immunology (EAACI)</strong></td>
<td>Benralizumab as add-on treatment:</td>
</tr>
<tr>
<td>EAACI Biologicals Guidelines – Recommendations</td>
<td>Uncontrolled severe eosinophilic asthma</td>
</tr>
<tr>
<td></td>
<td>- Adolescents 12-17 years: recommended for uncontrolled severe eosinophilic asthma despite optimal controlled treatment to decrease severe asthma exacerbations, improve QoL, improve asthma control, or improve lung function (conditional recommendation for all outcomes)</td>
</tr>
<tr>
<td></td>
<td>- Adults: recommended for uncontrolled severe eosinophilic asthma despite optimal controlled treatment to decrease severe asthma exacerbations (strong treatment)” (Conditional recommendation, low quality of evidence)</td>
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</table>
Table 4. Clinical Practice Guideline Recommendations for Biological Therapy in Severe Asthma

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<tbody>
<tr>
<td>for Severe Asthma, 2020¹</td>
<td>recommendation), decrease or withdraw OCS for blood eosinophils &gt; 150 cells/µL (strong recommendation), improve QoL (conditional recommendation), improve asthma control (conditional recommendation), or improve lung function (conditional recommendation)</td>
</tr>
</tbody>
</table>

**Uncontrolled severe allergic asthma (off-label use)**
- Adults: recommended as add-on treatment in adults with uncontrolled severe allergic asthma despite optimal controlled treatment to decrease severe asthma exacerbations, and improve QoL, asthma control, and lung function (conditional recommendation for all outcomes)

**Safety**
- Adults and adolescents 12-17 years: benralizumab demonstrated a good safety profile; however, patients should be periodically screened for parasitic infections in endemic areas (conditional recommendation)

**Dupilumab as add-on treatment**

**Uncontrolled severe eosinophilic asthma**
- Adolescents 12-17 years and adults: recommended for uncontrolled severe eosinophilic asthma despite optimal controlled treatment to decrease severe asthma exacerbations (strong recommendation), improve QoL (conditional recommendation), improve asthma control (conditional recommendation), improve lung function (strong recommendation), or decrease rescue medication use (conditional recommendation)

**Uncontrolled severe allergic asthma (off-label use)**
- Adolescents 12-17 years and adults: recommended for uncontrolled severe allergic asthma despite optimal controller treatment to decrease severe asthma exacerbations, improve asthma control, and improve lung function (conditional recommendation for all endpoints)

**Uncontrolled severe T2 asthma (off-label use)**
- Adolescents 12-17 years and adults: recommended for uncontrolled severe T2 asthma despite optimal controller treatment to reduce severe asthma exacerbations (strong recommendation), decrease or withdraw OCS (strong recommendation), improve QoL (conditional recommendation), improve asthma control (conditional recommendation), improve lung function (strong recommendation), and decrease rescue medication (conditional recommendation)

**Safety**
- Dupilumab showed a good safety profile; however, "longer-term data (up to 2 years) are extrapolated from atopic dermatitis studies and careful reporting of all drug-related adverse events is recommended" (conditional recommendation)

**Mepolizumab as add-on treatment**

**Uncontrolled severe eosinophilic asthma**
- Adolescents 12-17 years: recommended for uncontrolled severe eosinophilic asthma despite optimal controlled treatment to reduce severe asthma exacerbations, reduce or withdraw OCS, and improve QoL, asthma control, or lung function (conditional recommendation for all endpoints)
Table 4. Clinical Practice Guideline Recommendations for Biological Therapy in Severe Asthma

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<td></td>
<td>- Adults: recommended for uncontrolled severe eosinophilic asthma despite optimal controlled treatment to reduce severe asthma exacerbations (strong recommendation), reduce or withdraw OCS (strong recommendation), improve QoL (conditional recommendation), improve asthma control (conditional recommendation), or improve lung function (conditional recommendation)</td>
</tr>
<tr>
<td></td>
<td><strong>Safety</strong></td>
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<tr>
<td></td>
<td>- Mepolizumab showed a favorable safety profile with long-term safety data up to 5 years; however, patients should be periodically screened for parasitic infections in endemic areas (conditional recommendation)</td>
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<tr>
<td><strong>Omalizumab as add-on treatment</strong></td>
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</tr>
<tr>
<td><em>Uncontrolled severe eosinophilic asthma (both allergic and non-allergic)</em> <em>(off-label use)</em></td>
<td>- Adults: recommended for uncontrolled severe eosinophilic asthma despite optimal controlled treatment to reduce severe asthma exacerbations (strong recommendation), and improve QoL, improve lung function, or decrease rescue medication use (conditional recommendation for the last 3 outcomes)</td>
</tr>
<tr>
<td><em>Uncontrolled moderate-to-severe allergic asthma</em></td>
<td>- Children 6-11 years: recommended for uncontrolled moderate-to-severe allergic asthma despite optimal controlled treatment to reduce severe asthma exacerbations, improve asthma control, improve QoL, or reduce ICS use (conditional recommendation for all outcomes)</td>
</tr>
<tr>
<td></td>
<td>- Adolescents 12-17 years and adults: recommended for uncontrolled moderate-to-severe allergic asthma despite optimal controlled treatment to reduce severe asthma exacerbations (strong recommendation), improve asthma control, improve QoL, reduce ICS use, or reduce rescue medication use (conditional recommendation for the last 4 outcomes)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
</tr>
<tr>
<td>- Omalizumab showed a favorable safety profile with long-term safety data for more than 10 years; however, patients should be monitored 60 minutes after each of the first 3 administrations for the risk of anaphylaxis (conditional recommendation)</td>
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<tr>
<td></td>
<td>- In children 6-11 years, omalizumab may reduce viral-induced exacerbations (conditional recommendation). Serum IgE cut-offs do not have an impact in the response (conditional recommendation)</td>
</tr>
<tr>
<td><strong>Reslizumab as add-on treatment</strong></td>
<td></td>
</tr>
<tr>
<td><em>Uncontrolled severe eosinophilic asthma</em></td>
<td>- Adults: recommended for uncontrolled severe eosinophilic asthma despite optimal controlled treatment to reduce severe asthma exacerbations (strong recommendation), and improve QoL, asthma control, and lung function (conditional recommendation for the 3 last outcomes)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
</tr>
<tr>
<td>- Reslizumab showed a favorable safety profile; however, patients should be periodically screened for parasitic infections in endemic areas and monitored 30 minutes following IV administration for the potential for anaphylaxis (conditional recommendation)</td>
<td></td>
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</tbody>
</table>
**Table 4. Clinical Practice Guideline Recommendations for Biological Therapy in Severe Asthma**

<table>
<thead>
<tr>
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</tr>
</thead>
</table>
| **National Asthma Education and Prevention Program (NAEPP)** | Step 5 Care: Severe Persistent Asthma  
- Adolescents ≥12 years and adults: High-dose ICS AND LABA is the preferred treatment  
Step 6 Care: Severe Persistent Asthma  
- Adolescents ≥12 years and adults: High-dose ICS AND LABA AND OCS is the preferred treatment  
Add-on *omalizumab* may be considered as an alternative therapy in Step 5 or 6 for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA |

### Abbreviations:
- FDA, U.S. Food and Drug Administration; FeNO, exhaled nitric oxide fraction; GINA, Global Initiative for Asthma; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; IL-4R, interleukin 4 receptor; IL-5R, interleukin 5 receptor; IV, intravenous; LABA, long-acting beta 2 agonist; NAEPP, National Asthma Education and Prevention Program; OCS, oral corticosteroids; ppb, parts per billion; QoL, quality of life
- NAEPP guidelines were released prior to the FDA-approval of 4 biologic asthma therapies (benralizumab, dupilumab, mepolizumab, and reslizumab)

### Recommendation strength using the GRADE approach (for ERS/ATS and EAACI guidelines)²,¹⁹:
- Conditional/weak: trade-offs are uncertain, either because of low quality of evidence or because evidence suggests that desirable and undesirable effects are closely balanced
- Strong: desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not

### Quality of evidence using the GRADE approach (for ERS/ATS and EAACI guidelines)²,¹⁹:
- Very low: any estimate of effect is very uncertain
- Low: further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
- Moderate: further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
- High: further research is very unlikely to change the confidence in the estimate of effect

According to GINA guideline recommendations, severe asthma should be treated with Step 4 or 5 therapies (see Table 3)¹¹⁵:

- In **adults and adolescents**, preferred controller options in Step 4 include low dose ICS-formoterol (as maintenance and reliever therapy) or a medium-dose ICS-LABA plus PRN SABA. Alternative controller options include high dose ICS-LABA, add-on tiotropium, and add-on LTRA. Step 5 therapy consists of a high-dose ICS-LABA and referral to a specialist or severe asthma clinic (if available) for phenotypic evaluation and potential add-on therapy (e.g., add-on biological treatment, add-on tiotropium, add-on azithromycin, sputum-guided treatment, or add-on bronchial thermoplasty). Add-on low-dose OCS is an alternative option in Step 5¹¹⁵

- In **children 6 to 11 years of age**, Step 4 therapy includes a medium dose ICS-LABA as the preferred controller option and children should be referred to a specialist for expert advice. High dose ICS-LABA, add-on tiotropium, or add-on LTRA are alternative controller options. Step 5 therapy in children includes prompt referral to a specialist for phenotypic assessment and consideration of add-on therapy, including biological therapy. Add-on low-dose OCS or IL-5 antagonists are alternative options in Step 5¹
While combination high dose ICS-LABA is an option for all ages in Step 4 or 5, it is recommended “only on a trial basis for 3 to 6 months” due to increased risk of side effects and usually provides little additional benefit.

Add-on tiotropium has strong supportive evidence for its recommendation in patients uncontrolled with ICS-LABA to modestly improve lung function (Evidence A). Add-on low-dose OCS is a controller option for all ages in Step 5 when other add-on treatments have been tried, including biological treatment; however, it is associated with serious adverse effects (eg, cataracts, adrenal suppression).

A clinical decision tree for diagnosing and managing difficult-to-treat asthma and severe asthma is described in the GINA guideline. For difficult to treat asthma, patients can try add-on LABA, tiotropium, or LTRA, or high-dose ICS. Once type 2 airway inflammatory phenotype is confirmed and before starting treatment with biologics, the next step in the clinical decision tree should involve adherence assessment, a 3-6 month ICS dose increase, and/or treatment with non-biologic therapy for specific clinical Type 2 phenotypes including aspirin-exacerbated respiratory disease (AERD), allergic bronchopulmonary aspergillosis (ABPA), chronic rhinosinusitis, nasal polyposis, and atopic dermatitis. These should be done first, as appropriate, given the more excessive cost of biologic treatment options.

Add-on biologic type 2 targeted treatments, if accessible and affordable, are recommended for patients who have exacerbations or poor control of symptoms despite treatment with at least high dose ICS-LABA and who have allergic or eosinophilic biomarkers, or require maintenance OCS. It is also recommended to test for and treat any parasitic infections before initiating biological therapy.

The following section (ie, Selection of biological treatments for asthma) will describe the place in therapy for these biologics in further detail.

Selection of Biological Treatments for Asthma

Several clinical practice guidelines and published articles have expressed the need for head-to-head comparisons among the biological treatments for asthma. In addition, there is a need to identify novel biomarkers for the diagnosis and prognosis of asthma, and treatment response.

Biological treatment selection is based on predictors of asthma response and phenotypes as outlined for each drug class below. In addition, insurance coverage, cost, dosing frequency, route of administration (SQ or IV), and patient preference should be considered when selecting these therapies. Some biologics target the same pathway (eg, IL-5); however, there is no established “class effect.” A patient can have inadequate response to one anti-IL-5 agent but respond well to another anti IL-5 agent. As there is no real world data on biologicals, the EAACI guideline states that description of the phenotype for each biological therapy is based on inclusion and exclusion criteria from the clinical trials that led to drug approval. Appendix D summarizes the most relevant inclusion and exclusion criteria from phase 3 trials leading to drug approval in asthma patients.

a) Anti-IgE Therapy

Omalizumab is the only approved anti-IgE agent indicated for the treatment of patients ≥ 6 years with moderate-to-severe allergic asthma. The GINA guideline states that predictors of good asthma response to omalizumab include childhood-onset asthma, clinical history indicating allergen-driven
symptoms, blood eosinophils ≥260/µl, or FeNO ≥20 ppb. Of note, RCTs reported a greater reduction in exacerbations in those patients with eosinophils ≥260/µl or FeNO ≥20 ppb but an observational study showed a reduction in exacerbations regardless of baseline eosinophil count.1 It is also important to note that a patient’s baseline IgE level is not a strong predictor of asthma response. Common insurance eligibility criteria highlighted by the GINA guideline include:1

- Allergic sensitization to inhaled allergen(s) demonstrated by positive skin prick test or an allergen-specific IgE in vitro test, AND
- A certain number of exacerbations over the last year, with variation in threshold between payers, AND
- Body weight and total serum IgE within the dosing range. Prescribing information for omalizumab includes charts for adults and children ≥ 6 years with specific doses and dosage frequency of omalizumab depending on pretreatment serum IgE (between 30-1300 IU/mL) and body weight (between 20-150 kg).7

The 2020 ERS/ATS guideline suggests a blood eosinophil level of ≥260 cells/µl and FeNO ≥19.5 ppb to identify adults and adolescents with severe allergic asthma who have the highest probability of response to anti-IgE therapy (conditional recommendation, low quality of evidence).19 Guideline authors highlight that these biomarker cut-offs should be considered cautiously to guide therapy because there may be some patients with eosinophil or FeNO levels below the suggested cut-offs who can still show a good response to omalizumab.19

