Immunomodulators, Asthma
Therapeutic Class Review (TCR)

July 1, 2022

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Interleukin-4 (IL-4) Antagonist		
dupilumab*,† (Dupixent®)[1]	Regeneron/Sanofi-Aventis	▪ Add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥ 6 years with an eosinophilic phenotype or with oral corticosteroid-dependent asthma
Interleukin-5 (IL-5) Antagonists		
benralizumab* (Fasenra®, Fasenra Pen™)[2]	AstraZeneca	▪ Add-on maintenance treatment in patients with severe asthma aged ≥ 12 years, and with an eosinophilic phenotype
mepolizumab*,± (Nucala®)[3]	GlaxoSmithKline	▪ Add-on maintenance treatment of severe asthma in adults and pediatric patients aged ≥ 6 years with an eosinophilic phenotype ▪ Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA) ▪ Treatment of adult and pediatric patients aged ≥ 12 years with hypereosinophilic syndrome (HES) for ≥ 6 months without an identifiable non-hematologic secondary cause
reslizumab* (Cinqair®)[4]	Teva Specialty	▪ Add-on maintenance treatment of severe asthma in patients aged ≥ 18 years with an eosinophilic phenotype
Anti-Immune Globulin E (IgE) Antibody		
omalizumab*,‡ (Xolair®)[5]	Genentech	▪ Moderate to severe persistent asthma in patients ≥ 6 years of age with a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids ▪ Chronic spontaneous urticaria (CSU) in adults and adolescents ≥ 12 years of age who remain symptomatic despite H1 antihistamine treatment
Thymic Stromal Lymphopoietin (TSLP) Blocker		
tezepelumab-ekko (Tezspire™)[6]	Amgen	▪ Add-on maintenance treatment of severe asthma in adults and pediatric patients ≥ 12 years of age

* Products in this review are not indicated for the relief of acute bronchospasm or status asthmaticus.

† Dupilumab, with or without topical corticosteroids, is indicated for the treatment of patients aged ≥ 6 months with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It is also indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP) and for patients ≥ 12 years of age weighing ≥ 40 kg, with eosinophilic esophagitis. Use of dupilumab for AD, CRSwNP, and eosinophilic esophagitis will not be discussed in detail in this Therapeutic Class Review; see prescribing information for details.

± Mepolizumab is also indicated for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adults with inadequate response to nasal corticosteroids. Mepolizumab use for CRSwNP will not be discussed in detail in this Therapeutic Class Review; see prescribing information for details.

‡ Omalizumab is indicated for nasal polyps in adult patients ≥ 18 years of age with inadequate response to nasal corticosteroids, as add-on maintenance treatment. Detailed information regarding use for nasal polyps is discussed in another Therapeutic Class Review. It is not indicated for other allergic conditions or other forms of urticaria.

OVERVIEW

Asthma

The prevalence of asthma in the United States (US) continues to rise. An estimated 8.4% of adults and 5.8% of children (over 25.2 million Americans total) have asthma with > 40% reporting at least 1 asthma attack each year.[7,8] The National Asthma Education and Prevention Program (NAEPP) defines asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.[9]

Asthma phenotypes have been identified by clinical and/or pathophysiological characteristics.[10] Type 2 inflammation is present in the majority of individuals with severe asthma. It is characterized by the presence of cytokines (e.g., interleukin [IL]-4, IL-5, IL-13) and elevation of eosinophils or FeNO). Generally, patients with eosinophilic asthma have severe disease with high eosinophil levels in the blood and sputum despite treatment with a glucocorticoid.[11] Persistent levels of eosinophils in sputum may also be an indicator of disease severity.

The 2020 American Thoracic Society (ATS) and European Respiratory Society (ERS) Task Force guidelines define severe asthma as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.[12] The guidelines suggest add-on treatment with an IL-5 antagonist (benralizumab, mepolizumab, reslizumab) for adults with severe uncontrolled asthma with an eosinophilic phenotype or those with severe corticosteroid-dependent asthma (conditional recommendation; low quality). Due to a paucity of data, a recommendation was not made for use of these drugs in pediatric patients. The guidelines suggest initiation of IL-5 or IL-5R inhibitors for adults with a blood eosinophil count ≥ 150 cells/µL (conditional; low). In addition, patients ≥ 12 year of age with severe allergic asthma and blood eosinophils ≥ 260 cells/µL or FeNO ≥ 19.5 ppb are more likely to benefit from anti-IgE (omalizumab) therapy (conditional; low). However, ATS/ERS does not recommend using eosinophil counts to guide treatment decisions for individual drugs (conditional recommendation). The task force states that evidence does not correlate to absolute blood eosinophil thresholds for efficacy of individual IL-5 antagonists and there is limited evidence that sputum eosinophil count is predictive of response. ATS/ERS suggests an anti-IL4/13 agent (dupilumab) as add-on therapy for adults with severe eosinophilic asthma and those with severe corticosteroid-dependent asthma regardless of eosinophil levels (conditional; low). Tezepelumab was not available at the time of guideline publication.

The 2022 Global Initiative for Asthma (GINA) evidence-based report offers a management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects.[13] During this continuous cycle, a stepwise treatment approach is used to achieve control using the patient's current level of control as the baseline. If the patient is not controlled on the current regimen, treatment should be stepped up until control is achieved. According to GINA's stepwise approach, patients in steps 1 and 2 are considered to have mild asthma, patients well-controlled in steps 3 to 4 have moderate asthma, and asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA or requires high dose ICS-LABA to maintain control is considered to be severe. Treatment regimens are laid out in 2 tracks depending on the medication chosen by the patient for relief of breakthrough symptoms (reliever medication). Track 1 outlines the treatment approach when the reliever is low dose ICS-formoterol and is the preferred approach due to demonstrated efficacy in reducing severe exacerbations. Track 2 provides an alternative approach when the chosen reliever medication is a short-acting beta agonist

(SABA). To control asthma, treatment may be stepped up or down within a track while using the same reliever medication or switching between tracks. The 2022 GINA evidence-based report recommends that all adults and adolescents with asthma, regardless of track, receive an ICS-containing controller medication. Due to the increased risk of severe exacerbations and asthma-related death, SABA-only treatment is no longer recommended in adults and adolescents. For adults and adolescents ≥ 12 years of age with mild symptoms (step 1 and step 2), the preferred treatment to control symptoms and prevent exacerbations is as-needed low dose ICS-formoterol (step 1 and step 2). Patients should initiate low dose ICS-formoterol at a maintenance dose in step 3 if they experience symptoms most days or awaken with symptoms once a week or more. In patients whose asthma is uncontrolled on a low-dose ICS-containing controller despite good adherence and correct technique, a step up in treatment may be added (see tables below). Any step up in therapy should be re-assessed after 2 to 3 months; if there is not an adequate response, consider alternative treatment options or a referral. If asthma control is maintained for at least 3 months on the current regimen, treatment can be stepped down to the lowest step and dosage that maintains control. If asthma is uncontrolled after 3 to 6 months on high dose ICS-LABA (step 5), it is recommended to refer to a specialist and undergo phenotype assessment)(e.g., severe allergic, aspirin-exacerbated, or eosinophilic asthma), as this may guide the selection of add-on treatment. Add-on treatments for severe asthma include a long-acting muscarinic antagonist (LAMA), low-dose azithromycin (off-label), a leukotriene receptor antagonist (LTRA), or biologic therapy to target type-2 inflammation (anti-IgE, anti-IL5, anti-IL4, anti-TSLP). Addition of a low dose oral corticosteroid (OCS) should only be considered as a last resort. Patients ≥ 6 years old with severe allergic asthma and elevated immunoglobulin E (IgE) levels may benefit from omalizumab (anti-IgE) therapy (Evidence A), and those with severe eosinophilic asthma may benefit from benralizumab (≥ 12 years old), mepolizumab (≥ 6 years old), or reslizumab (≥ 18 years old) (anti-IL-5) therapy (Evidence A). Patients ≥ 6 years old with severe eosinophilic/Type 2 asthma or patients requiring maintenance OCS may benefit from dupilumab (anti-IL-4) therapy (Evidence A). Patients ≥ 12 years old with severe asthma may benefit from the addition of tezepelumab (anti-TSLP) (Evidence A).

Stepwise Approach to Asthma Control from 2022 GINA Guidelines – Controller and Reliever Therapy in Patients ≥ 12 Years Old [14]

Step	Track 1	Track 2	Other Controller Options
Reliever			
1 – 5	▪ As-needed low dose ICS-formoterol*,†	▪ As-needed SABA	--
Controller			
1	▪ As-needed low dose ICS-formoterol	▪ Low dose ICS whenever SABA is taken	--
2	▪ As-needed low dose ICS-formoterol	▪ Low dose maintenance ICS	▪ Low dose ICS whenever SABA is taken ▪ Daily low dose ICS-LABA ▪ LTRA
3	▪ Low dose maintenance ICS-formoterol	▪ Low dose maintenance ICS-LABA	▪ Medium dose ICS ▪ Add LTRA or HDM SLIT
4	▪ Medium dose maintenance ICS-formoterol	▪ Medium/high dose maintenance ICS-LABA	▪ Add LAMA or LTRA or HDM SLIT ▪ High dose ICS
5	▪ Add-on LAMA ▪ Refer for phenotypic assessment ▪ Consider high dose ICS-formoterol ± anti-IgE (omalizumab), anti-IL5/5R (benralizumab, mepolizumab, reslizumab), anti-IL4R (dupilumab), anti-TSLP (tezepelumab) ▪ Consider treatment guided by sputum eosinophil count	▪ Add-on LAMA ▪ Refer for phenotypic assessment ▪ Consider high dose ICS-LABA ± anti-IgE (omalizumab), anti-IL5/5R (benralizumab, mepolizumab, reslizumab), anti-IL4R (dupilumab), anti-TSLP (tezepelumab) ▪ Consider treatment guided by sputum eosinophil count	▪ Add azithromycin (adults) or LTRA; add low dose OCS (consider adverse effects)

HDM SLIT = house dust mite sublingual immunotherapy; ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IL-4R = Interleukin-4 receptor; IL-5/5R = interleukin-5/IL-5 receptor; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; SABA = short acting beta$_2$-agonist

* The data supporting the use of low-dose ICS/formoterol as a reliever medication are primarily derived from budesonide-formoterol.

† Low dose ICS-formoterol is the reliever for those prescribed budesonide-formoterol or beclomethasone dipropionate-formoterol maintenance and reliever therapy.