The 2020 EAACI guideline recommends add-on omalizumab for patients ≥ 6 years with uncontrolled moderate-to-severe allergic asthma despite optimal controller treatment.2 This population is defined by clinical trials as patients with “moderate-to-severe asthma, total IgE level of 30–700 IU/ml, and/or one perennial aeroallergen.”2 Based on subgroup analyses by biomarkers, guideline authors state that serum IgE levels do not impact response and blood eosinophil counts do not affect exacerbation response.2

b) Anti-IL-5 Therapies

Biologics of the anti-IL-5/IL-5R class, including mepolizumab (IL-5 antagonist), benralizumab (IL-5 receptor antagonist), and reslizumab (IL-5 antagonist) are indicated for the treatment of severe eosinophilic asthma.1 Reslizumab is indicated for patients ≥18 years of age, benralizumab for patients ≥12 years of age, and mepolizumab for patients ≥6 years of age (dosing varies with age). The GINA guideline states that strong predictors of good asthma response include higher blood eosinophils and a high rate of severe exacerbation over the prior year. Other predictors may include asthma with adult-onset, nasal polyposis, and baseline use of maintenance OCS. Common insurance eligibility criteria highlighted by the GINA guideline include:1

- A certain number of exacerbations in the previous year, with variation in threshold between payers, AND
- Blood eosinophils above a predetermined threshold such as ≥300 eosinophils/µl. If the patient is taking OCS, the predetermined threshold of eosinophils should be lower (eg, >150 eosinophils/µl)
The 2020 ERS/ATS guideline recommends anti-IL 5 strategy “as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma” (conditional recommendation, evidence low). No recommendation was provided for use of anti-IL5 in children and adolescents due to the insufficient number of children and adolescents treated with these therapies. This guideline suggests a blood eosinophil count threshold of ≥150/μl to guide anti-IL-5 therapy initiation in adults with severe asthma and a history of previous asthma exacerbations (conditional recommendation, evidence low).19

The 2020 EAACI guideline recommends add-on benralizumab, mepolizumab, and reslizumab for uncontrolled severe eosinophilic asthma despite optimal controller treatment in patients ≥12 years of age (benralizumab, mepolizumab) or adults (reslizumab).2 Blood eosinophil count threshold for predicting treatment response varies among anti IL-5 therapies and population definitions to formulate treatment recommendations differ depending on the anti IL-5 therapy:

- Population eligible for benralizumab is defined as patients with uncontrolled asthma on high dose ICS plus LABA and who have blood eosinophil levels of >300 cells/μL or >150 cells/μL (for OCS-dependent patients).2
- Population eligible for mepolizumab is defined as having blood eosinophil levels of ≥300 cells/μL in the previous 12 months or ≥150 cells/μL at baseline.2 Greater benefits for exacerbations are expected with mepolizumab in the subgroup of patients with higher blood eosinophil levels.2
- Population eligible for reslizumab is defined as having “at least one blood eosinophil count of 400 cells per μL or higher during a 2–4 weeks screening period and inadequately controlled asthma, receiving at least a medium dose of ICS with or without another controller drug including OCS.”2 Greater benefits for lung function and asthma control are expected with reslizumab in the subgroup of patients with higher levels of blood eosinophils.2

c) Anti-IL4 Receptor Therapy

Dupilumab is indicated for patients ≥12 years with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.9 The GINA guideline suggests higher blood eosinophils as a strong predictor and higher FeNO as a possible predictor of good asthma response.18 Typical insurance eligibility criteria highlighted by the GINA guideline include:1

- A certain number of severe exacerbations in the previous year, with variation in threshold between payers, AND
- Type 2 biomarkers above certain levels (blood eosinophils ≥150 cells/μl or FeNO ≥25 ppb) OR
- Need for maintenance OCS

The 2020 ERS/ATS guideline recommends dupilumab as add-on treatment in adults with severe eosinophilic asthma or with severe corticosteroid-dependent asthma irrespective of blood eosinophil counts (conditional recommendation, low quality of evidence).19 Greater benefits were reported in patients with blood eosinophils ≥150/μl or FeNO ≥25 ppb. No recommendation was provided for use of anti-IL-4 in adolescents due to the insufficient number of adolescents treated with this therapy.19
The 2020 EAACI guideline recommends add-on dupilumab for patients ≥12 years with uncontrolled severe eosinophilic asthma or uncontrolled severe T2 asthma despite of optimal controller treatment. In the clinical trials, these patients were uncontrolled on medium/high dose ICS plus up to 2 controllers such as OCS. Greater benefits were reported in the subgroup of patients with severe eosinophilic asthma and higher blood eosinophils and FeNO.

**Biologic Initiation and Discontinuation Considerations**

a) **Initiation and Re-Evaluation**

Initial add-on biological therapy should be trialed for at least 4 months, based on the GINA guideline. Patient’s response to each class of biologic therapy should be reviewed after 4 months and every 3-6 months thereafter, including assessment of asthma symptom control, exacerbations, lung function, type 2 comorbidities such as atopic dermatitis or nasal polyposis, other asthma-related medications, and patient satisfaction.

The EAACI guideline recommends a re-assessment of treatment response after 4 to 6 months based on the high cost of biologics; however, authors highlight the lack of validated definitions for a good response. Personalized predefined targets are recommended based on patient’s goals for asthma control.

b) **Switching**

If no response is observed after 4 months, biological therapy should be stopped and a switch to a different type 2 targeted biologic may be considered. If the patient is re-evaluated and does not present airway eosinophilia and neutrophilic inflammation, biological therapy should be withdrawn and appropriate treatment offered. If the patient develops neutralizing anti-drug antibodies (ADA), “consider switching to biologicals targeting a different pathway or to a biological targeting the same pathway but with different mechanism of action or route of administration.”

c) **Discontinuation**

For patients with good response to add-on biological therapy, discontinuation of the biologic therapy is not recommended for at least 1 year following initiation of treatment. Discontinuation should only be considered if asthma is well-controlled on medium-dose ICS and if there is no longer exposure to any previously documented allergic triggers. Based on a limited number of studies on treatment cessation, most patients experienced recurrence of exacerbations and worsening of symptoms after withdrawal of the biological treatment.

The EAACI guideline recommends continuing biological therapy if there is good treatment response based on personalized predefined targets.
Other FDA Approved Indications and Guideline Recommendations

Atopic Dermatitis

Dupilumab is additionally approved “for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.”

Atopic dermatitis (AD), also called atopic eczema, is a chronic inflammatory skin disorder characterized by intense pruritus and inflammatory eczematous lesions due to skin barrier dysfunction and immune system imbalances. AD is most common in young children 5 years of age or below (90% of cases), particularly in infants between 3 and 6 months of age. It affects up to 25% of children and approximately 2% to 3% of adults. The underlying mechanism of AD involves type 2 immune responses with the cytokines IL-4 and IL-13. AD is associated with a personal or family history of atopic diseases such as type I allergies, allergic rhinitis, and asthma.

American guidelines for the management of AD do not specifically define mild, moderate, and severe AD. In general, mild AD typically affects less body surface area (BSA), is more likely to resolve, has less intense itching, and responds to basic management alone compared to severe cases. Moderate-to-severe AD often affects larger BSA, lasts longer, has more severe pruritus, and requires additional maintenance therapy.

According to the 2014 American Academy of Dermatology (AAD) guideline, AD management includes (1) non-pharmacologic interventions such as topical moisturizers, bathing practices, and wet wrap therapy; (2) pharmacologic topical treatment such as topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs); and (3) phototherapy and systemic immunomodulatory or anti-inflammatory agents. Systemic immunomodulatory agents (eg, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil) are recommended for patients with moderate-to-severe AD who do not adequately respond to moisturizers, TCS, TCI, adjunctive methods, and/or phototherapy. No recommendations were provided for biologic agents due to the lack of data at that time.

The 2018 consensus-based European guidelines recommend dupilumab for patients with moderate-to-severe AD “in whom topical treatment is not sufficient and other systemic treatment is not advisable.” In addition, dupilumab is recommended to be used in combination with daily moisturizers and may be added to topical anti-inflammatory agents as-needed.

Chronic Rhinosinusitis with Nasal Polyposis

Rhinosinusitis is defined by the 2015 American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) guideline regarding adult sinusitis as “symptomatic inflammation of the paranasal sinuses and nasal cavity.” It is classified according to symptom duration as acute rhinosinusitis (ARS) with symptoms lasting <4 weeks and as chronic rhinosinusitis (CRS) with symptoms lasting >12 weeks. It can also be classified according to the presence or absence of nasal polyps as chronic rhinosinusitis with nasal polyposis (CRSwNP) and chronic rhinosinusitis without nasal polyposis (CRSsNP). CRSwNP causes loss of smell that can considerably impact the patient’s quality of life. The annual prevalence of rhinosinusitis in the US population is 12% to 15%. Around 4% of patients with CRS present with nasal polyps. Asthma occurs in 30%-70% of patients with CRSwNP. Management of
CRSwNP includes topical intranasal corticosteroid sprays or drops, saline irrigation, anti-leukotriene therapy, and a short-course of oral corticosteroids. If there is inadequate response to medical therapy, surgical intervention is recommended.37

Dupilumab was FDA approved in June 2019 as an add-on maintenance treatment in adult patients with inadequately controlled CRSwNP.9 The 2019 European guideline on biologics for CRSwNP proposed 5 criteria to prescribe biologics for CRSwNP. For initiation of therapy, these include (1) evidence of type 2 inflammation, (2) need for systemic corticosteroids in the previous 2 years, (3) the potential for significant reduction in quality of life, (4) significant loss of smell, and (5) diagnosis of comorbid asthma. As evidence regarding efficacy of biologics for preventing surgery is still inconclusive, the European expert team panel decided that biologics are recommended for patients with bilateral nasal polyps who had undergone sinus surgery in the past and met 3 of the 5 criteria.38 For patients with bilateral nasal polyps who have never undergone a sinus surgery, at least 4 of the 5 criteria should be met to receive a biologic.38 Type 2 biologics are not indicated for (1) CRSsNP without type 2 inflammation, (2) cystic fibrosis, (3) unilateral nasal polyps, (3) mucoceles, (4) contraindications for biologics, and (5) patient-related factors including nonadherence to therapy.

Response to biologic therapy after a year of treatment was defined by the European expert team panel as “(1) reduced nasal polyp size, (2) reduced need for systemic corticosteroids, (3) improved quality of life, (4) improved sense of smell, and (5) reduced impact of comorbidities.”38 Assessment for response to therapy was designated at week 16 in order to consider continuation or discontinuation of biologic treatment. If none of the 5 criteria is met, the biologic should be discontinued at 16 weeks.38

**Eosinophilic Granulomatosis with Polyangiitis**

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg Strauss syndrome, is a rare form of systemic vasculitis affecting small-to-medium sized vessels of multiple organ systems (eg, lungs, skin, heart, and nervous system).39-41 It is characterized by asthma, elevated blood eosinophil levels, and vasculitis.40,41 The etiology of this condition is not known, although it is thought to be an autoimmune disease.41 The prevalence of EGPA in the US is approximately 18 cases per million,42 with higher prevalence among asthmatic patients.40 Age of onset ranges from 15 to 70 years.40

According to the EGPA Consensus Task Force recommendations, published in 2015, “EGPA should be managed in collaboration with, or in, centers with established expertise in the management of small- and medium-sized-vessel vasculitides.”39 Treatment includes use of glucocorticoids (GC) as initial therapy. Patients with life and/or organ-threatening disease manifestations should be treated with GC in combination with immunosuppressants (eg, cyclophosphamide). Once remission is achieved with this combination, it is recommended to switch to maintenance therapy with azathioprine or methotrexate in addition to GC.39,43 Rituximab is an option for patients with renal impairment or refractory disease. Intravenous immunoglobulins or interferon-alpha may be reserved for EGPA refractory to other treatments.39

Mepolizumab has an orphan designation for EGPA and was approved in 2017 by the FDA for the treatment of adult patients with EGPA.8 Guidelines have not yet been updated to define its place in therapy with respect to other options. The phase 3 clinical trial generally included patients who had relapsing or refractory disease (see definitions below) while on GC.8,44 Around 50% of patients also received immunosuppressive therapy (eg, azathioprine, methotrexate, mycophenolic acid).8
• Relapsing disease: patients must have at least 1 confirmed EGPA relapse (while on steroid therapy of ≥7.5 mg/day equivalent of prednisolone) within the past 2 years requiring OCS dose increase, initiation/increased dose of immunosuppressive therapy, or hospitalization.

• Refractory disease: failure to achieve remission (Birmingham Vasculitis Activity Score [BVAS]=0 and OCS dose ≤7.5 mg/day prednisolone equivalent) within the past 6 months following induction treatment for at least 3 months on a standard regimen; or recurrence of EGPA symptoms while tapering OCS at any dose ≥7.5 mg/day prednisolone equivalent.

Chronic Idiopathic Urticaria

Urticaria is a cutaneous condition typically characterized by pruritic wheals and swellings, sometimes accompanied by angioedema. It is caused by the release of inflammatory mediators (eg, histamine, leukotrienes, and prostaglandins) from mast cells and basophils that can be activated by IgE or non-IgE. Urticaria is classified according to symptom duration as acute urticaria if symptoms last <6 weeks and chronic urticaria if symptoms last ≥6 weeks. The prevalence of chronic urticaria is approximately 0.5% to 5%. Chronic urticaria is also classified in 2 subgroups: (1) chronic spontaneous urticaria (CSU; formerly known as chronic idiopathic urticaria) if urticaria occurs spontaneously and there is an absence of an external trigger, and (2) chronic inducible urticaria (CINDU) if urticaria is induced by a known external trigger.

Omalizumab was approved in 2014 for the treatment of chronic idiopathic urticaria (CIU) in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.