Stepwise Approach to Asthma Control from 2022 GINA Guidelines – Controller and Reliever Therapy in Patients 6 to 11 Years Old[15]

Step	Preferred Controller	Other Controller Options	Reliever*
1	▪ Low dose ICS whenever SABA is taken	▪ Daily low dose ICS	▪ As needed SABA
2	▪ Daily low dose ICS	▪ Daily LTRA ▪ Low dose ICS whenever SABA is taken	▪ As needed SABA
3	▪ Low dose ICS-LABA ▪ Medium dose ICS ▪ Very low dose ICS-formoterol MART	▪ Low dose ICS + LTRA	▪ As needed SABA (or ICS/formoterol for MART)
4	▪ Medium dose ICS-LABA ▪ Low dose ICS-formoterol MART	▪ High pediatric dose ICS-LABA ▪ Add-on tiotropium or LTRA	▪ As needed SABA (or ICS/formoterol for MART)
5	▪ Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy (e.g., anti-IgE [omalizumab], anti-IL4R [dupilumab])	▪ Add-on anti-IL-5 (mepolizumab) or add-on low dose OCS (consider adverse effects)	▪ As needed SABA (or ICS/formoterol for MART)

ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IL-5 = interleukin-5; LABA = long acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist; MART = maintenance and reliever therapy; OCS = oral corticosteroid; SABA = short acting beta$_2$-agonist

* The data supporting the use of low-dose ICS/formoterol as a reliever medication are primarily derived from budesonide-formoterol.

Chronic Spontaneous Urticaria (CSU)

The prevalence of chronic urticaria (CU) is estimated to be 0.5% to 5% of the general US population.[16] Chronic urticaria is defined as episodic or daily hives lasting for 6 weeks or more that impairs quality of life. Main subtypes are chronic spontaneous urticaria (CSU), also referred to as chronic idiopathic urticaria (CIU), and inducible (physical) urticaria.[17] Chronic urticaria may be associated with the presence of mononuclear cells (CD4+ Th1 and Th2 lymphocytes), eosinophils, neutrophils, basophils, mast cells, and activated macrophages. In 2014, a Joint Task Force for the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI) updated practice parameters for acute and chronic urticaria (CU).[18] Diagnosis of CU is based on history and physical examination. Typically, CU presents as pruritic edematous red wheals of variable size and shape with surrounding erythema. The majority of cases of CU have an undetermined cause (idiopathic); however, infectious and autoimmune conditions can be associated with CU.[19]

The AAAAI/ACAAI/JCAAI recommend a stepwise approach to care for chronic urticaria.[20] Treatment should begin based on the patient's level of severity and previous treatment history. At each level, medications should be evaluated for efficacy and patient tolerance. Once consistent control is achieved, a step-down in treatment may be considered. In step 1, monotherapy with second-generation antihistamines is considered first-line for CU in addition to avoidance of triggers (e.g., nonsteroidal anti-inflammatory drugs, food allergens) and relevant physical factors. If CU is not controlled, the antihistamine dose can be increased (if appropriate for the particular agent) or one of the following can be added: another second-generation or a first-generation antihistamine, a histamine-2 antagonist, or

an LTRA (step 2). If control is still not achieved, dose advancement of a potent antihistamine (e.g., hydroxyzine or doxepin) may be considered, as tolerated (step 3). For CU that is refractory to maximal antihistamine therapy in step 3, alternative agents such as omalizumab or cyclosporine can be used; other anti-inflammatory, immunosuppressant, or biologic agents may be considered, but have a lower level of supporting evidence.

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a systemic vasculitis of small-to-medium vessels, characterized by allergic rhinitis, asthma, and hypereosinophilia.[21,22,23] EGPA is a rare disease state affecting 1 to 3 out of 100,000 adults per year, with a higher incidence of about 1 per 15,000 in patients with asthma. Onset may occur between 15 and 70 years of age, but diagnosis is typically made between 35 and 50 years of age.[24,25] While the direct cause of the disease is unknown, HLA-DRB4 positivity may be a genetic risk factor.[26] Symptoms can vary from mild to life-threatening.[27]

Diagnosis of EGPA is based on symptoms, laboratory tests, imaging studies, physical examination, and biopsy of affected tissues to determine severity of vasculitis.[28] A diagnosis may be confirmed if in addition to vasculitis, patients also have at least 4 of the following features: asthma, eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormalities, and eosinophilic vasculitis.[29] Scoring systems to assess the severity of vasculitis and guide initial therapy in patients with EGPA include the 5-factor score (FFS) and the Birmingham Vasculitis Activity Score (BVAS).[30] The FFS ranges from 0 to 2, and attributes a point for one of the following and 2 points if 2 or more of the following are met: age > 65 years, cardiac insufficiency, gastrointestinal involvement, renal insufficiency, and ear/nose/throat manifestations. The BVAS has historically been used to a greater extent in research than clinical practice and includes general symptoms in addition to organ involvement. BVAS can range from 0 to 68 with 1 point being allotted for persistent symptoms and 2 points for new or worsening symptoms.

The American College of Rheumatology (ACR) and the Vasculitis Foundation (VF) published guidelines in 2021 for the management of antineutrophil cytoplasmic antibody-associated vasculitis (AAV), including EGPA.[31] Due to a paucity of high-quality evidence for the treatment of EGPA, quality of evidence for recommendations is low and position statements provided are not graded as to recommendation strength. The guidelines state that for initial treatment of active, severe EGPA, IV pulse glucocorticoids or high-dose glucocorticoids may be prescribed as initial therapy. Cyclophosphamide or rituximab are options for induction of remission and are conditionally recommended over mepolizumab as patients with severe active disease were excluded from mepolizumab trials. Methotrexate, azathioprine, and mycophenolate mofetil are conditionally recommended over mepolizumab for maintenance of remission of severe disease. For patients with active, nonsevere disease, mepolizumab and glucocorticoids are conditionally recommended over methotrexate, azathioprine, or mycophenolate mofetil in combination with glucocorticoids. For patients who experience a nonsevere EGPA relapse while receiving low-dose glucocorticoids or during maintenance therapy with methotrexate, azathioprine, or mycophenolate mofetil, the guidelines conditionally recommend the addition of mepolizumab over switching to an alternative agent. Mepolizumab is also conditionally recommended over omalizumab as add-on therapy for patients with EGPA and high serum IgE levels who experience a nonsevere relapse. Notably, mepolizumab is the only US Food and Drug Administration (FDA)-approved medication for this disease state.

Hypereosinophilic Syndrome (HES)

HES is a group of blood disorders characterized by a marked proliferation of eosinophils causing organ infiltration, most commonly in the skin, lungs, heart, nervous system, and gastrointestinal tract.[32,33,34,35] The US prevalence is 3,000 to 30,000 individuals, mostly impacting patients 20 to 50 years of age at the time of diagnosis. Common symptomatology consists of skin rashes (e.g., urticaria, angioedema), dizziness, memory loss or confusion, cough, shortness of breath, fatigue, fever, and mouth sores. While the majority of cases have no known underlying cause (idiopathic HES), approximately 25% of cases involve disorders of the bone marrow (e.g., myeloproliferative neoplasms), increased interleukin-5, or family history of HES. Genetic abnormalities, specifically fusion tyrosine kinase genes, have been associated with a minority of idiopathic primary HES cases, of which, the *FIP1L1-PDGFRA* gene fusion is estimated to occur in 5% to 10% of cases. In the absence of other conditions that cause eosinophilia (e.g., allergy, autoimmune disease, drug reaction), a diagnosis of HES is confirmed by an absolute eosinophil count (AEC) > 1.5 x 10^9/L (or > 1,500 cells/µL) for at least 6 months and pathological confirmation of organ tissue involvement. If no tissue damage is evident, a diagnosis of idiopathic HES is considered.

The goal of treatment is to reduce blood and organ eosinophil concentrations and limit organ damage.[36] Treatment guidelines are lacking. Initial treatment includes oral corticosteroids (first-line), hydroxyurea, interferon-alfa, and cytotoxic chemotherapy. Hematopoietic stem cell transplantation has been used for aggressive forms of HES; however, the role of transplantation is not well established.[37] The only FDA-approved pharmacologic treatments for HES include the kinase inhibitor imatinib (Gleevec®) and mepolizumab.[38]

PHARMACOLOGY[39,40,41,42,43,44,45]

The airway inflammation associated with asthma is attributable to several cell types (e.g., eosinophils, lymphocytes) and mediators (e.g., histamine, cytokines). Generally, eosinophils circulate in the peripheral blood and are found in peripheral tissue and respiratory mucosa, and levels increase in the presence of acute inflammation. Eosinophils are recruited into the airway in allergic asthma by the action of cytokines and chemokines, such as interleukin-5 (IL-5), a potent eosinophil activator that facilitates recruitment into tissues.

Benralizumab (Fasenra), mepolizumab (Nucala), and reslizumab (Cinqair) are IL-5 antagonists. They block IL-5 from binding to eosinophils, resulting in the inhibition of eosinophil growth and differentiation, recruitment, activation, and survival.

While the exact mechanism of action for asthma has not been established, it is known that dupilumab (Dupixent) binds to interleukin-4-receptor alpha (IL4Rα) thereby inhibiting interleukin (IL)-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE.

Omalizumab (Xolair) is a recombinant humanized monoclonal anti-IgE antibody. In the treatment of asthma and nasal polyps, omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells, basophils, and dendritic cells, this in turn decreases the release of allergic response mediators. Approximately 30% to 50% of patients with chronic urticaria produce specific immunoglobulin G (IgG) antibodies against the FcεRIa subunit component of the high-affinity immunoglobulin E (IgE) receptor, and approximately 5% to 10% produce immunoglobulin G (IgG) antibodies against immunoglobulin E (IgE). The mechanism by which omalizumab influences chronic

urticaria is not fully understood; it reduces the number of FcεRI receptors on basophils and reduces free IgE levels, which have been associated with reduced basophil and mast cell activation.

Thymic stromal lymphopoietin (TSLP) is a cytokine involved in the pathogenesis of airway inflammation. It is thought that by blocking TSLP, the monoclonal antibody tezepelumab reduces biomarkers and cytokines downstream in the inflammatory cascade.