According to the 2014 American Academy of Allergy, Asthma, and Immunology (AAAAI) guideline, a stepwise pharmacological approach for the management of chronic urticaria is recommended:

- Step 1: 2nd generation H1 antihistamines as monotherapy are considered first-line treatment
- Step 2: second-line treatments include up-dosing the 2nd generation H1 antihistamine utilized in Step 1, add another 2nd generation H1 antihistamine, add H2 antagonist, or add leukotriene receptor antagonist. Adding a 1st generation antihistamine at bedtime may be an option for patients with uncontrolled urticaria despite higher doses of 2nd generation H1 antihistamines
- Step 3: Potent antihistamines (eg, hydroxyzine or doxepin) can be considered if patients are uncontrolled with Step 2 therapy
- Step 4: the addition of omalizumab (first option) or cyclosporine A (second-line option due to its toxicity) can be considered for refractory chronic urticaria (ie, urticaria uncontrolled with maximal antihistamine treatment [eg, step 3 therapy])

The 2014 European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) guideline provides a strong recommendation with high level of evidence for the use of omalizumab in combination with 2nd generation H1 antihistamines as third-line for the treatment of urticaria. First line treatment includes 2nd generation H1 antihistamines and second line treatment includes up-dosing of 2nd generation H1 antihistamines.
Off-Label Uses

The 2020 EAACI guideline provides the following recommendations for off-label uses with benralizumab, dupilumab, and omalizumab:

- Based on a post hoc analysis, benralizumab is recommended as add-on treatment in adults with *uncontrolled severe allergic asthma* despite optimal controlled treatment to decrease severe asthma exacerbations, and improve quality of life (QoL), asthma control, and lung function. The strength of this recommendation was rated as weak by guideline authors because desirable and undesirable effects of the biologic were closely balanced or uncertain.

- Based on a post hoc analysis, dupilumab is recommended as add-on therapy in adults and adolescents 12 to 17 years of age with *uncontrolled severe allergic asthma* despite optimal controller treatment to reduce severe asthma exacerbations, and improve asthma control and lung function. The strength of this recommendation was rated as weak by guideline authors.

- Based on an SR conducted by the EAACI, dupilumab is recommended as add-on therapy in adults and adolescents 12 to 17 years of age with *uncontrolled severe type 2 asthma* (allergic and non-allergic asthma) despite optimal controller treatment to reduce severe asthma exacerbations (strong recommendation), reduce or withdraw OCS (strong recommendation), improve QoL (conditional recommendation), improve asthma control (conditional recommendation), improve lung function (strong recommendation), and reduce rescue medication (conditional recommendation).

- Omalizumab is recommended for adults with *uncontrolled severe eosinophilic asthma* (both allergic and non-allergic) despite optimal controlled treatment to reduce severe asthma exacerbations (strong recommendation), and improve QoL, improve lung function, or decrease rescue medication use (conditional recommendation for the last 3 outcomes).

Efficacy of Biologicals for the Treatment of Asthma

Biological treatments for the management of asthma are efficacious for reducing exacerbations, controlling asthma symptoms, and decreasing OCS use, which is linked to serious adverse events.

Phase 3 clinical trials leading to FDA approval of benralizumab, dupilumab, mepolizumab, and reslizumab generally included patients with a history of at least 1 to 2 exacerbations requiring systemic corticosteroids in the previous year, and patients with uncontrolled asthma despite treatment with medium- to high-dose ICS plus additional controller medications including LABA, LTRA, or OCS. In 2 RCTs of benralizumab, patients were specifically required to be on high dose ICS plus LABA for at least 3 to 6 months before enrollment. Blood eosinophil level requirements varied between trials ranging from at least 150 cells/µL with benralizumab and mepolizumab to at least 400 cells/µL with reslizumab. The 2 mepolizumab RCTs required patients to have an eosinophilic phenotype (ie, documentation of blood eosinophil levels ≥150 cells/µL at study visit 1 or ≥300 cells/µL within 12 months prior to visit 1) for trial entry. The 2 RCTs of dupilumab and some trials of benralizumab and reslizumab did not specify or require a certain blood eosinophil count for trial entry.

Phase 3 clinical trials leading to FDA approval of omalizumab included patients with moderate-to-severe asthma despite treatment with ICS alone or with ICS plus SABA or other additional controller...
medications (eg, LABA, OCS), and patients with positive skin test reaction to at least 1 perennial aeroallergen. Other requirements for trial entry included body weight of 150 kg or lower and baseline total IgE levels between 30 to 700 IU/mL for adults and adolescents 12 years of age or older and 30 to 1300 IU/mL for children 6 to 11 years of age.7,58 Appendix D provides detailed information regarding inclusion and exclusion criteria from phase 3 trials leading to drug approval in asthma patients.

Based on RCTs and meta-analyses in patients with severe asthma, asthma exacerbations in the previous year, and varying requirements for eosinophil levels, anti-IL-5 and anti-IL-5 receptor therapies (benralizumab, mepolizumab, and reslizumab) were associated with approximately 55% reduction in severe asthma exacerbations and improvements in health-related quality of life, lung function (ie, FEV1), and symptom control compared to placebo.1,59 Changes in lung function and asthma symptoms were small but statistically significant; however, clinical relevance was unclear. Blood eosinophils were reduced with all these biologics, with nearly complete reduction with benralizumab.1,59 Patients taking OCS experienced a 50% reduction in the maintenance OCS dose with mepolizumab or benralizumab versus placebo.1,19 Limited data is available regarding the efficacy of mepolizumab in children.1

Reslizumab is not approved in the pediatric population.

Based on RCTs and a meta-analysis in patients with uncontrolled moderate-to-severe asthma and ≥1 exacerbation in the previous year, anti-IL-4 receptor therapy (dupilumab) significantly reduced the rate of severe exacerbation by approximately 50%, and improved health-related quality of life, lung function (ie, FEV1), and symptom control compared to placebo.1,55,60 Benefits were more pronounced in patients with higher blood eosinophil and FeNO levels compared to those with lower levels.55 Patients with OCS-dependent severe asthma experienced a 50% reduction in the median OCS dose at week 24 with anti-IL-4 receptor compared with placebo, regardless of baseline blood eosinophil or FeNO levels.1,56

A systematic review of RCTs in adults and children with moderate-to-severe asthma showed omalizumab (as add-on therapy to ICS) was more efficacious than placebo in decreasing asthma exacerbations, hospitalizations, withdrawing ICS therapy or reducing daily ICS doses, and improving asthma symptoms and quality of life.61 An RCT by Hanania et al (2011) comparing omalizumab with placebo in patients with severe allergic asthma inadequately controlled with high-dose ICS plus LABA (with or without additional controller medications) reported a significantly higher reduction in asthma exacerbations with omalizumab vs. placebo.62 These patients experienced a 25% relative reduction in the exacerbation rate with omalizumab vs. placebo. In the subgroup of patients with severe allergic asthma inadequately controlled with high-dose ICS and LABA alone (no additional controllers), the relative reduction in the exacerbation rate was 34%.62 Asthma symptoms and quality of life were significantly improved with omalizumab compared with placebo.62 Open-label studies including patients with severe allergic asthma and at least 1 severe exacerbation in the previous year found a 50-65% decrease in the rate of exacerbations, a significant improvement in health-related quality of life, and 40-50% decrease in maintenance OCS dose with omalizumab therapy.1 Pre-specified and post-hoc analyses of the RCT by Hanania et al reported better results with omalizumab vs. placebo regarding severe asthma exacerbations rates, FEV1, and time to first exacerbation in the subgroup of patients with baseline blood eosinophil levels ≥ 260 cells/µL compared to those with <260 cells/µL. Patients with FeNO ≥19.5 ppb had greater improvements in quality of life, exacerbation rate, and time to first exacerbation compared to those with FeNO <19.5 ppb.19,63
Safety

Immunogenicity

As biological agents are large proteins, there is a risk for immunogenicity. Clinical trials with biological treatments have detected the development of anti-drug antibodies (ADAs), including neutralizing antibodies (NAs).\textsuperscript{6-10} ADAs can increase the clearance of the biologic agent.\textsuperscript{6,8,9} The clinical significance of ADA formation may be undetectable or unknown, as stated in the prescribing information of mepolizumab and reslizumab.\textsuperscript{6,10} Mepolizumab prescribing information reported no correlation between ADA titers and eosinophil levels; however, benralizumab prescribing information reported elevated eosinophil levels associated with high ADA titers.\textsuperscript{6,8} In addition, some patients may experience adverse events. For instance, 2 patients receiving dupilumab experienced hypersensitivity reactions (eg, serum sickness reaction and serum sickness-like reaction) associated with high antibody titers.\textsuperscript{9}

Comparative immunogenicity among biologic agents may be misleading because the incidence of ADAs and NAs reported in clinical studies depends on several factors including “assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.”\textsuperscript{8,9} Incidence of antibodies to each biologic agent is summarized in Table 5.

Table 5. Immunogenicity Concerns for Biological Treatments for Asthma\textsuperscript{6-10}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name (RoA)</th>
<th>Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab</td>
<td>Fasenra (SQ)</td>
<td>- 13% of patients developed anti-benralizumab antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 12% of patients developed NAs</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Dupixent (SQ)</td>
<td>AD, asthma, and CRSwNP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with AD, asthma, and CRSwNP receiving DUPIXENT 300 mg Q2W for 52 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 5% of patients developed antibodies (2% of patients with ADA responses; 2% of patients developed NAs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adolescents with AD receiving DUPIXENT 300 mg or 200 mg Q2W for 16 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 16% developed antibodies (3% with persistent ADA responses and 5% with NAs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with asthma receiving DUPIXENT 200 mg Q2W for 52 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 9% developed antibodies (4% with persistent ADA responses and 4% had NAs)</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Nucala (SQ)</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 6% of patients on Nucala 100 mg developed anti-mepolizumab antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 patient on Nucala 100 mg develop NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EGPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- &lt;2% of patients developed anti-mepolizumab antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No NA were identified</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Xolair (SQ)</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.1% of patients developed anti-omalizumab antibodies in patients ≥ 6 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CIU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No detectable antibodies</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Cinqair (IV)</td>
<td>Approximately 5% of patients developed anti-reslizumab antibodies (NAs were not assessed)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, atopic dermatitis; ADA, antidrug antibody; CIU, chronic idiopathic urticaria; CRSwNP, chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis; IV, intravenous; NA, neutralizing antibody; SQ, subcutaneous
Warnings Common to All Biological Treatments for Asthma

- **Hypersensitivity Reactions**

Omalizumab and reslizumab carry a black box warning regarding anaphylaxis risk.\(^7,10\) With omalizumab, anaphylaxis has been reported following the first dose of omalizumab or after a year of treatment; some of these cases have been fatal.\(^7\) Signs and symptoms of anaphylaxis included bronchospasm, hypotension, syncope, urticaria, and angioedema of the throat or tongue. Anaphylaxis is estimated to occur in at least 0.2% of patients receiving omalizumab, based on postmarketing reports.\(^7\)

With reslizumab, anaphylaxis has been reported following the second dose in 0.3% of patients in placebo-controlled trials.\(^10\) Signs and symptoms of anaphylaxis included dyspnea, decreased oxygen saturation, wheezing, vomiting, and skin and mucosal impairment (e.g., urticaria).\(^10\)

Both agents should be administered in a healthcare setting by healthcare providers with experience in managing anaphylaxis. Patients should be under observation for an adequate period of time.

Benralizumab, dupilumab, and mepolizumab do not carry a black box warning for anaphylaxis; however, hypersensitivity reactions, including anaphylaxis, have been reported with these agents after hours or days of administration.\(^6,8,9\) Discontinue any biological treatment immediately if a hypersensitivity reaction occurs.\(^6-10\) All biological treatments are contraindicated if the patient experiences severe hypersensitivity reactions to the agent or components of the product.\(^6-10\)

- **Acute Asthma Symptoms or Deteriorating Disease**

Biological treatments are not indicated to treat acute asthma symptoms, acute exacerbations, acute bronchospasm, or status asthmaticus.\(^6-10\)

- **Reduction of Corticosteroid Dosage**

When initiating biological therapy, abrupt discontinuation of corticosteroids should be avoided. Corticosteroid dose reduction should be performed gradually and under the supervision of a health care provider. Dose reduction may cause systemic withdrawal symptoms and occurrence of conditions that were masked with corticosteroid therapy.\(^6-10\)

- **Parasitic (Helminth) Infection**

Patients should be screened and treated for parasitic (helminth) infections prior to therapy initiation with benralizumab, dupilumab, mepolizumab, or reslizumab.\(^6,8-10\) If the patient is infected while on treatment and does not respond to anti-helminth treatment, the biologic agent should be discontinued until the infection resolves.\(^6,8-10\)

Omalizumab prescribing information states that patients at high risk of geohelminth infection should be monitored during omalizumab therapy.\(^7\)

**Specific Warnings for Some Biological Treatments for Asthma**

- **Malignancy Risk**

Clinical trials in adults and adolescents with asthma and other allergic conditions reported malignant neoplasms in 0.5% of patients treated with omalizumab compared to 0.2% of patients receiving placebo.
Breast, non-melanoma skin, prostate, melanoma and parotid malignancies were the most commonly reported with omalizumab therapy. With reslizumab, placebo-controlled trials showed that 0.6% of patients receiving reslizumab reported at least 1 malignancy compared to 0.3% of patients receiving placebo.

Cases of malignancies are not reported in the prescribing information of benralizumab, dupilumab, and mepolizumab.

- **Eosinophilic Conditions**

Rare cases of eosinophilic conditions have been reported with omalizumab and dupilumab. They may occur following a reduction in the corticosteroid dose. Serious systemic eosinophilia may manifest as vasculitis consistent with EGPA.

Eosinophilic pneumonia has occurred with dupilumab in asthma patients. Vasculitis consistent with EGPA has occurred with dupilumab in asthma patients and CRSwNP patients with comorbid asthma.

- **Conjunctivitis and keratitis**

Conjunctivitis and keratitis occurred at a numerically higher rate in patients receiving dupilumab vs. placebo for atopic dermatitis, but rates in asthma patients were similar between dupilumab and placebo. In CRSwNP, 2% of patients receiving dupilumab experienced conjunctivitis vs. 1% in the placebo arm; no keratitis cases were reported.

- **Laboratory tests**

Increases in serum total IgE levels have been observed after omalizumab administration due to omalizumab:IgE complex formation. Elevation of IgE may continue for up to a year after withdrawal of omalizumab therapy.

- **Other Warnings**

Arthritis/arthralgia, rash, fever, and lymphadenopathy may occur with omalizumab therapy. Cases of herpes zoster have been reported with mepolizumab. Patients with atopic dermatitis or CRSwNP and comorbid asthma should not adjust or stop asthma treatment with dupilumab without consultation with a physician.

Table 6 summarizes warning and precautions for these biologics.

<table>
<thead>
<tr>
<th>Warnings/Precautions</th>
<th>BEN</th>
<th>DUP</th>
<th>MEP</th>
<th>OMA</th>
<th>RES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity reactions (eg, anaphylaxis, angioedema, and urticarial)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X²</td>
<td>X²</td>
</tr>
<tr>
<td>Do not use to treat acute asthma symptoms, exacerbations, bronchospasm, or status asthmaticus</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Do not suddenly discontinue use of corticosteroids when therapy is initiated</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patients should be screened and treated for parasitic (helminth) infections prior to therapy initiation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X²</td>
<td>X</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Eosinophilic conditions as indicated by vasculitic rash, declining pulmonary symptoms, cardiac complications, or neuropathy</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

27
Table 6. Warnings and Precautions for Biological Treatments for Asthma\(^{6-10}\)

<table>
<thead>
<tr>
<th>Warnings/Precautions</th>
<th>BEN</th>
<th>DUP</th>
<th>MEP</th>
<th>OMA</th>
<th>RES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis and keratitis</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with atopic dermatitis or CRSwNP and comorbid asthma should not adjust or stop treatment without consultation of physician</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes zoster opportunistic infection (consider vaccination as appropriate)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fever, arthritis/arthralgia, rash and lymphadenopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Increased serum total IgE levels that may continue for up to 1 year post-administration</td>
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</tr>
</tbody>
</table>

Abbreviations: BEN, benralizumab; CRSwNP, chronic rhinosinusitis with nasal polyposis; DUP, dupilumab; IgE, Immunoglobulin E; MEP, mepolizumab; OMA, omalizumab; RES, reslizumab

\(^a\) Black box warning regarding anaphylaxis risk

\(^b\) Simple monitoring in patients at high risk of geohelminth infection is all that is recommended for omalizumab in the prescribing information

Table 7 summarizes the most common adverse events for these biologics.

Table 7. Common Adverse Reactions for Biological Treatments for Asthma\(^{6-10}\)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name (RoA)</th>
<th>Most Common Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab</td>
<td>Fasenra (SQ)</td>
<td>Incidence ≥5%: headache and pharyngitis</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Dupixent (SQ)</td>
<td>AD (\geq 1%): injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye (\text{Asthma}) (\geq 1%): injection site reactions, oropharyngeal pain, and eosinophilia (\text{CRSwNP}) (\geq 1%): injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Nucala (SQ)</td>
<td>Incidence ≥5%: headache, injection site reaction, back pain, and fatigue</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Xolair (SQ)</td>
<td>Asthma (\text{Common AEs in patients} \geq 12\text{ years}:) arthralgia, pain, leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache (\text{Common AEs in children} 6\text{ to} &lt;12\text{ years}:) nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bites, and epistaxis (\text{CIU}) Incidence ≥ 2%: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Cinqair (IV)</td>
<td>Incidence ≥ 2%: oropharyngeal pain</td>
</tr>
</tbody>
</table>

Abbreviations: AD, atopic dermatitis; ADA, antidrug antibody; CIU, chronic idiopathic urticaria; CRSwNP, chronic rhinosinusitis with nasal polyposis; EGP, eosinophilic granulomatosis with polyangiitis; IV, intravenous; NA, neutralizing antibody; SQ, subcutaneous
Utah Medicaid Utilization Data

**Table 8** and **Table 9** provide pharmacy and medical utilization data for biological treatments in the overall Utah Medicaid fee-for-service (FFS) population. No FFS pediatric patients were identified.

Most recently, in 2020 there have been pharmacy fills only for dupilumab by 5 unique patients. Other biologics (benralizumab and omalizumab) were filled in 2019 by less than 5 patients. Regarding medical claims in 2020, there have been 8 patients receiving either benralizumab, mepolizumab, or omalizumab.

Recall that omalizumab and reslizumab are administered by a healthcare professional in a health care setting due to the risk of anaphylaxis that can be fatal; the others are self-administered. Though during the COVID-19 pandemic, certain patients can be allowed to self-administer omalizumab.

From 2018 through June 2020, pharmacy utilization data showed that 15 unique FFS patients filled a prescription for benralizumab, dupilumab, or omalizumab, with the majority of them filling a prescription for dupilumab. During the same time period, medical utilization data showed that 32 unique FFS patients filled a prescription for a biologic agent, with the majority for omalizumab.

**Table 8. Pharmacy Data for Biological Treatments in the Overall FFS Population From 2018 Through June 2020**

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab</td>
<td>FASENRA injection 30 mg/mL</td>
<td>0</td>
<td>0</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>DUPIXENT injection 300 mg/2mL</td>
<td>&lt;5</td>
<td>5</td>
<td>9</td>
<td>37</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>XOLAIR injection 150 mg/mL (prefilled syringe)</td>
<td>0</td>
<td>0</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
<td>&lt;5</td>
<td>5</td>
<td>12</td>
<td>43</td>
</tr>
</tbody>
</table>

**Table 9. Medical Data for Biological Treatments in the Overall FFS Population From 2018 Through June 2020**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab</td>
<td>FASENRA injection 30 mg/mL</td>
<td>&lt;5</td>
<td>15</td>
<td>&lt;5</td>
<td>36</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>DUPIXENT injection 300 mg/2mL</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>NUCALA injection 100 mg</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>XOLAIR injection 150 mg/mL (prefilled syringe)</td>
<td>0</td>
<td>0</td>
<td>&lt;5</td>
<td>12</td>
</tr>
</tbody>
</table>
Table 9. Medical Data for Biological Treatments in the Overall FFS Population From 2018 Through June 2020

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XOLAIR solution 150 mg (single-dose vial)</td>
<td>7</td>
<td>52</td>
<td>6</td>
<td>48</td>
<td>&lt;5</td>
<td>5</td>
<td>12</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>Reslizumab CINQAIR injection</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
<td>12</td>
<td>74</td>
<td>19</td>
<td>109</td>
<td>8</td>
<td>13</td>
<td>32</td>
<td>196</td>
</tr>
</tbody>
</table>

Table 10 provides the number of patients who filled a prescription for a biologic agent over the last year (June 2019 to June 2020) and had an ICD-10 diagnosis code submitted in the last 2 years (between June 2018 and June 2020) for moderate-to-severe asthma, eosinophilic asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyposis, eosinophilic granulomatosis with polyangiitis, or chronic idiopathic urticarial (ie, ICD-10 codes that relate to the approved indications of these biologics). Appendix E provides a complete list of ICD-10 diagnosis codes.

Table 10. Pharmacy and Medical Data for Biological Treatments and Diagnosis Codes Submitted

<table>
<thead>
<tr>
<th>Number of Unique Patients and ICD-10 Codes Submitted</th>
<th>FASENRA&lt;sup&gt;c&lt;/sup&gt; (benralizumab) injection 30mg/mL</th>
<th>DUPIXENT&lt;sup&gt;c&lt;/sup&gt; (dupilumab) injection 300mg/2mL</th>
<th>NUCALA&lt;sup&gt;c&lt;/sup&gt; (Mepolizumab) for injection 100mg</th>
<th>XOLAIR&lt;sup&gt;c&lt;/sup&gt; (omalizumab) injection 150mg/mL</th>
<th>XOLAIR&lt;sup&gt;c&lt;/sup&gt; (omalizumab) for injection 150mg</th>
<th>CINQAIR&lt;sup&gt;c&lt;/sup&gt; (reslizumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of unique patients receiving each biologic during the last year</td>
<td>6</td>
<td>13</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Moderate-to-severe asthma (J45.40, J45.50, or J45.909)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Asthma (J45.XXX)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Eosinophilic asthma (J82)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AD (L20.XX)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CRSwNP (J32.X, J33.X)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>EGPA (M30.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CIU (L50.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Any of the above ICD-10 codes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6</td>
<td>13</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AD, atopic dermatitis; CIU, chronic idiopathic urticaria; CRSwNP, chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis; ICD, International Classification of Diseases

<sup>a</sup> Number of unique patients receiving each biologic in the last year (June 2019 to June 2020) AND who had an ICD-10 code submitted in the last 2 years (between June 2018 and June 2020) for each of the FDA approved indications

<sup>b</sup> Number of unique patients receiving each biologic in the last year (June 2019 to June 2020) AND who had at least one of the specified ICD-10 codes related to the approved indications of these biologics (ie, moderate-to-severe asthma, asthma, eosinophilic asthma, AD, CRSwNP, EGPA, or CIU) submitted in the last 2 years (between June 2018 and June 2020)

<sup>c</sup> A prior authorization is currently in place for this product to ensure use aligns with approved indications
Considerations for Prior Authorization Criteria

Utah Medicaid currently has prior authorization (PA) criteria in place for benralizumab, dupilumab, and omalizumab, last updated in March, October, and December 2019, respectively. These PA request forms are included in Appendix F. While highlighting clinical/prescribing aspects for consideration during the development of PA for these biological products, some potential areas where modifications may be considered on the current PA criteria are also discussed.

PA Criteria Considerations for Benralizumab

Criteria for Severe Eosinophilic Asthma

1. Patients should be 12 years of age or older based on the approved indication
2. Patients should have a diagnosis of severe asthma AND an eosinophilic phenotype based on the approved indication
   - Severe asthma is defined by the 2020 GINA guideline as uncontrolled asthma (ie, poor symptom control and exacerbations) despite Step 4 or 5 treatment with fully optimized asthma management (eg, good adherence, appropriate inhaler technique, and treatment of comorbidities); or that deteriorates when decreasing high dose treatment.\(^1\) The 2020 ERS/ATS guideline defines severe asthma (once diagnosis is confirmed and comorbidities managed) as "asthma that requires treatment with high dose inhaled corticosteroids [...] plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy"\(^19\)
   - Consider specifying a certain number of severe exacerbations in the last 12 months (eg, ≥2) and requiring a specific level of blood eosinophils (eg, ≥150 eosinophils/µl). The 2020 GINA guideline describes the following most common insurance eligibility criteria for benralizumab:
     - A certain number of severe exacerbations in the previous year
       - GINA defines uncontrolled asthma as having poor symptom control and/or ≥2 exacerbations within 1 year requiring OCS or ≥1 serious exacerbations requiring hospitalization\(^1\)
       - Two phase 3 clinical trials of benralizumab (SIROCCO and CALIMA trials) included patients with ≥2 exacerbations within 1 year requiring ≥3 day increase of OCS dose, emergency department visit resulting in OCS, or hospitalization

   - Blood eosinophil levels above a predetermined threshold
     - Payer eligibility criteria may include a blood eosinophil cut-off level of ≥300 eosinophils/µl for anti-IL-5 therapies. If the patient is taking OCS, the predetermined threshold of eosinophils may be lower (eg, >150 eosinophils/µl)\(^1\)
- The 2020 ERS/ATS guideline provides a weak recommendation for a blood eosinophil count threshold of ≥150 eosinophils/µl to guide anti-IL-5 therapy initiation in adults with severe asthma and a history of previous asthma exacerbations\textsuperscript{19}

- The EAACI guideline specifies a blood eosinophil cut-off level for patients eligible for benralizumab of >300 cells/µL or >150 cells/µL (for OCS-dependent patients)\textsuperscript{2}

- One of the 3 confirmatory clinical trials (ZONDA study) required patients to have a blood eosinophil level of 150 cells/µL or more. This trial included patients who received OCS for at least 6 months prior to enrollment. The other 2 confirmatory trials did not specify eosinophil levels

3. Benralizumab should be administered as add-on maintenance therapy based on the approved indication

4. Consider requiring prescription of benralizumab by or in consultation with a specialist with expertise in treating severe asthma

   - The GINA guideline states that patients with uncontrolled asthma despite optimized Step 4 or 5 therapy should be referred to a specialist with expertise in managing severe asthma or severe asthma clinic, if possible\textsuperscript{1}

5. Consider trial and failure, or intolerability of high dose ICS plus LABA, based on the GINA guideline. This regimen should be tried for at least 3 months with all comorbidities and factors influencing asthma control (eg, adherence, inhaler technique) appropriately addressed\textsuperscript{1,19}

   - According to the 2020 GINA guideline, add-on biologic therapy for severe asthma should be considered for “patients with exacerbations or poor symptom control on at least high dose ICS-LABA, who have eosinophilic or allergic biomarkers, or need maintenance OCS.”\textsuperscript{1} GINA states that uncontrolled type 2 inflammation is commonly caused by poor adherence and inappropriate use of inhalers\textsuperscript{1}

   - Other non-biologic alternative treatments that can be used in severe asthma include the triple therapy with medium to high-dose ICS-LABA plus tiotropium. Tiotropium has strong supportive evidence as an add-on therapy to modestly improve lung function in patients not well controlled on ICS-LABA alone (Evidence A per GINA). However, GINA suggests add-on tiotropium if there is no evidence of type 2 inflammation or if add-on biologic therapy is not affordable or available.\textsuperscript{1} In addition, add-on LTRA or add-on macrolide may be considered if add-on biologic therapy is not affordable or available.\textsuperscript{1} Add-on low-dose OCS should be considered for some patients when other add-on treatments, including biologic therapy, have been tried\textsuperscript{1}

   - The 3 phase 3 trials of benralizumab in asthma patients included patients using medium or high dose ICS plus LABA and other asthma controller medications in the previous 3 to 6 months before enrollment
Current PA criteria for benralizumab includes “trial and failure of at least one preferred single agent and one preferred combo agent.” The following amendments may be considered:

- Modifying the PA to require trial and failure, or intolerability of at least a high dose ICS-LABA that has been taken for at least 3 months AND with prescriber attestation that optimal adherence, using the correct inhaler technique, has occurred during that time

- Requiring blood eosinophil level of ≥150 eosinophils/µl prior to benralizumab initiation

PA Criteria Considerations for Dupilumab

Criteria for Moderate-to-Severe Asthma Indication

1. Patients should be 12 years of age or older, based on the approved indication

2. Patients should have a diagnosis of moderate-to-severe asthma AND an eosinophilic phenotype OR oral-corticosteroid dependent asthma, based on the approved indication

   - Consider specifying a certain number of severe exacerbations in the last 12 months (eg, ≥1) and requiring a specific level of Type 2 biomarkers (eg, ≥150 eosinophils/µl or FeNO ≥25 ppb) or need for maintenance OCS. The 2020 GINA guideline describes the following most common insurance eligibility criteria for dupilumab:

   ✓ Certain number of severe exacerbations in the previous year

      o GINA guideline defines uncontrolled asthma as having poor symptom control and/or ≥2 exacerbations within 1 year requiring OCS or ≥1 serious exacerbations requiring hospitalization\(^1\)

      o Two phase 3 clinical trials of dupilumab (AS trial 1 and AS trial 2) included patients with history of ≥1 exacerbations requiring systemic corticosteroids or hospital visit in the previous year\(^9\)

   ✓ Blood eosinophil or FeNO levels above a predetermined threshold for severe eosinophilic asthma/type 2 asthma

      o Payer eligibility criteria usually include a blood eosinophil cut-off level of ≥300 eosinophils/µl or ≥150 eosinophils/µl, or FeNO ≥25 ppb\(^1\)

      o The 2020 ERS/ATS guideline does not suggest blood eosinophil count or FeNO thresholds to guide anti-IL-4 therapy initiation. Greater benefits were reported in patients with blood eosinophils ≥150/µl or FeNO ≥25 ppb\(^19\)

      o The EAACI guideline does not specify blood eosinophil count or FeNO thresholds to guide anti-IL-4 therapy initiation. Greater benefits were reported in the subgroup of patients with severe eosinophilic asthma and with higher blood eosinophils and FeNO\(^2\)

      o Phase 3 clinical trials of dupilumab did not require patients to have a baseline minimum blood eosinophil count or FeNO level to enter the trials

✓ Need for maintenance OCS
3. Dupilumab should be administered as add-on maintenance therapy based on the approved indication.

4. Consider requiring prescription of dupilumab by or in consultation with a specialist with expertise in treating severe asthma.
   - GINA states that patients with severe asthma should be referred to a specialist with expertise in managing severe asthma or severe asthma clinic, if possible.

5. Consider trial and failure, or intolerability of high dose ICS plus LABA, based on the GINA guideline. This regimen should be tried for at least 3 months with all comorbidities and factors influencing asthma control (eg, adherence, inhaler technique) appropriately addressed.
   - According to the 2020 GINA guideline, add-on biologic therapy for severe asthma should be considered for “patients with exacerbations or poor symptom control on high dose ICS-LABA, who have eosinophilic or allergic biomarkers, or need maintenance OCS.” GINA states that uncontrolled type 2 inflammation is commonly caused by poor adherence and inappropriate use of inhalers.
   - Other non-biologic alternative treatments that can be used in severe asthma include the triple therapy with medium to high-dose ICS-LABA plus tiotropium. Tiotropium has strong supportive evidence as an add-on therapy to modestly improve lung function in patients not well controlled on ICS-LABA alone (Evidence A per GINA). However, GINA suggests add-on tiotropium if there is no evidence of type 2 inflammation or if add-on biologic therapy is not affordable or available. In addition, add-on LTRA or add-on macrolide may be considered if add-on biologic therapy is not affordable or available. Add-on low-dose OCS should be considered for some patients when other add-on treatments, including biologic therapy, have been tried.
   - There are 2 phase 3 clinical trials of dupilumab in asthma patients that led to FDA approval. One RCT included patients with moderate-to-severe asthma taking medium- to high-dose ICS plus other controller medications including LABA or LTRA. The other RCT included patients with severe asthma requiring maintenance OCS and high-dose ICS plus other controller medications including LABA or LTRA.

Criteria for Atopic Dermatitis Indication

1. Patients should be 6 years of age or older, per approved indication.
2. Patients should have a diagnosis of moderate-to-severe atopic dermatitis, per approved indication.
3. Consider trial and failure, or contraindication to at least topical prescription therapies (eg, topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and/or phototherapy).
   - Dupilumab is approved for patients not adequately controlled with topical prescription therapies or when those are not advisable with respect to patient-specific factors.
   - The 2014 AAD guideline recommends systemic immunomodulatory agents (eg, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil) for patients with moderate-to-severe AD who do not adequately respond to moisturizers, TCS, TCI, adjunctive methods,
and/or phototherapy. No recommendations were provided for biologic agents due to the lack of data at that time. The 2018 consensus-based European guideline recommends dupilumab for patients with moderate-to-severe AD “...in whom topical treatment is not sufficient and other systemic treatment is not advisable.”

Criteria for Chronic Rhinosinusitis with Nasal Polyposis Indication

1. Patients should be 18 years of age or older, per approved indication
2. Patients should have a diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP), per approved indication
3. Dupilumab should be administered as add-on maintenance therapy, per approved indication
4. Consider the following criteria for initiation of biologic treatment as recommended in the 2019 European guideline for the treatment of CRSwNP:
   - (1) evidence of type 2 inflammation, (2) need for systemic corticosteroids in the previous 2 years, (3) disease causing significant reduction in quality of life, (4) significant loss of smell, and (5) diagnosis of comorbid asthma. Authors recommended biologics for patients with bilateral nasal polyps who had undergone sinus surgery and still met 3 of the 5 criteria. For those with bilateral nasal polyps but no history of surgery, 4 of the 5 criteria should be met to initiating a biologic.
   - The usual management of CRSwNP includes topical intranasal corticosteroid sprays or drops, saline irrigation, anti-leukotriene therapy, and a short-course of an oral corticosteroid. If there is inadequate response to medical therapy, surgical intervention is recommended. Biologic therapy may be tried before or after surgery while also considering criteria in the previous bullet point.

Current PA criteria for dupilumab

For the asthma indication, the following amendments may be considered:

- Requiring trial and failure, or intolerability of at least a high dose ICS-LABA that has been taken for at least 3 months AND with prescriber attestation that optimal adherence, using the correct inhaler technique, has occurred during that time
- Requiring blood eosinophil levels of ≥150 eosinophils/µl or FeNO levels of ≥25 ppb for patients with severe eosinophilic asthma; OR requiring dependence on OCS

PA Criteria Considerations for Mepolizumab

Criteria for Severe Eosinophilic Asthma Indication

1. Patients should be 6 years of age or older, based on the approved indication
2. Patients should have a diagnosis of severe asthma AND an eosinophilic phenotype, based on the approved indication
Severe asthma is defined by the 2020 GINA guideline as uncontrolled asthma (ie, poor symptom control and exacerbations) despite Step 4 or 5 treatment with fully optimized asthma management (eg, good adherence, appropriate inhaler technique, and treatment of comorbidities); or that deteriorates when decreasing high dose treatment. The 2020 ERS/ATS guideline defines severe asthma (once diagnosis is confirmed and comorbidities managed) as “asthma that requires treatment with high dose inhaled corticosteroids [...] plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy”.

Consider specifying a certain number of severe exacerbations in the last 12 months (eg, ≥2) and requiring a specific level of blood eosinophils (eg, ≥150 cells/µl). The 2020 GINA guideline describes the following most common insurance eligibility criteria for mepolizumab:

- A certain number of severe exacerbations in the previous year
  - GINA defines uncontrolled asthma as having poor symptom control and/or ≥2 exacerbations within 1 year requiring OCS or ≥1 serious exacerbations requiring hospitalization¹
  - One phase 3 trial of mepolizumab (MENSA study) included patients with a history of ≥2 exacerbations in the prior year despite regular use of high dose ICS plus a second controller (with or without OCS). The other phase 3 trial (SIRIUS study) did not require patients to have a history of exacerbations in the last year⁵²,⁵³

- Blood eosinophil levels above a predetermined threshold
  - Payer eligibility criteria usually include a blood eosinophil cut-off level of ≥300 eosinophils/µl for anti-IL-5 therapies. If the patient is taking OCS, the predetermined threshold of eosinophils may be lower (eg, >150 eosinophils/µl)¹
  - The 2020 ERS/ATS guideline provides a weak recommendation for a blood eosinophil count threshold of ≥150 eosinophils/µl to guide anti-IL-5 therapy initiation in adults with severe asthma and a history of previous asthma exacerbations¹⁹
  - The 2020 EAACI guideline defines the population eligible for mepolizumab as patients with blood eosinophil levels of ≥300 cells/µL in the previous 12 months or ≥150 cells/µL at screening.² Greater benefits for exacerbations are expected with mepolizumab in the subgroup of patients with higher levels of blood eosinophils²
  - The 2 confirmatory trials of mepolizumab in severe asthma patients included patients with blood eosinophil levels of ≥300 cells/µL in the previous 12 months before enrollment or ≥150 cells/µL at screening⁵²,⁵³
3. Mepolizumab should be administered as add-on maintenance therapy based on the approved indication.

4. Consider requiring prescription of mepolizumab by or in consultation with a specialist with expertise in treating severe asthma.
   - The GINA guideline states that patients with uncontrolled asthma despite optimized Step 4 or 5 therapy should be referred to a specialist with expertise in managing severe asthma or severe asthma clinic, if possible.

5. Consider trial and failure, or intolerability of high dose ICS plus LABA, based on the GINA guideline. This regimen should be tried for at least 3 months with all comorbidities and factors influencing asthma control (e.g., adherence, inhaler technique) appropriately addressed.
   - According to the 2020 GINA guideline, add-on biologic therapy for severe asthma should be considered for “patients with exacerbations or poor symptom control on at least high dose ICS-LABA, who have eosinophilic or allergic biomarkers, or need maintenance OCS.” GINA states that uncontrolled type 2 inflammation is commonly caused by poor adherence and inappropriate use of inhalers.
   - Other non-biologic alternative treatments that can be used in severe asthma include the triple therapy with medium to high-dose ICS-LABA plus tiotropium. Tiotropium has strong supportive evidence as an add-on therapy to modestly improve lung function in patients not well controlled on ICS-LABA alone (Evidence A per GINA). However, GINA suggests add-on tiotropium if there is no evidence of type 2 inflammation or if add-on biologic therapy is not affordable or available. In addition, add-on LTRA or add-on macrolide may be considered if add-on biologic therapy is not affordable or available. Add-on low-dose OCS should be considered for some patients when other add-on treatments, including biologic therapy, have been tried.
   - The 2 phase 3 trials of mepolizumab included patients with severe asthma despite regular use of high dose ICS plus additional controller(s) (with or without OCS).

Criteria for Eosinophilic Granulomatosis with Polyangiitis Indication

1. Patients should be 18 years of age or older based on the approved indication.

2. Patients should have a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) based on the approved indication.

3. “EGPA should be managed in collaboration with, or in, centers with established expertise in the management of small- and medium-sized-vessel vasculitides,” according to the 2015 EGPA Consensus Task Force recommendations.

4. Consider trial and failure (i.e., EGPA relapse) of at least a systemic glucocorticoid as monotherapy.
   - According to the 2015 EGPA Consensus Task Force recommendations, glucocorticoids are the mainstay of EGPA treatment.
The RCT leading to FDA approval of mepolizumab in EGPA included patients who had a history of relapsing or refractory disease and were receiving a stable dosage of OCS before enrollment.\textsuperscript{8,44}

**PA Criteria Considerations for Omalizumab**

*Criteria for Moderate-to-Severe Allergic Asthma Indication*

1. Patients should be *6 years of age or older*, based on the approved indication.

2. Patients should have a diagnosis of *moderate to severe persistent asthma* with a *positive skin test or in vitro reactivity to a perennial aeroallergen* AND symptoms that are inadequately controlled with inhaled corticosteroids, based on the approved indication.

3. Consider requiring a minimum pre-treatment IgE level of 30 IU/mL and minimum body weight of 20 kg, as these are the minimum values specified in the product labeling for initiation/dosing of omalizumab for patients 6 years and older.\textsuperscript{7}

4. Additional considerations based on the most common insurance eligibility criteria for omalizumab, as described by the GINA guideline:
   - A certain number of exacerbations in the previous year
     - GINA defines uncontrolled asthma as having poor symptom control and/or ≥2 *exacerbations within 1 year requiring OCS* or ≥1 *serious exacerbations requiring hospitalization*.\textsuperscript{1}
     - Clinical trials of omalizumab did not require patients to have a specific number of exacerbation in the last year for trial entry.\textsuperscript{7}

5. Omalizumab should be administered as add-on maintenance therapy based on the approved indication.

6. Consider requiring prescription of omalizumab by or in consultation with a specialist with expertise in treating severe asthma. In addition, omalizumab should be administered by a healthcare professional in a health care setting due to the risk of anaphylaxis that can be fatal (see exception due to the Covid-19 pandemic on page 4).\textsuperscript{7}
   - The GINA guideline states that patients with uncontrolled asthma despite optimized Step 4 or 5 therapy should be referred to a specialist with expertise in managing severe asthma or severe asthma clinic, if possible.\textsuperscript{1}

7. Consider trial and failure, or intolerability of *high dose ICS plus LABA*, based on the GINA guideline. This regimen should be tried for at least 3 months with all comorbidities and factors influencing asthma control (eg, adherence, inhaler technique) appropriately addressed.\textsuperscript{1,19}
   - According to the GINA guideline, add-on biologic therapy for severe asthma should be considered for “patients with exacerbations or poor symptom control on high dose ICS-LABA, who have eosinophilic or allergic biomarkers, or need maintenance OCS”.\textsuperscript{1}
- The 2007 NAEPP Expert Panel Report 3 states that add-on omalizumab may be considered as an alternative therapy in Step 5 or 6 for “patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA”.