PHARMACOKINETICS[46,47,48,49,50,51]

Drug	Half-Life (days)	Metabolism	Time to Peak Concentration (days)
Interleukin-4 (IL-4) Antagonist			
dupilumab (Dupixent)	nr*	N/A*	7
Interleukin-5 (IL-5) Antagonists			
benralizumab (Fasenra)	15.5	Enzymatic proteolysis	nr
mepolizumab (Nucala)	16-22	Enzymatic proteolysis	nr
reslizumab (Cinqair)	24	Enzymatic proteolysis	End of infusion
Anti-Immune Globulin E (IgE) Antibody			
omalizumab (Xolair)	24-26	N/A†	7-8
Thymic Stromal Lymphopoietin (TSLP) Blocker			
tezepelumab-ekko (Tezspire)	26	Enzymatic proteolysis	3–10

nr = not reported

* The metabolic pathway of dupilumab has not been established but it is expected to be degraded through the same catabolic pathways as endogenous IgG forming small peptides and amino acids. After the last steady-state dose of 300 mg every 4 weeks, 300 mg every 2 weeks, 300 mg once weekly, 200 mg every 4 weeks, or 200 mg every 2 weeks regimens, the median times to non-detectable concentration (<78 ng/mL) of dupilumab ranged from 9 to 13 weeks in patients ≥ 12 years old and were 1.5-times longer in those 6 to 11 years old.

† No formal drug metabolism studies were conducted.[52]

CONTRAINDICATIONS/WARNINGS[53,54,55,56,57,58]

Agents in this review are contraindicated in patients with a known hypersensitivity to any component of the product.

Omalizumab (Xolair) and reslizumab (Cinqair) carry boxed warnings regarding anaphylaxis. Anaphylaxis has been reported to occur after the first dose and up to 1 year after beginning omalizumab treatment; time to onset of the reaction was reported 90 to 120 minutes after administration. The majority of anaphylaxis cases (60% to 70%) have occurred within the first 3 doses of omalizumab, with additional cases occurring sporadically beyond the third dose. Anaphylaxis has been reported during reslizumab infusion and up to 20 minutes after infusion completion. Although the labels for benralizumab (Fasenra), mepolizumab (Nucala), and tezepelumab (Tezspire) do not contain a boxed warning, hypersensitivity reactions can occur within hours to days of the dosage being given. Tezepelumab requires administration by a healthcare professional (HCP). Reslizumab should only be administered in a healthcare setting by a HCP; patients should be closely monitored for an appropriate time period after administration of the dose. Omalizumab requires *initiation* in a healthcare setting where patients can be closely observed following administration; after therapy has been established, certain patients may be selected by an HCP

for self-administration (patient or caregiver administration) of the prefilled syringe outside of a healthcare setting, based on consideration and criteria for mitigating the risk from anaphylaxis (e.g., past history of anaphylaxis, ability to recognize and treat anaphylaxis, ability to properly inject omalizumab, received ≥ 3 doses of omalizumab under HCP guidance without event).

Although benralizumab and mepolizumab should also be used under the guidance of a HCP, and monitoring following administration is recommended, these products are available as prefilled autoinjectors and syringes for patient/caregiver administration following appropriate assessment and training by a HCP. The prefilled syringe formulation of benralizumab continues to require administration by a HCP, as does the vial preparation of mepolizumab.

Dupilumab (Dupixent) labeling also contains a warning for hypersensitivity, including anaphylaxis, serum sickness, angioedema, erythema nodosum, and erythema multiforme. Dupilumab is intended for use under the guidance of a HCP and may be self-administered with proper training using the prefilled syringe.

None of the agents within this class should be used to treat acute asthma symptoms or asthma exacerbations.

Herpes zoster has been reported more often in patients treated with mepolizumab than with placebo. Varicella vaccination may be considered prior to starting therapy.

In clinical trials for asthma, conjunctivitis and keratitis were reported at similar rates with dupilumab and placebo; however, a higher incidence of both conditions was reported in atopic dermatitis trials in patients treated with dupilumab compared to placebo. Patients should be advised to consult their HCP if new onset or worsening eye symptoms develop.

When appropriate, gradually reduce dosages of systemic or inhaled corticosteroids; avoid abrupt discontinuation or dose reductions.

Pre-existing helminth infections should be treated prior to initiating asthma immunomodulator therapy, since it may reduce the immunological response to some helminth infections. If patients become infected while receiving treatment with benralizumab, dupilumab, mepolizumab, reslizumab, or tezepelumab and do not respond to anti-helminth treatment, discontinue treatment with the agent until infection resolves. Response to anti-helminth treatment does not appear to be affected by omalizumab.

In placebo-controlled trials, malignant neoplasm was reported in 0.6% of patients treated with reslizumab (compared to 0.3% with placebo) and in 0.5% of patients treated with omalizumab (compared to 0.2% with placebo). Long-term studies to evaluate the carcinogenicity of mepolizumab have not been performed; risk is unknown.

DRUG INTERACTIONS[59,60,61,62,63,64]

The use of live vaccines should be avoided in patients taking dupilumab (Dupixent) and tezepelumab (Tezspire).

There have been no formal drug interaction studies conducted with benralizumab (Fasenra), mepolizumab (Nucala), omalizumab (Xolair), reslizumab (Cinqair), and tezepelumab (Tezspire).

Concomitant use of omalizumab and allergen immunotherapy has not been assessed in patients with asthma. Combination treatment of omalizumab and immunosuppressive therapies has not been studied in CSU.

ADVERSE EFFECTS[65,66,67,68,69,70]

Drug	Arthralgia	Headache	Fatigue	Injection Site Reaction	Pruritus	Nasopharyngitis
Interleukin-4 (IL-4) Antagonist						
dupilumab (Dupixent)	nr*	nr	nr	Asthma: 14-18 (6)	nr	nr
Interleukin-5 (IL-5) Antagonists						
benralizumab (Fasenra)	nr	8-8.2 (5.3-6)	nr	2.2 (1.9)	nr	5† (3)
mepolizumab (Nucala)‡	Asthma: nr EGPA: nr HES: nr	Asthma: 19 (18) EGPA: nr HES: nr	Asthma: 5 (4) EGPA: reported HES: nr	Asthma: 8-15 (3-13) EGPA: 15 (13) HES: 7 (4)	Asthma: 3 (2) EGPA: reported HES: nr	Asthma: ≥ 3 EGPA: nr HES: nr
reslizumab (Cinqair)	nr	nr	nr	nr	nr	nr
Anti-Immune Globulin E (IgE) Antibody						
omalizumab (Xolair)	Asthma: 8 (6) CSU: 2.9 (0.4)	Asthma: Aged ≥ 12 years – 15; 6 to < 12 years – 0.2 CSU: 6.1-12 (2.9)	Asthma: 3 (2) CSU: nr	Asthma: 45 (43) CSU: 0.6-2.7 (0.8)	Asthma: 2 (1) CSU: nr	Asthma: 2 (1) CSU: 6.6-9.1 (7)
Thymic Stromal Lymphopoietin (TSLP) Blocker						
tezepelumab (Tezspire)	4 (3)	nr	nr	3.3 (2.7)	nr	4† (3)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo group are reported in parentheses. nr = not reported

* While arthralgia was not reported in dupilumab studies for asthma, it was reported in studies for CRSwNP (3% with dupilumab versus 2% with placebo) and eosinophilic esophagitis (2% with dupilumab versus 1% with placebo).

† Reported as pharyngitis.

‡ Adverse reaction profile for subjects 6 to 11 years of age was similar to that observed in subjects aged ≥ 12 years.

Other adverse effects reported with benralizumab (Fasenra) not indicated above include hypersensitivity reactions (e.g., urticaria), which occurred in 3% of both placebo and treatment groups, and pyrexia, which occurred in 2.7% to 3% of patients treated with benralizumab compared to 1.3% to 2% of patients treated with placebo.

Other adverse effects reported with dupilumab (Dupixent) in patients with asthma were oropharyngeal pain (2%) and eosinophilia (2%).

Common adverse reactions reported for mepolizumab (Nucala) in patients ≥ 12 years of age with asthma with an incidence greater than placebo include: back pain (5% versus 4%), eczema (3% versus < 1%), and

muscle spasms (3% versus < 1%). The safety profile in patients 6 to 11 years of age was similar to that in patients older than 12 years. No additional adverse reactions were noted in the EPGA study. However, 4% of patients receiving 300 mg every 4 weeks for EPGA experienced systemic hypersensitivity reactions including rash, pruritus, flushing, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, and stridor; compared to 1% of patients in the placebo group. In the clinical trial for HES in patients ≥ 12 years treated with 300 mg every 4 weeks, no patient experienced systemic allergic reactions; however multifocal skin reaction was reported on the day of administration.

Many adverse reactions reported with omalizumab (Xolair) were infectious in nature, including nasopharyngitis, sinusitis, upper respiratory tract infection (including viral) pharyngitis streptococcal, otitis media, viral gastroenteritis, and arthropod bites. Generalized pain, arthralgia, pain of the leg, arm, ear, upper abdomen and headache were also reported. Injection site reactions occurred in 45% of patients treated with omalizumab compared to 43% treated with placebo.

In a 5-year observational cohort study in asthmatic patients (≥ 12 years of age) a higher rate of overall cardiovascular and cerebrovascular serious adverse events was reported in patients treated with omalizumab (13.4/1,000 patient-years) compared to non-omalizumab-treated patients (8.1/1,000 patient-years). Rates of transient ischemic attack, myocardial infarction, pulmonary hypertension, and venous thrombosis/pulmonary embolism were at least 2-fold greater in omalizumab-treated patients; the incidence of ischemic stroke and cardiovascular death were similar between cohorts. However, a pooled analysis of 25 randomized double-blind, placebo-controlled trials of up to 52 weeks in duration could not confirm or reject the conclusion of the observational study due to limitations such as shorter study duration and lower number of events reported.

In clinical studies, oropharyngeal pain occurred more often in patients treated with reslizumab (Cinqair) than those who received placebo (2.6% versus 2.2%). Musculoskeletal adverse reactions were reported on the day of infusion in 2.2% and 1.5% of patients treated with reslizumab and placebo, respectively. Elevated creatine phosphokinase (CPK), including levels > 10 times the upper limit of normal, were reported, but were asymptomatic and did not lead to treatment discontinuation.

In clinical trials, 4% of patients reported back pain with tezepelumab (Tezspire) compared to 3% with placebo.

As with all therapeutic proteins, there is a potential for immunogenicity with the products in this review. In clinical trials, anti-drug antibodies (ADA) developed in 13% of patients treated with benralizumab (12% considered neutralizing antibodies), 9% of patients with asthma treated with dupilumab (4% with neutralizing antibodies), 6% of patients with asthma treated with mepolizumab (1 patient with neutralizing antibodies), 4.8% to 5.4% of patients treated with reslizumab, and 5% of patients treated with tezepelumab (1 patient with neutralizing antibodies). In clinical trials with mepolizumab for asthma and EGPA, 6% and < 2% of patients, respectively, developed ADAs. No impact of ADAs on clinical efficacy was observed for benralizumab, mepolizumab, or reslizumab. ADA to omalizumab were detected in < 0.1% of asthmatic patients > 12 years of age treated with omalizumab; data were not sufficient to draw any relevant conclusions.