- Other non-biologic alternative treatments that can be used in severe asthma include the triple therapy with medium to high-dose ICS-LABA plus tiotropium. Tiotropium has strong supportive evidence as an add-on therapy to modestly improve lung function in patients not well controlled on ICS-LABA alone (Evidence A per GINA). However, GINA suggests add-on tiotropium if there is no evidence of type 2 inflammation or if add-on biologic therapy is not affordable or available. In addition, add-on LTRA or add-on macrolide may be considered if add-on biologic therapy is not affordable or available. Add-on low-dose OCS should be considered for some patients when other add-on treatments, including biologic therapy, have been tried.

- Clinical trials of omalizumab in moderate-to-severe asthma included patients with symptomatic asthma treated with ICS plus SABA (for adults and adolescents) or medium- to high-dose ICS with or without an additional controller medication (for children 6 to < 12 years).

Criteria for Chronic Idiopathic Urticaria

1. Patients should be 12 years of age and older, per labeled indication

2. Patients should have a diagnosis of chronic idiopathic urticaria (now called chronic spontaneous urticaria), per labeled indication

3. Consider trial and failure of at least H1 antihistamine treatment, based on the approved indication. Alternatively, may consider trial and failure of other regimen options proposed in the 2014 AAAAI guideline: combination of a 2nd generation H1 antihistamine with another 2nd generation antihistamine, combination of a 2nd generation H1 antihistamine with an H2 antagonist, combination of a 2nd generation H1 antihistamine with a 1st generation antihistamine for bedtime, combination of a 2nd generation H1 antihistamine with a leukotriene receptor antagonist, AND hydroxyzine or doxepin

- FDA approved indication for omalizumab includes treatment of patients with CIU "who remain symptomatic despite H1 antihistamine treatment”.

- Based on the 2014 AAAAI guideline, the addition of omalizumab can be considered for refractory chronic urticaria (ie, urticaria uncontrolled with maximal antihistamine treatment [eg, step 3 therapy that includes hydroxyzine or doxepin]).

- The 2014 EAACI/GA²LEN/EDF/WAO guideline provides a strong recommendation with high quality of evidence for the use of omalizumab in combination with 2nd generation H1 antihistamines as third-line for the treatment of urticaria. Patients who have inadequate response with up-titration of H1 antihistamine dose can proceed to this third-line treatment according to the guideline.
The 2 RCTs leading to FDA approval of omalizumab in CIU included patients who were already on H1 antihistamine therapy.  

**Current PA criteria for omalizumab:**

For the asthma indication, the following amendments may be considered:

- Requiring trial and failure, or intolerability of at least a high dose ICS-LABA that has been taken for at least 3 months AND with prescriber attestation that optimal adherence, using the correct inhaler technique, has occurred during that time
- Requiring a minimum pre-treatment IgE of 30 IU/mL and minimum body weight of 20 kg, as these are the minimum values specified in the product labeling for initiation/dosing of omalizumab for patients 6 years and older.

**PA Criteria Considerations for Reslizumab**

**Criteria for Severe Eosinophilic Asthma Indication**

1. Patients should be 18 years of age or older based on the approved indication

2. Patients should have a diagnosis of severe asthma AND an eosinophilic phenotype based on the approved indication

- Severe asthma is defined by the 2020 GINA guideline as uncontrolled asthma (ie, poor symptom control and exacerbations) despite Step 4 or 5 treatment with fully optimized asthma management (eg, good adherence, appropriate inhaler technique, and treatment of comorbidities); or that deteriorates when decreasing high dose treatment. The 2020 ERS/ATS guideline defines severe asthma (once diagnosis is confirmed and comorbidities managed) as “asthma that requires treatment with high dose inhaled corticosteroids [...] plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy.”

- Consider specifying a certain number of severe exacerbations in the last 12 months (eg, ≥2) and requiring a specific level of blood eosinophils (eg, >150 eosinophils/µl). The 2020 GINA guideline describes the following most common insurance eligibility criteria for reslizumab:

  ✓ A certain number of severe exacerbations in the previous year

  - GINA defines uncontrolled asthma as having poor symptom control and/or ≥2 exacerbations within 1 year requiring OCS or ≥1 serious exacerbations requiring hospitalization.

  - Two of the 4 phase 3 clinical trials of reslizumab included patients with ≥1 exacerbations requiring systemic corticosteroids in the last 12 months. The remaining 2 trials did not specify the number of exacerbations required. Demographics and baseline characteristics of patients in the 4 trials showed a mean number of exacerbations in the prior year of 2
Blood eosinophil levels above a predetermined threshold

- Payer eligibility criteria usually include a blood eosinophil cut-off level of \( \geq 300 \text{ eosinophils/} \mu\text{l} \) for anti-IL-5 therapies. If the patient is taking OCS, the predetermined threshold of eosinophils may be lower (eg, \( >150 \text{ eosinophils/} \mu\text{l} \))\(^1\)

- The 2020 ERS/ATS guideline provides a weak recommendation for a blood eosinophil count threshold of \( \geq 150 \text{ eosinophils/} \mu\text{l} \) to guide anti-IL-5 therapy initiation in adults with severe asthma and a history of previous asthma exacerbations\(^19\)

- The EAACI guideline defines the population eligible for reslizumab as patients having “at least one blood eosinophil count of 400 cells per μL or higher during a 2–4 weeks screening period and inadequately controlled asthma, receiving at least a medium dose of ICS with or without another controller drug including OCS.”\(^2\) Greater benefits on lung function and asthma control are expected with reslizumab in the subgroup of patients with higher blood eosinophils\(^2\)

- Three of the 4 confirmatory clinical trials of reslizumab required patients to have a blood eosinophil count of \( \geq 400 \text{ cells/} \mu\text{L} \) at screening (within 3 to 4 weeks of dosing). Study IV did not require patients to have a specific blood eosinophil count (80% of patients had a blood eosinophil level of <400 cells/\( \mu\text{L} \) at screening)\(^10\)

3. Reslizumab should be administered as add-on maintenance therapy based on the approved indication

4. Consider requiring prescription of reslizumab by or in consultation with a specialist with expertise in treating severe asthma. In addition, reslizumab should be administered by a healthcare professional in a health care setting due to the risk of anaphylaxis that can be fatal\(^10\)

   - The 2020 GINA guideline states that patients with uncontrolled asthma despite optimized Step 4 or 5 therapy should be referred to a specialist with expertise in managing severe asthma or severe asthma clinic, if possible\(^1\)

5. Consider trial and failure, or intolerability of high dose ICS plus LABA, based on the GINA guideline. This regimen should be tried for at least 3 months with all comorbidities and factors influencing asthma control (eg, adherence, inhaler technique) appropriately addressed\(^1,19\)

   - According to the 2020 GINA guideline, add-on biologic therapy for severe asthma should be considered for “patients with exacerbations or poor symptom control on high dose ICS-LABA, who have eosinophilic or allergic biomarkers, or need maintenance OCS.” Uncontrolled type 2 inflammation is commonly caused by poor adherence and inappropriate use of inhalers\(^1\)
Three of the 4 phase 3 trials of reslizumab included patients taking medium or high dose ICS with or without additional controller medications (eg, LABA) and with or without OCS at baseline.

Re-Authorization Criteria for Biological Treatments in the Management of Asthma

The following points for discussion may be considered:

1. Initial authorization of add-on biological therapy for at least 4 months

   - The GINA guideline suggests trial of add-on biological therapy for at least 4 months. The EAACI guideline recommends a re-assessment of treatment response after 4 to 6 months based on the high cost of biologics. Although GINA and EAACI guidelines highlight the lack of well-defined criteria for a good response, the following general criteria to evaluate patient’s response may be considered:

     ✓ Frequency and severity of exacerbations over the trial period
     ✓ Asthma symptom control
     ✓ Lung function: Increased FEV₁ compared to baseline
     ✓ Type 2 comorbidities such as nasal polyposis and atopic dermatitis
     ✓ Treatment intensity (including OCS dose, if previously on OCS)
     ✓ Patient satisfaction
     ✓ Side-effects

   If the response is unclear after 4 months, biological trial extension during 6 to 12 months should be considered. If no response is observed after the first 4 months, biological therapy should be stopped and a switch to a different type 2 targeted biologic may be considered.

2. Re-evaluation of response is suggested after 4 months and then every 3 to 6 months thereafter, based on the GINA guideline

Summary

Severe asthma is defined by GINA guidelines as uncontrolled asthma despite step 4 or 5 treatment (medium or high dose ICS with a second controller, or maintenance OCS) and fully optimized asthma management (eg, optimal adherence, correct inhaler technique, and treatment of comorbidities); or asthma that deteriorates when decreasing high dose treatment. This report focuses on Type 2 inflammatory asthma phenotypes (eg, early onset allergic asthma and late-onset eosinophilic asthma) that occur in half of patients with severe asthma. There are currently 5 biological treatments (benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab) indicated as add-on maintenance therapy for patients with asthma and type 2 inflammatory phenotype (allergic asthma or eosinophilic asthma). Omalizumab, an IgE antagonist, is the only product approved for moderate-to-severe allergic asthma. The 3 IL-5 antagonists (benralizumab, mepolizumab, and reslizumab) are approved for severe eosinophilic asthma and the IL-4 receptor antagonist (dupilumab) is approved for moderate-to-severe asthma with an eosinophilic phenotype or with OCS-dependent asthma. All
biological treatments are administered subcutaneously, except reslizumab that is administered intravenously only.

Biological treatments for asthma are efficacious for reducing exacerbations, controlling asthma symptoms, and decreasing OCS use, which is linked to serious adverse events. Omalizumab and reslizumab have a black box warning regarding anaphylaxis risk. Other warnings related to these agents include hypersensitivity reactions, screening and potential treatment of parasitic infections prior to therapy initiation, caution regarding reduction of corticosteroid dosage, and avoiding their use for acute asthma symptoms or status asthmaticus.

Based on the 2020 GINA guideline, add-on biologic treatment should be considered for patients who have exacerbations or poor control of symptoms despite treatment with high dose ICS-LABA and who have allergic or eosinophilic biomarkers or need for maintenance OCS. There are specific biomarkers associated with type 2 inflammation that may predict a good asthma response to biological treatment such as high levels of eosinophils or FeNO, and for some products, a certain threshold was used for inclusion criteria in clinical trials. Biological treatment selection is based on predictors of asthma response and phenotypes. In addition, insurance coverage, cost, dosing frequency, route of administration (SQ or IV), and patient preference should be considered when selecting these therapies.

Regarding asthma indication, prior authorization (PA) criteria for all biological treatments may require use according to FDA approved indications (asthma severity, age, asthma phenotype, and add-on therapy), trial and failure of at least high dose ICS plus LABA, and prescription by or in consultation with a specialist with expertise in treating severe asthma. In addition, specific PA criteria for each biological treatment may be required. Omalizumab PA criteria may require positive skin prick test or allergen-specific IgE test, meeting a certain number of exacerbations over the last year (eg, ≥2), a minimum serum IgE of 30 IU/mL and minimum body weight of 20 kg, and administration by a healthcare professional in a health care setting due to the risk of anaphylaxis. PA criteria for IL-5 antagonists may require meeting a certain number of exacerbations over the last year (eg, ≥2) and blood eosinophil levels above a predetermined threshold (eg, ≥150 cells/µl). In addition, reslizumab should be administered by a healthcare professional in a health care setting due to the risk of anaphylaxis. Dupilumab PA criteria may require meeting a certain number of exacerbations over the last year (eg, ≥1), type 2 biomarkers above certain levels (eg, blood eosinophils ≥150 cells/µl or FeNO ≥25 ppb), or dependence on OCS. Initial reauthorization criteria for all biological treatments in asthma patients may include positive response to add-on biological therapy after at least 4 months.