SPECIAL POPULATIONS[71,72,73,74,75,76]

Pediatrics

Safety and efficacy have not been established for reslizumab (Cinqair) in patients < 18 years for the treatment of asthma. Benralizumab (Fasenra) and tezepelumab (Tezspire) are indicated for the treatment of asthma in patients ≥ 12 years of age; safety and efficacy in pediatric patients < 12 have not been established. Dupilumab (Dupixent), mepolizumab (Nucala), and omalizumab (Xolair) are indicated for use in patients ≥ 6 years to treat asthma; safety and efficacy for treatment of asthma in patients younger than this have not been established. Mepolizumab is indicated for the treatment of HES in patients ≥ 12 years. Safety and efficacy of mepolizumab for conditions other than asthma and HES have not been established in pediatrics. Omalizumab is also indicated for the treatment of CSU in patients ≥ 12 years; its safety and efficacy in treating CSU in those < 12 years have not been established.

Pregnancy

Clinical data on use of benralizumab, mepolizumab, reslizumab, and tezepelumab during pregnancy are insufficient to inform on drug-associated risks. Potential fetal risks may be greater during the second and third trimesters of pregnancy as monoclonal antibodies can cross the placenta as pregnancy progresses. No fetal harm has been detected in animal studies.

Drug-associated risk of maternal or fetal harm have not been detected in the available data with dupilumab use in pregnant women; enrollment in the pregnancy registry for dupilumab is encouraged.

A prospective cohort registry study in pregnant women exposed to omalizumab showed no increase in the incidence of major birth defects or miscarriage. The risk of low birth weight infants was increased; however, pregnant women taking omalizumab had more severe asthma, which may have contributed.

Increased risk of preeclampsia in the mother and neonates born prematurely, with low birth weight, and small for gestational age have been reported in pregnant women with poorly or moderately controlled asthma. Asthma control should be closely monitored during pregnancy and adjustments made to maintain optimal control.

There is an ongoing registry that monitors pregnancy outcomes in women treated for asthma with benralizumab and mepolizumab. Healthcare providers (or the patient) are encouraged to enroll their patient.

Geriatrics

No differences in safety or efficacy were seen in patients ≥ 65 years old treated with benralizumab or reslizumab compared to younger patients; however, a greater sensitivity in some individuals cannot be ruled out. In clinical trials for asthma, no differences in safety or efficacy were detected between patients aged ≥ 65 years and younger patients who were treated with dupilumab or tezepelumab. There were insufficient numbers of patients ≥ 65 years old in clinical studies of mepolizumab and omalizumab to identify differences in response from younger populations.

Renal and Hepatic Impairment

No pharmacokinetic studies have been performed to assess the impact of renal or hepatic impairment on benralizumab, dupilumab, mepolizumab, reslizumab, or tezepelumab. Renal and hepatic impairment are not addressed in the omalizumab label.

DOSAGES[77,78,79,80,81,82]

Drug	Dose	Dosage/Administration Comments	Dosage Forms
Interleukin-4 (IL-4) Antagonist			
dupilumab (Dupixent)	**Asthma:** **A**dults and adolescents ≥ 12 years of age: ▪ Initial dose of 400 mg (two 200 mg injections) followed by 200 mg every other week; or ▪ Initial dose of 600 mg (two 300 mg injections) followed by 300 mg every other week (recommended dose for steroid-dependent asthma) Children 6 to 11 years of age*: ▪ Weight 15-29 kg: 100 mg every other week or 300 mg every 4 weeks ▪ Weight ≥ 30 kg: 200 mg every other week	For subcutaneous (SC) use only; may be given in the thigh, abdomen, or upper arm The 600 mg initial and 300 mg maintenance regimen is for patients with oral corticosteroid-dependent asthma, or with co-morbid moderate-to-severe atopic dermatitis for which dupilumab is indicated The prefilled pen is for use in adults and adolescents ≥ 12 years of age The prefilled syringe is available for all age groups; must be administered by a caregiver in patients 6 months to 11 years of age	SDP syringe: 100 mg/0.67 mL 200 mg/1.14 mL 300 mg/2 mL Prefilled pen: 200 mg/1.14 mL 300 mg/2 mL
Interleukin-5 (IL-5) Antagonists			
benralizumab (Fasenra, Fasenra Pen)	**Asthma:** 30 mg SC every 4 weeks for 3 doses, followed by 30 mg once every 8 weeks thereafter	For SC use only (upper arm [HCP administration only], thigh, abdomen) The SDP syringe should only be administered by an HCP; the autoinjector can be administered by the patient or a caregiver	SDP syringe: 30 mg/mL SDP autoinjector: 30 mg/mL
mepolizumab (Nucala)	**Asthma:** ▪ Adults and adolescents ≥ 12 years of age - 100 mg SC every 4 weeks ▪ Children 6 to 11 years of age – 40 mg SC every 4 weeks **EPGA (adults):** 300 mg (3 x 100 mg injections spaced ≥ 5 cm apart) SC every 4 weeks **HES (adults and children ≥ 12 years of age):** 300 mg (3 x 100 mg injections spaced ≥ 5 cm apart) SC every 4 weeks	For SC use only; administer in the upper arm, thigh, or abdomen The vial for reconstitution should only be administered by an HCP The prefilled autoinjector and prefilled syringe can be administered by the patient or a caregiver	SDV: 100 mg lyophilized powder for injection SDP syringe: 40 mg/0.4 mL, 100 mg/mL SDP autoinjector: 100 mg/mL
reslizumab (Cinqair)	**Asthma:** 3 mg/kg every 4 weeks by intravenous (IV) infusion over 20 to 50 minutes	For IV infusion only; do not administer via IV push or bolus Should only be administered in a healthcare setting by an HCP who can manage anaphylaxis Discontinue infusion immediately if anaphylaxis occurs	SDV: 100 mg/10 mL solution

SDP = single-dose, prefilled; SDV = single-dose vial

*Pediatric patients 6 to 11 years of age with asthma and comorbid moderate to severe atopic dermatitis require an initial loading dose outlined in the prescribing information.

Dosages (continued)

Drug	Dose	Dosage/Administration Comments	Dosage Forms
Anti-Immune Globulin E (IgE) Antibody			
omalizumab (Xolair)	**Asthma:** 75 mg to 375 mg SC every 2 or 4 weeks Dose and frequency are determined by serum total IgE level before the start of treatment, and body weight, as instructed in the package insert **CSU:** 150 mg to 300 mg SC every 4 weeks Dosing is not dependent on serum IgE or body weight	For SC use only (thigh, abdomen, outer area of upper arm [caregiver/HCP only]) Therapy is initiated in a healthcare setting; HCP may determine self-administration by patient or caregiver is appropriate (with prefilled syringe) The lyophilized powder for injection may take 5 to 10 seconds to administer due to the solution viscosity Doses > 150 mg should be divided among ≥ 2 injection site; new injection site should be ≥ 1 inch from other areas used for injection	SDV: 150 mg lyophilized powder for injection SDP syringe: 75 mg/0.5 mL 150 mg/mL
Thymic Stromal Lymphopoietin (TSLP) Blocker			
tezepelumab (Tezspire)	**Asthma:** 210 mg SC every 4 weeks	HCP-administered in the upper arm, thigh, or abdomen rotating sites with each injection	SDP syringe: 210 mg/1.91 mL

SDP = single-dose, prefilled; SDV = single-dose vial

Reslizumab should only be administered in a healthcare setting by a HCP; patients should be closely monitored for an appropriate time period after administration of the dose. In April of 2020, the FDA allowed for the *temporary* self-administration of the prefilled syringe (PFS) of omalizumab during the COVID-19 pandemic.[83] Since patients with moderate to severe asthma are considered high-risk for severe COVID-19 related illness, HCPs are to determine those patients who are able to self-administer depending on local pandemic guidelines and restrictions, as well as patient parameters. The manufacturer has provided criteria to assist HCPs in determining appropriate patients; the criteria are detailed in their published communication. In April 2021, the FDA approved label updates to allow for patient or caregiver administration of omalizumab *pre-filled syringes* in patients deemed appropriate by an HCP. Omalizumab is still required to be initiated in a healthcare setting; however, once therapy has been established, the HCP can decide if self-administration is appropriate, based on a careful evaluation of the risk for anaphylaxis and mitigation strategies. Prescribing information details factors to consider (e.g., risk factors for anaphylaxis) for selection of patients for self-administration of omalizumab *prefilled syringe* as well as administration instructions for patients/caregivers. For pediatric patients 6 to 11 years of age, the omalizumab *prefilled syringes* should be administered by a caregiver; for adolescents ≥ 12 years of age, omalizumab *prefilled syringe* may be self-administered under the supervision of an adult. The *lyophilized powder* formulation should only be prepared and injected by a HCP. Patients or caregivers can administer benralizumab, dupilumab, or mepolizumab using the prefilled autoinjector (benralizumab and mepolizumab), prefilled pen (dupilumab), or prefilled syringe (dupilumab and mepolizumab) following proper training if an HCP determines it to be appropriate. The vial preparation of mepolizumab requires reconstitution and administration by a HCP; the prefilled syringe formulation of benralizumab also requires administration by a HCP. In general, patients receiving benralizumab or

mepolizumab should also be monitored following administration. Tezepelumab is intended for HCP administration.

Total IgE levels remain elevated during treatment and for up to 1 year after therapy discontinuation of omalizumab. If therapy is interrupted for more than 1 year, retest total serum IgE level to determine dosage. For interruptions less than 1 year in duration, the dosage may be based on the original baseline serum IgE levels.

The need for continued therapy of agents in this class should be reassessed periodically based on current disease severity and asthma control.

Benralizumab, dupilumab, omalizumab, reslizumab, and tezepelumab should be stored under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Benralizumab prefilled syringe and autoinjector can be stored at room temperature (≤ 25°C [77°F]) for up to 14 days in the original carton, after which time the product must be used or discarded. Likewise, dupilumab may be kept at room temperature for up to 14 days, after which time the product must be used or discarded. If needed, tezepelumab may be stored at room temperature for a maximum of 30 days, then used or discarded. Omalizumab lyophilized powder (vial) and solution (prefilled syringe) should be shipped at controlled ambient temperature (≤ 30°C [≤ 86°F]). Omalizumab reconstituted lyophilized powder and prefilled syringe must be used within 4 hours if placed at room temperature. Mepolizumab vials should be stored at temperatures below 25°C (77°F); mepolizumab prefilled syringes and prefilled autoinjectors should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) prior to and following dispensing. If required, an unopened carton may be stored at up to 30°C (86°F) for a maximum of 7 days. The prefilled syringe and prefilled autoinjectors should be placed at room temperature for 30 minutes prior to administration; these are required to be used within 8 hours of being removed from the carton.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Placebo-controlled trials are included when no comparative trials are available. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Asthma

benralizumab (Fasenra) versus placebo

SIROCCO: A multinational, randomized, double-blind, parallel-group, placebo-controlled study compared the efficacy of benralizumab to placebo in patients with severe asthma (n=1,205).[84] Eligible patients, which included those ages 12 to 75 years with a diagnosis of asthma ≥ 1 year and ≥ 2 exacerbations while on ICS plus LABA in the previous year, were randomly assigned 1:1:1 to SC benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first 3 doses every 4 weeks) or placebo Q4W for 48 weeks as add-on to their standard treatment. Patients were stratified based on blood eosinophil counts. Compared with placebo, both benralizumab dosing regimens reduced the annual asthma exacerbation rate over 48 weeks, the primary endpoint (Q4W rate ratio, 0.55 [95% CI, 0.42 to 0.71; p<0.0001]; Q8W rate ratio, 0.49 [95% CI, 0.37 to 0.64; p<0.0001]). A benefit versus placebo was also seen in notable secondary endpoints, including pre-bronchodilator FEV_1 and asthma symptoms (Q8W regimen only).

CALIMA: Another multinational, randomized, double-blind, parallel-group, placebo-controlled study compared the efficacy of benralizumab to placebo in patients with severe asthma (n=1,306).[85] Eligible patients, which included those ages 12 to 75 years with ≥ 2 exacerbations while on ICS plus LABA in the previous year, were randomly assigned 1:1:1 to SC benralizumab 30 mg either Q4W or Q8W (first 3 doses every 4 weeks) or placebo Q4W for 56 weeks as add-on to their standard treatment. Patients were stratified based on blood eosinophil counts. Compared with placebo, both benralizumab dosing regimens reduced the annual asthma exacerbation rate over 56 weeks, the primary endpoint (Q4W rate ratio, 0.64 [95% CI, 0.49 to 0.85; p=0.0018]; Q8W rate ratio, 0.72 [95% CI, 0.54 to 0.95; p=0.0188]). As seen in the SIROCCO trial above, a benefit versus placebo was also seen in key secondary endpoints, including pre-bronchodilator FEV_1 and asthma symptoms (Q8W regimen only).

ZONDA: A 28-week, multinational, randomized, placebo-controlled trial assessed the impact of benralizumab versus placebo on the reduction in the oral glucocorticoid dose (while maintaining asthma control) in adult patients with severe asthma (n=220).[86] Eligible patients were randomized to SC benralizumab 30 mg either Q4W or Q8W (first 3 doses every 4 weeks) or placebo Q4W. Both benralizumab dosing regimens significantly reduced the percentage change in the oral glucocorticoid dose from baseline to week 28, the primary endpoint (75% reduction for both active treatments versus 25% with placebo; p<0.001 for both comparisons). Both benralizumab groups also resulted in a lower rate of annual exacerbations compared to placebo (Q4W: 55% lower [marginal rate, 0.83 versus 1.83, respectively; p=0.003]; Q8W: 70% lower [marginal rate, 0.54 versus 1.83, respectively; p<0.001]). However, a statistically significant difference versus placebo was not found in FEV_1, and results were mixed in other secondary endpoints.

BISE: A multinational, randomized, double-blind, placebo-controlled study assessed the impact of benralizumab on lung function in adults with asthma (n=211).[87] Eligible patients included those with a postbronchodilator reversibility in FEV_1 ≥ 12% at screening receiving either low- to medium-dosage ICS or low-dosage ICS/LABA with a morning pre-bronchodilator FEV_1 of ≥ 50% to 90% predicted and ≥ 1 of the following symptoms at screening: a daytime or night-time asthma symptom score ≥ 1 for ≥ 2 days, rescue SABA use for ≥ 2 days, or night-time awakenings due to asthma ≥ 1 night. All patients received standardized converted budesonide and were then assigned to either placebo or benralizumab SC 30 Q4W for 12 weeks. Treatment with benralizumab resulted in an 80 mL improvement in pre-bronchodilator FEV_1 after 12 weeks versus placebo, the primary endpoint (95% CI, 0 to 150; p=0.04).

dupilumab (Dupixent) versus placebo

LIBERTY ASTHMA QUEST: This study enrolled 1,902 patients ≥ 12 years of age with uncontrolled moderate-to-severe asthma who were on a medium- or high-dose inhaled corticosteroid (ICS) and 1 to 2 additional controller medications.[88,89] Patients were randomized to add-on therapy with dupilumab 200 mg or 300 mg SC every 2 weeks (following initial doses of 400 mg and 600 mg, respectively) or matching placebo for 52 weeks. Treatment with the dupilumab 200 mg and 300 mg regimens resulted in a lower adjusted annualized rate of severe asthma exacerbations (coprimary endpoint) compared to placebo, by 47.7% and 46%, respectively (p<0.001 for both), at 52 weeks. Prespecified subgroup analyses showed a significant difference in exacerbation rates with either dose of dupilumab compared to placebo among patients with an eosinophil count of ≥ 300 mm^3, but not in patients with eosinophil count < 150 mm^3. In the overall trial population, the change from baseline in the FEV_1 before bronchodilator use at week 12 (the other coprimary endpoint) was 0.32 L with dupilumab 200 mg versus 0.18 L with matching placebo (difference, 0.14 L; p<0.001) and 0.34 L with dupilumab 300 mg versus 0.21 L with matching placebo (difference, 0.13 L; p<0.001).

LIBERTY ASTHMA VENTURE: This 24-week trial enrolled 210 patients ages ≥ 12 years with asthma on daily oral corticosteroids (OCS) and regular use of high-dose ICS plus an additional controller.[90,91] Patients were randomized to add-on therapy with dupilumab 300 mg or matching placebo SC every 2 weeks for 24 weeks. The background OCS dose was titrated downward every 4 weeks during weeks 4 to 20, as long as asthma control was maintained. The change in OCS dose from baseline at week 24 (primary endpoint) was -70.1% with dupilumab and -41.9% with placebo (p<0.001). In the dupilumab group 80% of patients experienced at least a 50% reduction in OCS dose and 48% were able to discontinue OCS therapy compared 50% and 25%, respectively in the placebo group. In addition, dupilumab treatment resulted in a greater reduction in OCS dose compared to placebo, regardless of the baseline blood eosinophil count.

LIBERTY ASTHMA VOYAGE: This 52-week, double-blind, placebo-controlled study enrolled 408 patients 6 to 11 years of age, with moderate to severe asthma on a medium or high-dose ICS and a second controller medication or high-dose ICS alone.[92] Patients had a history at least 1 asthma exacerbation that required treatment with systemic corticosteroids or emergency department visit or hospitalization in the previous year. Subjects were randomized 2:1 to dupilumab or matching placebo every other week in addition to background asthma therapy. The dosage was based on body weight; patients weighing < 30 kg received dupilumab 100 mg and those ≥ 30 kg received 200 mg. Among patients with the type 2 inflammatory phenotype (blood eosinophils ≥ 150/mm^3 or a fraction of exhaled nitric oxide [FeNO] ≥ 20 ppb at baseline), the primary endpoint of adjusted annualized rate of severe asthma exacerbations with dupilumab was 0.31 (95% CI, 0.22 to 0.42) and with placebo was 0.75 (95% CI, 0.54 to 1.03) (RRR with dupilumab, 59.3%; 95% CI, 39.5 to 72.6; p<0.001). In patients with baseline eosinophils ≥ 300/mm^3 at baseline, the adjusted annualized rate of severe asthma exacerbations was 0.24 (95% CI, 0.16 to 0.35) with dupilumab and 0.67 (95% CI, 0.47 to 0.95) with placebo (RRR with dupilumab, 64.7%; 95% CI, 43.8 to 77.8; p<0.001). The effectiveness of dupilumab 300 mg administered every 4 weeks was extrapolated from efficacy date for the 100 mg every 2 week dosage in the VOYAGE trial and based on pharmacokinetic data.[93]

mepolizumab (Nucala) versus placebo

MENSA: A 32-week placebo-controlled trial randomized 576 patients, ages 12 to 82 years, with recurrent asthma exacerbations and evidence of eosinophilic inflammation to receive mepolizumab 75 mg intravenously (IV), mepolizumab 100 mg subcutaneously (SC), or placebo every 4 weeks.[94] Adult patients enrolled had a forced expiratory volume in 1 second (FEV_1) < 80% predicted; patients 12 to 18 years had FEV_1 < 90% predicted or FEV_1 to forced vital capacity (FVC) ratio < 0.8. Background therapy was continued. Patients had either a peripheral blood eosinophil count ≥ 150 cells/µL at screening or ≥ 300 cells/µL at some time during the previous year. The study reported a reduction in the primary endpoint, rate of exacerbations, by 47% (95% confidence interval [CI], 28 to 60) in those treated with IV mepolizumab and 53% (95% CI, 36 to 65) in those treated with SC mepolizumab, both as compared to placebo (p>0.001, for both). Emergency department or hospitalization due to asthma exacerbation was 32% less with IV mepolizumab and 61% less with SC mepolizumab, each as compared to placebo. By study end the mean increases over placebo in the secondary endpoints for IV and SC mepolizumab were as follows: FEV_1, - 100 mL and 98 mL, respectively; St George's Respiratory Questionnaire (SGRQ), -6.4 and 7 points, respectively; and improvement in asthma control questionnaire (ACQ-5), -0.42 and 0.44 points, respectively (p<0.001 for all comparisons). Mepolizumab by the IV route is not FDA-approved.

SIRIUS: A 24-week double-blind, placebo-controlled steroid-reduction study randomized 135 patients (≥ 12 years of age) with severe asthma with eosinophilic inflammation to mepolizumab 100 mg SC or placebo once every 4 weeks.[95,96] The study included 4 phases. Phase 1 was the 3 to 10 week oral corticosteroid (OCS) optimization phase that titrated patients to the lowest OCS dose to maintain asthma control. Mepolizumab and placebo were initiated during the 4-week phase 2. In the 16-week phase 3, doses of OCS were titrated according to a recommended schedule. Phase 4 was a 4-week maintenance phase in which no further OCS titration was made. Patients had either a peripheral blood eosinophil count ≥ 150 cells/µL during the optimization phase or ≥ 300 cells/µL during the 12 months prior to screening. Compared with placebo, patients in the mepolizumab group achieved greater reductions in daily maintenance OCS dose, while maintaining asthma control. Twenty-three percent of mepolizumab patients versus 11% placebo patients had a 90% to 100% OCS dose reduction; 17% versus 8%, respectively, had a reduction of 70% to < 90%. The median percentage reduction from baseline in OCS dose was 50% in the mepolizumab group, as compared with no reduction in the placebo group (p=0.007).