PA criteria for indications other than asthma are included on pages 34 to 40.
References


### Appendix A: Literature Search Strategy

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to June 05, 2020  
Search Strategy (Date of search: June 7, 2020)

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<thead>
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<th>Searches</th>
<th>Results</th>
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</thead>
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</tr>
<tr>
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<td>Dupilumab.ti,ab,kw,kf.</td>
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</tr>
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<td>6</td>
<td><em>Antibodies, Monoclonal, Humanized/ or <em>Antibodies, Monoclonal/ or <em>Biological Products/ or <em>Anti-Asthmatic Agents/ or <em>Anti-Allergic Agents/ or (monoclonal antibod</em> or biologic</em> or anti-asthmatic</em> or antiasthmatic</em> or antiasthmatic</em> or anti-allergic* or antiallergic*).ti,ab,kw,kf.</td>
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</tr>
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</tr>
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<td>16</td>
<td>limit 14 to yr=&quot;2019 -Current&quot;</td>
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<tr>
<td>17</td>
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## Appendix B: Special Population Considerations

### Table 1. Special Population Considerations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name (RoA)</th>
<th>Pregnancy</th>
<th>Breast Feeding</th>
<th>Pediatric Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benralizumab</strong></td>
<td>Fasenra (SQ)</td>
<td>No adequate data is available in pregnant women. Monoclonal antibodies are known to cross the placenta; benralizumab may be transmitted from mother to fetus. No evidence of fetal harm was reported in animal studies at doses higher than the MRHD</td>
<td>Lack of data on the presence of the drug in human or animal milk, effects on breast fed infants, and milk production. Benefits of breastfeeding, mother’s clinical need for benralizumab, and potential adverse effects on infants should be considered</td>
<td>Indicated for patients ≥12 years of age. The safety and efficacy in patients &lt; 12 years of age has not been established</td>
</tr>
<tr>
<td><strong>Dupilumab</strong></td>
<td>Dupixent (SQ)</td>
<td>Human IgG antibodies are known to cross the placenta; dupilumab may be transmitted from mother to fetus. No adverse developmental effects were observed in animal studies at doses higher than the MRHD. Case reports and case series suggested no increased risk for major birth defects, miscarriages, or negative maternal or fetal outcomes in pregnant women exposed to dupilumab</td>
<td>Lack of data on the presence of the drug in human milk, effects on breast fed infants, and milk production. Benefits of breastfeeding, mother’s clinical need for dupilumab, and potential adverse effects on infants should be considered</td>
<td>Indicated for patients ≥ 12 years of age. The safety and efficacy in patients &lt; 12 years of age has not been established</td>
</tr>
<tr>
<td><strong>Mepolizumab</strong></td>
<td>Nucala (SQ)</td>
<td>Available data in pregnant women is insufficient to determine drug-related risks. Monoclonal antibodies are known to cross the placenta; mepolizumab may be transmitted from mother to fetus. No evidence of fetal harm was reported in animal studies at doses higher than the MRHD</td>
<td>Lack of data on the presence of the drug in human milk, effects on breast fed infants, and milk production. Benefits of breastfeeding, mother’s clinical need for mepolizumab, and potential adverse effects on infants should be considered</td>
<td>Indicated for patients ≥ 6 years of age. The safety and efficacy in patients &lt; 6 years of age has not been established</td>
</tr>
<tr>
<td><strong>Omalizumab</strong></td>
<td>Xolair (SQ)</td>
<td>Human IgG antibodies are known to cross the placenta; omalizumab may be transmitted from mother to fetus. No adverse developmental effects were reported in animal studies at doses higher than the MRHD. A registry study suggested no increased rate of major birth defects or miscarriage and an increased rate of low birth weight in pregnant women exposed to omalizumab</td>
<td>Lack of data on the presence of the drug in human milk, effects on breast fed infants, and milk production. Benefits of breastfeeding, mother’s clinical need for omalizumab, and potential adverse effects on infants should be considered. A registry study did not show significant increases in “infection and infestations” events in infants exposed to omalizumab via breast milk</td>
<td>Indicated for patients ≥ 6 years of age. The safety and efficacy in patients &lt; 6 years of age has not been established</td>
</tr>
</tbody>
</table>
### Table 1. Special Population Considerations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name (RoA)</th>
<th>Pregnancy</th>
<th>Breast Feeding</th>
<th>Pediatric Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reslizumab</td>
<td>Cinqair (IV)</td>
<td>Monoclonal antibodies are known to cross the placenta; reslizumab may be transmitted from mother to fetus. No adverse developmental effects were observed in animal studies at doses higher than the MRHD</td>
<td>Lack of data on the presence of the drug in human milk, effects on breast fed infants, and milk production. Benefits of breastfeeding, mother’s clinical need for reslizumab, and potential adverse effects on infants should be considered</td>
<td>The safety and efficacy in pediatric patients have not been established.</td>
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</tbody>
</table>

Abbreviations: IgG, immunoglobulin G; IV, intravenous; MRHD, maximum recommended human dose; RoA, route of administration; SQ, subcutaneous
### Appendix C: Daily Doses of Inhaled Corticosteroids

**Table 1. Daily Doses of Inhaled Corticosteroids (Extracted from GINA Guideline)**

<table>
<thead>
<tr>
<th></th>
<th>Adults and Adolescents (≥ 12 years)</th>
<th>Children (6 to 11 years)</th>
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</thead>
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<tr>
<td></td>
<td>Low Dose (µg/day)</td>
<td>Medium Dose (µg/day)</td>
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<tr>
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<td>200-500</td>
<td>&gt;500-1000</td>
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<tr>
<td>Beclometasone dipropionate (pMDI, extrafine particle)</td>
<td>100-200</td>
<td>&gt;200-400</td>
</tr>
<tr>
<td>Budesonide (DPI)</td>
<td>200-400</td>
<td>&gt;400-800</td>
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<tr>
<td>Ciclesonide (pMDI, extrafine particle)</td>
<td>80-160</td>
<td>&gt;160-320</td>
</tr>
<tr>
<td>Fluticasone furoate (DPI)</td>
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<td>100</td>
</tr>
<tr>
<td>Fluticasone propionate (DPI)</td>
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<td>&gt;250-500</td>
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<tr>
<td>Fluticasone propionate (pMDI, standard particle)</td>
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<td>&gt;250-500</td>
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<tr>
<td>Mometasone furoate (DPI)</td>
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<td>Mometasone furoate (pMDI, standard particle)</td>
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<tr>
<td>Beclometasone dipropionate (pMDI, standard particle)</td>
<td>100-200</td>
<td>&gt;200-400</td>
</tr>
<tr>
<td>Beclometasone dipropionate (pMDI, extrafine particle)</td>
<td>50-100</td>
<td>&gt;100-200</td>
</tr>
<tr>
<td>Budesonide (DPI)</td>
<td>100-200</td>
<td>&gt;200-400</td>
</tr>
<tr>
<td>Budesonide (nebules)</td>
<td>250-500</td>
<td>&gt;500-1000</td>
</tr>
<tr>
<td>Ciclesonide (pMDI, extrafine particle)</td>
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<td>&gt;80-160</td>
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<tr>
<td>Fluticasone furoate (DPI)</td>
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<td>50</td>
</tr>
<tr>
<td>Fluticasone propionate (DPI)</td>
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<td>&gt;100-200</td>
</tr>
<tr>
<td>Fluticasone propionate (pMDI, standard particle)</td>
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<td>&gt;100-200</td>
</tr>
<tr>
<td>Mometasone furoate (pMDI, standard particle)</td>
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<td>100</td>
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</table>

Abbreviations: DPI, dry powder inhaler; pMDI, pressurized metered dose inhaler
Appendix D: Inclusion and Exclusion Criteria in Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Phase 3 Trial</th>
<th>Inclusion Criteria&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exclusion Criteria&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Benralizumab (Fasenra)<sup>b</sup> | SIROCCO<sup>50</sup> (NCT01928771) | • Age 12–75 years  
• ≥40 kg  
• History of asthma requiring medium- or high-dose ICS (>250-μg fluticasone dry powder formulation equivalents total daily dosage) + LABA for ≥1 year before enrollment  
• ≥2 documented asthma exacerbations requiring systemic corticosteroids or a transitory increase in the maintenance dosage of OCS within 1 year before enrollment  
• Use of ICS + LABA +/- OCS and other asthma controllers for ≥3 months before enrollment:  
  o Patients ≥18 years of age: high-dose ICS treatment only (>500 μg/day fluticasone propionate dry powder formulation or equivalent daily)  
  o Patients 12-17 years of age: medium- or high-dose ICS (≥500 μg/day fluticasone propionate dry powder formulation or equivalent daily)  
• ACQ-6 score of ≥1.5 at enrollment (questionnaire used to assess symptoms and rescue therapy use on a scale of 0–6)  
• Allowance of additional maintenance asthma controller agents (eg, tiotropium, LTRAs, chromone, theophylline, and OCS) for ≥30 days before the first visit  
• There was no required baseline minimum blood eosinophil count | • History of anaphylaxis to any biologic drug  
• Any pulmonary disease other than asthma  
• Untreated or refractory parasitic infection in prior 24 weeks  
• Acute upper or lower respiratory infections treated with antibiotics or antivirals in prior 30 days  
• Use of immunosuppressive medication in prior 3 months  
• Immunoglobulin or blood products in prior 30 days  
• Live attenuated vaccines in prior 30 days  
• Inactive/killed vaccines in prior 1 week  
• New allergen immunotherapy in prior 30 days  
• Current use of oral or ophthalmic nonselective β-blocker  
• Use of 5-lipoxygenase inhibitors or roflumilast |
### Table 1. Inclusion and Exclusion Criteria in Phase 3 Clinical Trials Leading to FDA Approval

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Phase 3 Trial</th>
<th>Inclusion Criteriaa</th>
<th>Exclusion Criteriaa</th>
</tr>
</thead>
</table>
| CALIMA\textsuperscript{57} (NCT01914757) | | - Age 12–75 years  
- ≥40 kg  
- History of asthma requiring medium- or high-dose ICS (>250 μg [medium] or ≥500 μg [high] fluticasone dry powder formulation or equivalent total daily dosage) + LABA for ≥1 year before enrollment  
- ≥2 documented asthma exacerbations requiring systemic corticosteroids or a transitory increase in the maintenance dosage of OCS within 1 year before enrollment  
- Use of medium- or high-dose ICS (≥500 μg per day fluticasone propionate dry powder formulation or equivalent total daily dosage) + LABA +/- OCS and other asthma controllers for ≥3 months before enrollment  
- ACQ-6 score of ≥1.5 at enrollment (questionnaire used to assess symptoms and rescue therapy use on a scale of 0–6)  
- Allowance of additional maintenance asthma controller agents (eg, tiotropium, LTRAs, chromone, theophylline, and OCS) for ≥30 days before enrollment  
- There was no required baseline minimum blood eosinophil count | - History of anaphylaxis from any biologic drug  
- Any pulmonary disease not asthma  
- Untreated or refractory parasitic infection in prior 24 weeks  
- Acute upper or lower respiratory infections treated with antibiotics or antivirals in prior 30 days.  
- Use of immunosuppressive medication  
- Immunoglobulin or blood products in prior 30 days  
- Live attenuated vaccines in prior 30 days  
- Inactive/killed vaccines in prior 1 week  
- Current use of any nonselective β-blocker  
- Use of 5-lipoxygenase inhibitors or roflumilast |
| ZONDA\textsuperscript{51} (NCT02075255) | | - Age 18–75 years  
- ≥40 kg  
- Blood eosinophil count of ≥150 cells/μl  
- History of asthma requiring medium- or high-dose ICS (total daily dose equivalent to >250 μg fluticasone dry powder formulation) + LABA for ≥1 year prior to enrollment  
- Use of high-dose ICS (>500 μg fluticasone dry powder formulation) + LABA for≥ 6 months before enrollment  
- Oral glucocorticoid therapy during ≥6 consecutive months immediately prior to enrollment. Patients received oral prednisolone at trial entry  
- Allowance of additional maintenance asthma controller agents (eg, tiotropium, LTRAs, chromone, theophylline) | - History of anaphylaxis to any biologic drug  
- Any pulmonary disease other than asthma  
- Untreated or refractory parasitic infection in prior 24 weeks  
- Acute upper or lower respiratory infections treated with antibiotics or antivirals in prior 30 days.  
- Use of immunosuppressive medication  
- Asthma control achieved using OCS at ≤5mg/d during run-in phase  
- Oral glucocorticoid controller that is not prednisone or prednisolone  
- Immunoglobulin or blood products in prior 30 days  
- Live attenuated vaccines in prior 30 days  
- Inactive/killed vaccines in prior 1 week |
Table 1. Inclusion and Exclusion Criteria in Phase 3 Clinical Trials Leading to FDA Approval

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Phase 3 Trial</th>
<th>Inclusion Criteria&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exclusion Criteria&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Dupilumab (Dupixent)<sup>9</sup> | LIBERTY ASTHMA QUEST, (NCT02414854)<sup>55</sup> | • Age ≥ 12 years  
  • Patients with moderate to severe asthma taking medium or high-dose ICS (≥250 μg of fluticasone propionate twice daily or equipotent inhaled glucocorticoid daily dosage) + up to 2 second controllers (eg, LABA or LTRA) for ≥ 3 months  
  • History of ≥1 exacerbation needing systemic corticosteroids or hospital visit in the previous year  
  • There was no required baseline minimum blood eosinophil count or biomarkers of type 2 inflammation | • Current use of any oral or ophthalmic nonselective β-blocker  
  • Use of 5-lipoxygenase inhibitors or roflumilast  
  • Blood eosinophil level >1500 cells/μl at screening  
  • Age < 12 years  
  • Weight < 30 kg  
  • Patients with any pulmonary disease other than asthma  
  • Patients with an asthma exacerbation leading to emergency treatment, hospitalization, or treatment with systemic corticosteroids within 4 weeks prior to first visit |
| | LIBERTY ASTHMA VENTURE, (NCT02528214)<sup>56</sup> | • Age ≥ 12 years  
  • Patients with severe asthma requiring daily maintenance OCS in the 6 months prior to first visit  
  • Treatment with regular high-dose ICS (>500 μg or equipotent equivalent) + up to 2 controllers (eg, LABA, LTRA)  
  • There was no required baseline minimum blood eosinophil count | • Blood eosinophil level >1500 cells/μl at screening  
  • Age < 12 years  
  • Weight < 30 kg  
  • Patients with any pulmonary disease other than asthma  
  • Patients with an asthma exacerbation leading to emergency treatment or hospitalization within 4 weeks prior to first visit |
| Mepolizumab (Nucala)<sup>8</sup> | MENSA study (NCT01691521)<sup>53</sup> | • Age 12-82 years  
  • Eosinophilic asthma documented by blood eosinophils ≥150 cells/μl at screening (within 6 weeks of dosing) or ≥300 cells/μl within 12 months of enrollment; and evidence of asthma  
  • Severe asthma  
  • History of ≥2 exacerbations requiring OCS in the prior year despite regular use of high dose ICS (≥880 μg/day fluticasone propionate) | • Patients with a concurrent respiratory disease  
  • Patients with an eosinophilic disease  
  • Patients who received Xolair (omalizumab) within 130 days of visit 1 |
Table 1. Inclusion and Exclusion Criteria in Phase 3 Clinical Trials Leading to FDA Approval