COSMEX: A 52-week, open-label, extension study that included 340 patients from SIRIUS and MENSA with life-threatening/seriously debilitating asthma did not identify new safety signals; it reported a clinically significant exacerbation rate of 0.93 events/year (95% CI, 0.81 to 1.06), an exacerbation requiring hospitalization or emergency department visit rate of 0.13 (95% CI, 0.1 to 0.18), and an exacerbation requiring hospitalization rate of 0.07 (95% CI, 0.05 to 0.1).[97]

MUSCA: A randomized, double-blind, placebo-controlled phase 3b trial enrolled 551 patients (≥ 12 years of age) with severe eosinophilic asthma and a history of ≥ 2 exacerbations, despite regular use of high-dose ICS plus other controller medicines that required treatment in the previous 12 months.[98] Patients received mepolizumab 100 mg or placebo SC every 4 weeks, in addition to standard of care, for 24 weeks. In the modified intent-to-treat population, mepolizumab versus placebo resulted in significant improvements at week 24 from baseline in SGRQ total score (least squares mean change from baseline -15.6 versus -7.9, a treatment difference of -7.7 (95% CI, -10.5 to -4.9; p<0.0001). Most common adverse effects with mepolizumab and placebo were headache (16% versus 21%, respectively) and nasopharyngitis (11% versus 17%, respectively).

The efficacy of mepolizumab for add-on therapy for severe asthma with eosinophilic phenotype in children 6 to 11 years of age has been extrapolated from efficacy studies in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety analyses.[99] An open-label clinical trial was conducted in 36 patients between the ages of 6 and 11 years old with severe asthma (mean age, 8.6 years; 31% female).[100] Subjects had a history of ≥ 2 exacerbations in the previous year despite treatment with medium or high-dose ICS plus additional controller medications with or without oral corticosteroids (OC) and had blood eosinophils of ≥ 150 cells/µL at screening or ≥ 300 cells/µL within the 12 months prior to enrollment. Based on the 12-week pharmacokinetic data from this trial, a dose of 40 mg every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg SC. An open-label extension study of 52 weeks (n=30) reported a safety profile similar to that seen in adults and adolescents.[101]

omalizumab (Xolair) versus placebo

Two double-blind, placebo-controlled trials included patients 12 to 76 years of age with moderate to severe persistent asthma and a positive skin test to a perennial aeroallergen.[102] Patients were randomized to omalizumab based on body weight and baseline serum total IgE level according to pre-specified dosing instructions; maximum dose per 4 weeks was 750 mg. In studies 1 (n=525) and 2 (n=546), baseline FEV_1 was 40% to 80% predicted. During a run-in period, patients were converted to and stabilized on inhaled beclomethasone dipropionate. Long-acting beta-agonist (LABA) therapy was not allowed in this study. Patients receive omalizumab for 16 weeks, then entered a 12-week ICS dose-reduction phase. In studies 1 and 2 the mean number of exacerbations per patient was statistically significantly reduced with omalizumab compared to placebo. A reduction in asthma exacerbation was not observed in the omalizumab-treated patients who had baseline FEV_1 > 80% predicted or in patients who required maintenance therapy with oral steroids.

A third double-blind, placebo-controlled trial included patients (n=341) 12 to 76 years of age with moderate to severe persistent asthma and a positive skin test to at least 1 perennial aeroallergen.[103] During the run-in phase, patients were stabilized on fluticasone propionate. LABA therapy was allowed. Patients were randomized to omalizumab or placebo and were stratified by use of ICS-only or ICS plus oral steroids. After 16 weeks of omalizumab therapy, patients entered a 16-week ICS dose reduction phase. The number of exacerbations was similar for omalizumab and placebo groups. No reduction of asthma exacerbations was seen in patients who had a baseline FEV_1 > 80% predicted or in patients who required maintenance therapy with oral steroids.

A 52-week, placebo-controlled trial evaluated safety and efficacy of omalizumab therapy in 628 patients 6 to < 12 years of age with moderate to severe asthma, uncontrolled with ICS with or without other controller medications.[104] Patients had been diagnosed with asthma for at least 1 year and had positive skin tests for perennial aeroallergen. During the first 24 weeks, steroid doses were unchanged. At week 24, the rate of asthma exacerbations was statistically significantly lower for the omalizumab group compared to placebo (0.45 versus 0.634; rate ratio [RR], 0.69 [95% CI, 0.53 to 0.9]). During the next 28 weeks, adjustment of steroid doses was allowed. A reduced rate of asthma exacerbations was also observed with omalizumab during the entire 52-week study (0.78 versus 1.36; RR, 0.57 [95% CI, 0.45 to 0.72]). No significant difference was seen in nocturnal symptom scores, beta-agonist use, and FEV_1 between the omalizumab and placebo groups.

An additional 28-week double-blind, placebo-controlled study included 334 patients with moderate to severe asthma, 298 of which were 6 to < 12 years old.[105] Patients were well-controlled on ICS. Fewer

asthma exacerbations were reported in the omalizumab group during the 16-week ICS fixed-dose period (0.18 versus 0.32; RR, 0.58 [95% CI, 0.35 to 0.96]) and the 28-week treatment period (0.38 versus 0.76; RR, 0.5 [95% CI, 0.36 to 0.71]).

reslizumab (Cinqair) versus placebo

Two similar 52-week phase 3, double-blind, placebo-controlled trials included 953 patients 12 to 75 years of age with eosinophilic asthma as evidenced by a blood eosinophil count ≥ 400 cells/µL within the previous 3 or 4 weeks and at least 1 asthma exacerbation requiring systemic corticosteroid use in the past 12 months. Patients received IV reslizumab 3 mg/kg or placebo every 4 weeks.[106,107,108] Both studies reported a significant reduction in rate of asthma exacerbation. The point estimate for exacerbation rate ranged from 0.86 to 0.9 per year in reslizumab-treated patients versus 1.8 to 2.1 per year in placebo patients. In addition, mepolizumab reduced the rate of exacerbations requiring emergency department visit and/or hospitalization; however, the difference was not statistically significant.

A 16-week, phase 3, double-blind, placebo-controlled study included a total of 315 patients aged 12 to 75 years with eosinophilic asthma.[109,110,111,112] Patients had a blood eosinophil count ≥ 400 cells/µL. Patients were randomized to reslizumab 0.3 mg/kg or 3 mg/kg or placebo every 4 weeks. Maintenance OCS were not allowed. Primary endpoint was change in FEV_1 from baseline to week 16. Mean difference in change in FEV_1 between study drug and placebo was 115 mL for the lower dose of reslizumab and 160 mL for the higher dose. Reslizumab 0.3 mg/kg is not an FDA approved dosage.

A 16-week, phase 3, double-blind, placebo-controlled trial included 496 adults who were unselected for baseline serum eosinophil levels (approximately 80% of patients had eosinophil count < 400 cells/µL).[113,114,115,116] Patients were randomized to IV reslizumab 3 mg/kg or placebo every 4 weeks. Mean change in FEV_1 was 76 mL (95% CI, -6 to 158). A modest treatment effect was reported in patients with baseline eosinophil count < 400/µL (treatment difference, 31 mL) and a larger effect for those with a baseline eosinophil count > 400/µL (treatment difference, 270 mL; p=0.0436). Due to the small number of patients in the eosinophil count > 400/µL cohort, interpretation of these results is limited.

A 24 month, open-label extension study evaluating long-term safety and efficacy of IV reslizumab 3 mg/kg given every 4 weeks, included 740 patients who received continuous exposure for at least 12 months and 249 patients with continuous exposure for at least 24 months.[117] The most common adverse effects experienced were worsening of asthma and nasopharyngitis. Serious adverse effects were experienced by 7% of patients, however only 2% discontinued due to these adverse effects. Over the course of treatment, patients maintained lung function and asthma control for up to 2 years.

tezepelumab (Tezspire) versus placebo

NAVIGATOR: A phase 3, randomized, double-blind, placebo-controlled trial evaluated the efficacy of tezepelumab 210 mg every 4 weeks in 1,059 patients aged 12 to 80 years with asthma.[118] Participants had been receiving medium- or high-dose ICS therapy for ≥ 12 months prior to screening and ≥ 1 other controller medication for ≥ 3 months prior to screening and had ≥ 2 exacerbations in the previous 12 months. Adults were also required to have morning prebronchodilator FEV_1 < 80% of predicted and adolescents 12 to 17 years old had FEV_1 < 90% of predicted. The primary endpoint was the annualized rate of asthma exacerbations over the 52-week treatment period. Patients treated with tezepelumab experienced an exacerbation rate of 0.93 (95% CI, 0.8 to 1.07) while those in the placebo group had a rate of 2.1 (95% CI, 1.84 to 2.39) resulting in a rate ratio of 0.44 (p<0.001). FEV_1 also improved by

0.23 L over baseline in the tezepelumab group compared to 0.09 L in the placebo group (difference, 0.13 L; 95% CI, 0.08 to 0.18, p<0.001).

SOURCE: Patients 18 to 80 years of age with corticosteroid-dependent asthma were evaluated in a phase 3, randomized, double-blind, placebo-controlled trial.[119] Eligible patients had ≥ 1 exacerbation in the previous 12 months and FEV_1 < 80% of predicted normal value. Oral corticosteroids were optimized to a daily dose of 7.5 to 30 mg prior to randomization. Participants received tezepelumab 210 mg SC (n=74) or placebo SC (n=76) every 4 weeks for 48 weeks. The primary endpoint was percentage reduction from baseline in daily oral corticosteroid dose at week 48 while maintaining asthma control. The odds of achieving reduction in maintenance oral corticosteroid dose was similar between tezepelumab and placebo groups and the primary endpoint was not met. However, the cumulative odds were higher with tezepelumab compared to placebo in patients with a baseline blood eosinophil ≥ 150 cells/µL (2.58; 95% CI, 1.16 to 5.75]), but not in those with baseline eosinophil < 150 cells/µL (0.4; 95% CI, 0.14 to 1.13).

Chronic Spontaneous Urticaria

omalizumab (Xolair) versus placebo

Two placebo-controlled, multiple-dose trials evaluated the safety and efficacy of omalizumab in adults and adolescents with CSU. Trial 1 was 24 weeks duration (n=319), while trial 2 was 12 weeks (n=322).[120] Omalizumab SC 75 mg, 150 mg, or 300 mg or placebo were added to the patients baseline H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week observation period. Urticaria activity score (UAS7) was measured weekly. Baseline UAS7 ranged between 13.7 and 14.5. In trial 1, more patients treated with omalizumab 300 mg (36%) reported no itch or hives (UAS7=0) compared to omalizumab 150 mg (15%), omalizumab 75 mg (12%), and placebo (9%). In both trials, omalizumab 150 mg and 300 mg were associated with greater reductions in itch severity scores (-2.95 [95% CI, -4.72 to -1.18] and -5.8 [95% CI, -7.49 to -4.1], respectively) and hive count scores (-3.44 [95% CI, -5.57 to -1.32] and -6.93 [95% CI, -9.1 to -4.76], respectively) compared to placebo at week 12; similar findings were reported at the end of trial 2. Omalizumab 75 mg did not result in consistent effectiveness and is not an FDA approved dose for CSU.

Eosinophilic Granulomatosis with Polyangiitis

mepolizumab (Nucala) versus placebo

A 52-week placebo-controlled trial randomized 136 adults with EGPA to receive mepolizumab 300 mg or placebo SC every 4 weeks while continuing on their stable oral corticosteroid (OCS) therapy, with or without immunosuppressive therapy.[121,122] After week 4, OCS use was tapered based on the investigator's discretion. A patient was considered in remission if on < 4 mg/day of OCS and achieving a BVAS score of zero. After 52 weeks, mepolizumab resulted in significantly more accrued weeks of remission compared to placebo (28% versus 3% of patients had ≥ 24 weeks of accrued remission, odds ratio, 5.9 [95% CI, 2.7 to 13]). A greater proportion of patients were in remission at both the 36 and 48 week timeframes with mepolizumab (odds ratio, 16.7 [95% CI, 3.6 to 77.6]) and were stable on < 4 mg/day of OCS at week 52 (odds ratio, 5.1 [95% CI, 2.5 to 10.4]). The annualized relapse rate was 1.14 with mepolizumab and 2.27 with placebo (rate ratio, 0.5; 95% CI, 0.36 to 0.7; p<0.001). The safety profile of mepolizumab was similar to that reported in previous studies.

Hypereosinophilic Syndrome

mepolizumab (Nucala) versus placebo

A 32-week, double-blind, placebo-controlled trial enrolled 108 patients ≥ 12 years old with *FIP1L1-PDGFRA*-negative HES. At screening, patients had uncontrolled HES (defined as a history of > 2 flares within the past 12 months and a blood eosinophil count > 1,000 cells/mL). Patients were randomized 1:1 to mepolizumab 300 mg or placebo SC every 4 weeks as add-on to stable background therapy (e.g., episodic oral corticosteroids [OSC], immunosuppressive, or cytotoxic therapy).[123,124] During the 32-week treatment period, the proportion of patients who experienced an HES flare (defined as HES symptom worsening or increased eosinophil count on ≥ 2 occasions necessitating an increase in HES therapy; primary endpoint), was significantly less with mepolizumab (26%) compared to placebo (52%) (odds ratio, 0.28; 95% CI, 0.12 to 0.64; p=0.002). No HES flares were experienced in 74% and 48% of patients in the mepolizumab and placebo groups, respectively. At week 32, a 92% reduction from baseline in blood eosinophil count, a secondary endpoint, was observed with mepolizumab compared with placebo (least squares mean blood eosinophil counts at week 32: 70 and 900 cells/mL, respectively). In addition, at week 32, the change from baseline in the Brief Fatigue Inventory (BFI) Item 3 score (10-point scale) was significantly greater with mepolizumab compared to placebo (-0.66 versus +0.32, respectively; p=0.036).

META-ANALYSES

A systematic review used data from drug inception to February 2016 of randomized controlled trials that individually assessed the effectiveness of omalizumab and mepolizumab in severe asthma treatment.[125] A mean difference of 0.38 (95% CI, 0.21 to 0.55; p<0.0001) in the Asthma Quality of Life Questionnaire (AQLQ) that favored omalizumab was found; however, the difference did not reach the minimal clinically important difference of 0.5. Similar improvements in Asthma Control Questionnaire, FEV_1, and Peak Expiratory Flow Rate (PEFR) were seen with both agents. Both agents achieved approximately a 50% reduction in the calculated annualized rates of asthma exacerbations compared to placebo.

A meta-analysis included 13 randomized controlled trials (n=6,000) comparing mepolizumab, reslizumab, and benralizumab versus placebo in adults and children with severe eosinophilic asthma as an adjunct to standard of care.[126] All agents reduced rates of clinically significant asthma exacerbation (defined by treatment with systemic corticosteroids for ≥ 3 days) by approximately half. Limited evidence for improved health-related quality of life scores (Asthma Control Questionnaire [ACQ] and Asthma Quality of Life Questionnaire [AQLQ]) and lung function (FEV_1) were found. No serious adverse events were reported with any of the agents. There was also no difference compared to placebo regarding discontinuation due to adverse effects with mepolizumab or reslizumab, but there were significantly more discontinuations of benralizumab than placebo, although the absolute numbers were small (36/1,599 benralizumab versus 9/998 placebo). While all 3 agents markedly reduced blood eosinophils, benralizumab resulted in almost complete depletion; the impact of this on efficacy and/or safety are unclear. A network meta-analysis of these 3 agents did not find statistical superiority of 1 agent over another, although each has demonstrated a benefit in reduction of exacerbations in published clinical trials.[127] Similarly, another network meta-analysis that compared only reslizumab and mepolizumab also did not find superiority of 1 agent over another.[128]

A network meta-analysis included 26 randomized controlled trials (n=8,444) from drug inception to December 2017 with patients receiving asthma treatment with mepolizumab, benralizumab, reslizumab,

dupilumab, tralokinumab, and lebrikizumab.[129] Development of lebrikizumab and tralokinumab, anti-IL-13 monoclonal antibodies, has been discontinued due to a mixture of positive and negative trial outcomes. All agents, except tralokinumab, were superior to placebo with regard to changes in FEV_1, ACQ, and AQLQ. Dupilumab showed the greatest increase in FEV_1 compared to placebo, followed by reslizumab and benralizumab. Mepolizumab showed the greatest reduction in ACQ scores, while dupilumab and mepolizumab showed the greatest increase in AQLQ scores. Decreased asthma exacerbation rates were only significant for dupilumab and reslizumab (rate ratios, 0.37 [95% CI, 0.17 to 0.8; p<0.011] and 0.64 [95% CI, 0.53 to 0.78; p<0.001])

A network meta-analysis included 21 randomized clinical trials published between 2003 and 2017 with patients treated with anti-interleukin-5 monoclonal antibody therapy versus placebo.[130] Anti-IL-5 agents included mepolizumab, reslizumab, and benralizumab. Using placebo as the reference, there were no statistically significant differences in FEV_1, AQLQ scores, or risk of exacerbation between the 3 anti-IL-5 agents. Reslizumab had a significantly lower rate of adverse events compared to benralizumab; no other statistically significant differences in adverse events among the other comparisons were observed. Ranking analyses suggested that reslizumab had the greatest likelihood of improving FEV_1 and AQLQ scores and reducing adverse event rates, while mepolizumab had the lowest exacerbation risk.

A network meta-analysis of 8 placebo-controlled phase 3 studies evaluated the efficacy of mepolizumab, benralizumab, dupilumab, and tezepelumab and stratified subjects by inflammatory biomarker levels.[131] Studies included patients ≥ 12 years of age with inadequately controlled asthma. The primary endpoint was annualized exacerbation rate (AER). AERs between patients treated with tezepelumab and those treated with dupilumab were not significantly different (rate ratio [RR], 0.815; 5% credible interval (CrI), 0.609 to 1.092). The only subgroup of patients that demonstrated better AER outcomes with tezepelumab versus dupilumab was the cohort of patients with a peripheral blood eosinophil count (PBEC) < 150 cells/mm^3 (RR, 0.531; 95% CrI, 0.302 to 0.939). Compared with benralizumab, patients receiving tezepelumab demonstrated significantly better AERs in the overall population and the subgroups of patients with PBEC ≥ 150 cells/mm^3 and ≥ 300 cells/mm^3. When compared with mepolizumab, benralizumab demonstrated a significantly higher AER in the overall population. Dupilumab had better AER rates than benralizumab in the subgroup of patients with ≥ 300 cells/mm^3 and mepolizumab had better AER rates than benralizumab in the subgroup of patients with PBEC ≥ 150 cells/mm^3. When overall populations were compared, there were no significant differences in the Asthma Quality of Life Questionnaire or adverse events between drugs.

SUMMARY

Benralizumab (Fasenra), dupilumab (Dupixent), mepolizumab (Nucala), and reslizumab (Cinqair) are interleukin antagonists (IL-4/13 or IL-5) indicated as add-on maintenance treatment of patients with severe asthma and with an eosinophilic phenotype. Dupilumab is also indicated in patients with asthma who are dependent on oral corticosteroids. Mepolizumab and dupilumab are indicated in patients as young as 6 years old, benralizumab is approved for use in asthma patients as young as 12 years, and reslizumab is only approved for use in adults. Omalizumab (Xolair) is an anti-IgE monoclonal antibody indicated to treat patients with moderate to severe persistent asthma in patients ≥ 6 years of age with a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids. Tezepelumab-ekko (Tezspire) is a thymic stromal lymphopoietin (TSLP) blocker indicated as add-on maintenance treatment of severe asthma in adults and pediatric patients ≥ 12 years of age.

At least 40% of patients report at least 1 asthma attack each year. Patients with eosinophilic asthma generally have severe disease with high eosinophil levels in the blood and sputum despite treatment with glucocorticoids. The 2022 Global Initiative for Asthma (GINA) guidelines advise a stepwise approach to asthma management, adjusting treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects. Patients with severe allergic asthma with elevated immunoglobulin E (IgE) levels may benefit from omalizumab (anti-IgE) therapy (Evidence A), those with severe eosinophilic asthma may benefit from benralizumab, mepolizumab, or reslizumab (interleukin-5 [IL-5] antagonists) therapy (Evidence A), those with severe eosinophilic/type 2 asthma or patients requiring maintenance oral corticosteroids may benefit from dupilumab (interkleukin-4 [IL-4] antagonist) therapy (Evidence A), and patients ≥ 12 years old with severe asthma may benefit from the addition of tezepelumab.

Subcutaneous (SC) mepolizumab, SC tezepelumab, and intravenous (IV) reslizumab are dosed every 4 weeks, SC benralizumab is dosed every 8 weeks (initially every 4 weeks for 3 dose), SC dupilumab is dosed every 2 weeks, and SC omalizumab is dosed every 2 or 4 weeks for asthma. All agents can cause hypersensitivity reactions, including anaphylaxis, and should be administered by a healthcare provider (HCP) (reslizumab, tezepelumab) or used under the guidance of an HCP (benralizumab, dupilumab, mepolizumab, omalizumab); patients should be carefully monitored for an appropriate time period after the completion of the dose. Benralizumab, dupilumab, mepolizumab, and omalizumab are available in formulations allowing for self- or caregiver-administration with proper training.