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Phase 3 Trial</th>
<th>Inclusion Criteriaa</th>
<th>Exclusion Criteriaa</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Omalizumab</em> (Xolair)<em>7</em></td>
<td>Asthma Trial 1 (Study 008)<em>7,58</em></td>
<td>Age 12 to 76 years</td>
<td>Weight &gt;150 kg</td>
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<tr>
<td></td>
<td></td>
<td>Moderate to severe persistent asthma (per NHLBI NAEPP criteria) for ≥1 year and positive skin test reaction to at least one perennial aeroallergen</td>
<td>Patients receiving additional concomitant controller therapy (including LABA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline IgE 30-700 IU/mL</td>
<td>Currently smoking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Body weight ≤ 150 kg</td>
<td></td>
</tr>
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<td></td>
<td>Asthma Trial 2 (Study 009)<em>7,58</em></td>
<td>Age 12 to 76 years</td>
<td>Weight &gt;150 kg</td>
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<tr>
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<td></td>
<td>Moderate to severe persistent asthma (per NHLBI NAEPP criteria) for ≥1 year and positive skin test reaction to at least one perennial aeroallergen</td>
<td>Patients receiving additional concomitant controller therapy (excluding LABA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline IgE 30-700 IU/mL</td>
<td>Currently smoking</td>
</tr>
<tr>
<td></td>
<td>Asthma Trial 3 (Study 011 - steroid-reduction trial)<em>7,58</em></td>
<td>Age 12 to 76 years</td>
<td>Weight &gt;150 kg</td>
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<td></td>
<td></td>
<td>Severe persistent asthma (per NHLBI NAEPP criteria) for ≥1 year and positive skin test reaction to at least one perennial aeroallergen</td>
<td>Patients receiving additional concomitant controller therapy (excluding LABA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients were receiving high dose ICS (≥ 1000 µg/day of fluticasone propionate) and a subset was also receiving LABA and OCS</td>
<td>Currently smoking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline IgE 30-700 IU/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Body weight ≤ 150 kg</td>
<td>Concomitant LABA was allowed</td>
</tr>
<tr>
<td></td>
<td>Asthma Trial 4<em>7,58</em></td>
<td>Age 6-&lt;12 years</td>
<td>Not reported in the prescribing information</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthma diagnosis &gt;1 year</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1. Inclusion and Exclusion Criteria in Phase 3 Clinical Trials Leading to FDA Approval\(^5\)\(^-\)\(^10\)

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Phase 3 Trial</th>
<th>Inclusion Criteria(^a)</th>
<th>Exclusion Criteria(^a)</th>
</tr>
</thead>
</table>
| Reslizumab (Cinqair)\(^10\) | Study I\(^10,54\) | • Moderate to severe persistent asthma (Step 3 or 4 per NHLBI NAEPP criteria) uncontrolled on ICS (fluticasone propionate DPI ≥200 µg/day or equivalent) +/- additional controller medications  
  • Positive skin test reaction to at least a perennial aeroallergen  
  • History of symptoms and exacerbations in past year  
  • Baseline IgE 30-1300 IU/mL  
  • Body weight 20-150 Kg | • Patients with any pulmonary disease other than asthma  
  • Other relevant comorbidities that may interfere with the study  
  • Known hyper-eosinophilic syndrome  
  • Active parasitic infection within 6 months before screening |
|                           | Study II\(^10,54\) | • Age 12 to 75 years  
  • Patients with asthma uncontrolled on medium to high dose ICS (≥440 mg/day of fluticasone propionate or equivalent) with or without other controllers, including OCS. 82% of patients were on medium to high dose ICS plus LABA at baseline  
  • Blood eosinophil count ≥400 cells/µL at screening (within 3-4 weeks of dosing)  
  • History of ≥ 1 exacerbation requiring systemic CS in the past year  
  • Maintenance OCS were allowed | • Not reported in the prescribing information |
|                           | Study III\(^10\) | • Blood eosinophil count ≥400 cells/µL at screening (within 3-4 weeks of dosing)  
  • Maintenance OCS were not allowed | • Patients with any pulmonary disease other than asthma  
  • Other relevant comorbidities that may interfere with the study  
  • Known hyper-eosinophilic syndrome  
  • Use of systemic immunosuppressive or immunomodulating therapy such as anti-IgE ≤6 months prior to study entry |
|                           | Study IV\(^10,64\) | • Age 18 to 65 years  
  • Patients with asthma uncontrolled on medium dose ICS (≥440 mg/day of fluticasone propionate or equivalent) at screening  
  • Additional controllers (LABA, LTRA, 5-lipoxengase inhibitors, or cromolyn) were allowed if regimen was stable during 30 days before screening  
  • Maintenance OCS were not allowed  
  • No requirement for a blood eosinophil count at screening  
  • 80% of patients had a blood eosinophil count <400 cells/µL at screening | • Patients with any pulmonary disease other than asthma  
  • Other relevant comorbidities that may interfere with the study  
  • Known hyper-eosinophilic syndrome  
  • Use of systemic immunosuppressive or immunomodulating therapy such as anti-IgE ≤6 months prior to study entry |

Abbreviations: ACQ-6, Asthma Control Questionnaire, six-question version; CS, corticosteroid; FDA, U.S. Food and Drug Administration; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IU, international units; LABA, long-acting beta 2 agonist; LTRA, leukotriene receptor antagonists; NHLBI-NAEPP, National Heart, Lung, and Blood Institute-National Asthma Education and Prevention Program; OCS, oral corticosteroid; SABA, short-acting beta 2 agonist

\(^a\) See study publication and supplementary information for a complete list of inclusion and exclusion criteria
Appendix E: ICD-10 Diagnosis Codes

1. Benralizumab
   ICD-10 codes for asthma
   a. J45.XXX asthma
   b. 45.50 severe persistent asthma, uncomplicated
   c. J82 eosinophilic asthma

2. Dupilumab
   ICD-10 codes for asthma
   a. J45.XXX asthma
   b. J45.40 moderate persistent asthma, uncomplicated
   c. J45.50 severe persistent asthma, uncomplicated
   d. J45.909 unspecified asthma, uncomplicated (it includes oral steroid-dependent asthma)
   e. J82 eosinophilic asthma

   ICD-10 codes for atopic dermatitis:
   a. L20.XX atopic dermatitis-related codes

   ICD-10 codes for chronic rhinosinusitis with nasal polyposis:
   a. J32.X chronic sinusitis
   b. J33.X nasal polyp

3. Mepolizumab
   ICD-10 codes for asthma
   a. J45.XXX asthma
   b. J45.50 severe persistent asthma, uncomplicated
   c. J82 eosinophilic asthma

   ICD-10 codes for eosinophilic granulomatosis with polyangiitis
   a. M30.1 polyarteritis with lung involvement [Churg-Strauss]

4. Omalizumab
   ICD-10 codes for asthma
   a. J45.XXX asthma
b. J45.40 moderate persistent asthma, uncomplicated (it includes allergic asthma)
c. J45.50 severe persistent asthma, uncomplicated (it includes allergic asthma)

ICD-10 codes for chronic idiopathic urticaria
a. L50.1 idiopathic urticaria

5. Reslizumab

ICD-10 codes for asthma
a. J45.xxx asthma
b. J45.50 severe persistent asthma, uncomplicated
c. J82 eosinophilic asthma
Appendix F: Existing Prior Authorization Request Forms
# Dupixent (dupilumab)

## Member and Medication Information (required)

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<th>Member ID:</th>
<th>Member Name:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOB:</td>
<td>Weight:</td>
</tr>
<tr>
<td>Medication Name/ Strength:</td>
<td>Dose:</td>
</tr>
</tbody>
</table>

**Directions for use:**

## Provider Information (required)

<table>
<thead>
<tr>
<th>Name:</th>
<th>NPI:</th>
<th>Specialty:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact Person:</td>
<td>Office Phone:</td>
<td>Office Fax:</td>
</tr>
</tbody>
</table>

All information to be legible, complete and correct or the request may be denied. FAX DOCUMENTATION INCLUDING PROGRESS NOTES or UPDATED LETTER OF MEDICAL NECESSITY TO 855-828-4992

### Criteria for Approval (all criteria must be met):

#### Moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma
- Age 12 years or older
- The prescriber is or has consulted with:  
  - Allergist
  - Pulmonologist
  - Immunologist
- Moderate to severe oral corticosteroid (OCS) dependent asthma with an eosinophilic phenotype
- Trial and failure of at least one preferred medium or high dose inhaled corticosteroid / long acting beta agonist combination
  - Medication used: Chart Note Page #:
  - Details of failure:

#### Moderate to severe chronic atopic dermatitis
- The prescriber is or has consulted with:  
  - Allergist
  - Dermatologist
  - Immunologist
- Trial and failure of at least ONE preferred high potency topical corticosteroid (Must be used for at least 4 weeks)
  - Medication used: Chart Note Page #:
  - Date of use: Length of therapy:
- Trial and failure of at least ONE preferred topical immunomodulator (Must be used for at least 4 weeks)
  - Medication used: Chart Note Page #:
  - Date of use: Length of therapy:
- Trial and failure of at least ONE listed oral systemic immunosuppressive therapy: (Must be used for at least 4 weeks)
  - Cyclosporine Date of use: Length of therapy:  
  - Azathioprine Date of use: Length of therapy:  
  - Methotrexate Date of use: Length of therapy:  
  - Mycophenolate Date of use: Length of therapy:  

#### Chronic rhinosinusitis with nasal polyps
- Age 18 years or older
- Trail and failure to one medication in EACH listed drug category within the past year:
  - Nasal corticosteroid spray: Medication used: Chart Note Page #:
  - Details of failure:
  - Oral corticosteroid: Medication used: Chart Note Page #:
  - Details of failure:

### Re-authorization Criteria:

Updated letter of medical necessity or updated chart notes demonstrating positive clinical response.

**Authorization:** Two (2) months  
**Re-authorization:** Six (6) months

### PROVIDER CERTIFICATION

I hereby certify this treatment is indicated, necessary and meets the guidelines for use.

Prescriber’s Signature ______________________  Date ______________________

---

Last Updated 10/30/2019
# FASENRA (benralizumab)

## Member and Medication Information (required)

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<tr>
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<th>Member Name:</th>
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<tbody>
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<table>
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<tr>
<th>DOB:</th>
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<table>
<thead>
<tr>
<th>Medication Name/ Strength:</th>
<th>Dose:</th>
</tr>
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</tbody>
</table>

Directions for use:

## Provider Information (required)

<table>
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<tr>
<th>Name:</th>
<th>NPI:</th>
<th>Specialty:</th>
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<table>
<thead>
<tr>
<th>Contact Person:</th>
<th>Office Phone:</th>
<th>Office Fax:</th>
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</table>

All information to be legible, complete and correct or form will be returned. FAX DOCUMENTATION INCLUDING PROGRESS NOTES or UPDATED LETTER OF MEDICAL NECESSITY TO 855-828-4992

### Criteria for approval:

- Use must follow FDA-approved labeling: Add-on maintenance treatment of severe asthma, with an eosinophilic phenotype.
- Patient age must be ≥ 12 years old
- Describe other asthma treatment(s) the patient currently takes
  - Medication used: __________________________
  - Details of failure: _________________________
  - Chart Note Page #: _________________________
- Trial and failure of at least one preferred single agent and one preferred combo agent:
  - Single agent:
    - Medication used: __________________________
    - Details of failure: _________________________
    - Chart Note Page #: _________________________
  - Combination agent:
    - Medication used: __________________________
    - Details of failure: _________________________
    - Chart Note Page #: _________________________

### Re-authorization Criteria:

- Documented reduction in use of rescue inhaler(s) Chart Note Page #: _________________________
- Documented reduction in use of concurrent inhaled corticosteroids and/or long-acting beta agonists, if applicable Chart Note Page #: _________________________
- Documented positive clinical response pre-bronchodilator FEV1 Please submit pre-treatment and current information

**Initial Authorization:** Six (6) months  
**Re-authorization:** Up to one (1) year

### PROVIDER CERTIFICATION

I hereby certify this treatment is indicated, necessary and meets the guidelines for use.

Prescriber’s Signature ___________________________ Date ______________

Last Updated 3/28/2019
**Xolair (omalizumab)**

<table>
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<th>Member and Medication Information (required)</th>
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<tbody>
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</tr>
<tr>
<td><strong>DOB:</strong></td>
</tr>
<tr>
<td><strong>Medication Name/ Strength:</strong></td>
</tr>
<tr>
<td><strong>Directions for use:</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Provider Information (required)</th>
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<tbody>
<tr>
<td><strong>Name:</strong></td>
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<td><strong>Contact Person:</strong></td>
</tr>
</tbody>
</table>

All information to be legible, complete and correct or form will be returned. FAX DOCUMENTATION INCLUDING PROGRESS NOTES or UPDATED LETTER OF MEDICAL NECESSITY TO 855-828-4992

**Criteria for Approval:**

**Moderate to severe persistent asthma**

- 6 years of age or older
- Positive skin test or in vitro reactivity to a perennial aeroallergen. Chart Note Page #:
- Inadequate control of asthma symptoms with high dose inhaled corticosteroids for at least 2 months
  - Medication used: 
  - Details of failure:
- Include the patient's baseline IgE value (30 – 700 IU/ml): 
- Include the patient's baseline weight (≤150 kg):

**Chronic Idiopathic Urticaria**

- 12 years of age or older
- Trial and failure of standard therapeutic dose second generation antihistamine for at least 2 months
  - Medication: 
  - Details of failure:
- Trial and failure of one or more of the following for at least 2 months
  - 1st generation antihistamine: 
  - 2nd generation antihistamine: 
  - H2 antagonist: 
  - Leukotriene receptor antagonist: 

**Re-authorization Criteria:**

Updated letter of medical necessity or updated chart notes demonstrating positive clinical response.

**Notes:** Use appropriate HCPCS code for billing


The patient must have regular appointments to receive the medication in the prescriber’s office. The patient must remain in the office for a minimum of 90 minutes to allow for observation and treatment of anaphylaxis, if necessary. If/when any change of dose is requested, the prescriber must indicate, in writing, the reasoning for the dose increase.

**Initial Authorization:** Six months
**Re-authorization:** Up to one (1) year

**PROVIDER CERTIFICATION**

I hereby certify this treatment is indicated, necessary and meets the guidelines for use.

________________________________________

Prescriber’s Signature

________________________________________

Date

Last Updated 12/24/2019