Placebo-controlled clinical studies have demonstrated that treatment with benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, or tezepelumab was associated with significant reductions in asthma exacerbations. In trials, benralizumab, dupilumab, reslizumab, and tezepelumab led to improved airway obstruction as revealed by improvement in forced expiratory volume in 1 second (FEV_1). Treatment with benralizumab, dupilumab, and mepolizumab were associated with a reduction in daily maintenance oral corticosteroids dosages while maintaining asthma control. In a trial of patients with corticosteroid-dependent asthma, treatment with tezepelumab did not result in reductions in dosage of daily maintenance oral corticosteroids. There are no comparative trials among the agents in this class to suggest preference of 1 agent over another for the treatment of severe asthma.

Omalizumab (Xolair) is also indicated to treat patients as young as 12 years with chronic spontaneous urticaria (CSU) who remain symptomatic despite H_1 antihistamine treatment. Clinical studies report greatest improvement in itching and hives with omalizumab 300 mg SC every 4 weeks; the 75 mg dosage is not indicated in the treatment of CSU. Omalizumab also carries the indication of nasal polyps in adult patients ≥ 18 years of age with inadequate response to nasal corticosteroids, as add-on maintenance treatment.

Mepolizumab (Nucala) also is approved for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome. The recommended dose is 300 mg SC every 4 weeks (administered as 3 separate 100 mg injections). Mepolizumab is also indicated for hypereosinophilic syndrome (HES) in patients ≥ 12 years of age with the same dosing as EGPA.

Although not discussed in this Therapeutic Class Review, dupilumab (Dupixent) also carries indications for moderate-to-severe atopic dermatitis in patients ≥ 6 months of age and eosinophilic esophagitis in select patients ≥ 12 years of age. Dupilumab and mepolizumab are also indicated for the treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults.

REFERENCES

1 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
2 Fasenra [package insert]. Wilmington, DE; AstraZeneca; February 2021.
3 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
4 Cinqair [package insert]. West Chester, PA; Teva Respiratory; February 2020.
5 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
6 Tezspire [package insert]. Thousand Oaks, CA; Amgen; December 2021.
7 Centers for Disease Control and Prevention. Fast stats: Asthma. Updated February 1, 2022. Available at: https://www.cdc.gov/nchs/fastats/asthma.htm. Accessed June 27, 2022.
8 Centers for Disease Control and Prevention. Most Recent National Asthma Data. Updated May 25, 2022. Available at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Accessed June 27, 2022.
9 2020 Focused updates to the asthma management guidelines: A report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. Accessed June 27, 2022.
10 Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention - Updated 2022. Available at: http://ginasthma.org. Accessed June 27, 2022.
11 Medical Letter. Mepolizumab (Nucala) for severe eosinophilic asthma. January 18, 2016. Med Lett Drugs Ther. 2016 Jan 18;58(1486):11-2 Available at: http://secure.medicalletter.org/TML-article-1486e. Accessed June 27, 2022.
12 Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2019. DOI: 0.1183/13993003.00588-2019. Available at: https://www.thoracic.org/statements/. Accessed June 27, 2022.
13 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention - Updated 2022. Available at: http://ginasthma.org. Accessed June 27, 2022.
14 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention - Updated 2022. Available at: http://ginasthma.org. Accessed June 27, 2022.
15 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention - Updated 2022. Available at: http://ginasthma.org. Accessed June 27, 2022.
16 Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology. Practice parameter for the diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133:1270-7. DOI: 10.1016/j.jaci.2014.02.036. Available at: https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters/Practice-Parameters-Guidelines. Accessed June 29, 2022.
17 Greenberger: Chronic urticaria: new management options. World Allergy Organization Journal 2014 7:31. DOI:10.1186/1939-4551-7-31. Available at: https://waojournal.biomedcentral.com/track/pdf/10.1186/1939-4551-7-31. Accessed June 29, 2022.
18 Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology. Practice parameter for the diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133:1270-7. DOI: 10.1016/j.jaci.2014.02.036. Available at: https://www.aaaai.org/practice-resources/statements-and-practice-parameters/practice-parameter-guidelines. Accessed June 29, 2022.
19 Greaves MW. Chronic Idiopathic Urticaria. Available at: http://www.medscape.com/viewarticle/461843_3. Accessed June 29, 2022.
20 Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology. Practice parameter for the diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133:1270-7. DOI: 10.1016/j.jaci.2014.02.036. Available at: https://www.aaaai.org/practice-resources/statements-and-practice-parameters/practice-parameter-guidelines. Accessed June 29, 2022.
21 The Vasculitis Foundation. Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss Syndrome). Available at: https://www.vasculitisfoundation.org/education/forms/eosinophilic-granulomatosis-with-polyangiitis-churg-strauss-syndrome/. Accessed June 29, 2022.
22 Churg Strauss Syndrome. Available at: https://rarediseases.org/rare-diseases/churg-strauss-syndrome/. Accessed June 29, 20221.
23 Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology. Practice parameter for the diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133:1270-7. DOI: 10.1016/j.jaci.2014.02.036. Available at: https://www.aaaai.org/practice-resources/statements-and-practice-parameters/practice-parameter-guidelines. Accessed June 29, 2022.
24 The Vasculitis Foundation. Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss Syndrome). Available at: https://www.vasculitisfoundation.org/education/forms/eosinophilic-granulomatosis-with-polyangiitis-churg-strauss-syndrome/. Accessed June 29, 2022.
25 Orphanet. Eosinophilic granulomatosis with polyangiitis. Updated October 2020. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=183. Accessed June 29, 2022.
26 Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Updated December 2, 2020. Available at: https://emedicine.medscape.com/article/333492-overview#a5. Accessed June 29, 2022.
27 Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis with Polyarteritis (EGPA). Available at: https://www.aaaai.org/conditions-and-treatments/related-conditions/churg-strauss-syndrome. Accessed June 29, 2022.
28 Talmadge, KE. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Treatment and prognosis. Last updated May 10, 2022. Available at: https://www.uptodate.com/contents/treatment-and-prognosis-of-eosinophilic-granulomatosis-with-polyangiitis-churg-strauss. Accessed June 29, 2022.
29 Orphanet. Eosinophilic granulomatosis with polyangiitis. Updated October 2020. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=183. Accessed July 22. 2021.
30 Talmadge, KE. Treatment and prognosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Updated June 23, 2020. In: UpToDate. Hollingworth H, Flaherty KR, Glassock RJ, et al (ED). UpToDate, Waltham, MA, 2020. Available at: https://www.uptodate.com/contents/treatment-and-prognosis-of-eosinophilic-granulomatosis-with-polyangiitis-churg-strauss. Accessed June 29, 2022.

31 Chung SA, Landford CA, Maz M et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. 2021; DOI: 10.1002/art.41773. Available at: https://www.vasculitisfoundation.org/2021-acr-vf-vasculitis-guidelines/. Accessed June 29, 2022.
32 Hypereosinophilic Syndrome. Reviewed September 28, 2020. Available at: https://www.aaaai.org/conditions-treatments/related-conditions/hypereosinophilic-syndrome. Accessed July 1, 2022.
33 Roufosse F, Klion AD, et al. Hypereosinophilic syndromes: clinical manifestations, pathophysiology, and diagnosis. Last updated April 6, 2020. Available at: https://www.uptodate.com/contents/hypereosinophilic-syndromes-clinical-manifestations-pathophysiology-and-diagnosis?search=hypereosinophilic%20syndrome&source=search_result&selectedTitle=1~62&usage_type=default&display_rank=1#references. Accessed July 1, 2022.
34 Hypereosinophilic syndrome. Last updated November 8, 2021. Available at: https://rarediseases.info.nih.gov/diseases/2804/hypereosinophilic-syndrome. Accessed July 1, 2022.
35 Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. Hematology. 2022;97(1):129-148. DOI: 10.1002/ahj.26352. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajh.26352. Accessed July 13, 2022.
36 Hypereosinophilic syndrome. Updated November 8, 2021. Available at: https://rarediseases.info.nih.gov/diseases/2804/hypereosinophilic-syndrome. Accessed July 1, 2022.
37 Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. Hematology. 2022;97(1):129-148. DOI: 10.1002/ahj.26352. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajh.26352. Accessed July 13, 2022.
38 Gleevec [package insert]. East Hanover, NJ; Novartis; March 2022.
39 Fasenra [package insert]. Wilmington, DE; AstraZeneca; February 2021.
40 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
41 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
42 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
43 Cinqair [package insert]. West Chester, PA; Teva Respiratory; February 2020.
44 Medical Letter. Omalizumab (Xolair) for Chronic Urticaria. May 27, 2013. Available at: http://secure.medicalletter.org/TML-article-1417b. Accessed July 12, 2022.
45 Tezspire [package insert]. Thousand Oaks, CA; Amgen; December 2021.
46 Fasenra [package insert]. Wilmington, DE; AstraZeneca; February 2021.
47 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
48 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
49 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
50 Cinqair [package insert]. West Chester, PA; Teva Respiratory; February 2020.
51 Tezspire [package insert]. Thousand Oaks, CA; Amgen; December 2021.
52 Food and Drug Administration. Xolair Clinical Pharmacology Review. Available at: https://web.archive.org/web/20190424002835/http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM393855.pdf. Accessed July 12, 2022.
53 Fasenra [package insert]. Wilmington, DE; AstraZeneca; February 2021.
54 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
55 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
56 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
57 Cinqair [package insert]. West Chester, PA; Teva Respiratory; January 2019.
58 Tezspire [package insert]. Thousand Oaks, CA; Amgen; December 2021.
59 Fasenra [package insert]. Wilmington, DE; AstraZeneca; February 2021.
60 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
61 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
62 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
63 Cinqair [package insert]. West Chester, PA; Teva Respiratory; January 2019.
64 Tezspire [package insert]. Thousand Oaks, CA; Amgen; December 2021.
65 Fasenra [package insert]. Wilmington, DE; AstraZeneca; February 2021.
66 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
67 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
68 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
69 Cinqair [package insert]. West Chester, PA; Teva Respiratory; January 2019.
70 Tezspire [package insert]. Thousand Oaks, CA; Amgen; December 2021.
71 Fasenra [package insert]. Wilmington, DE; AstraZeneca; February 2021.
72 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
73 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
74 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
75 Cinqair [package insert]. West Chester, PA; Teva Respiratory; February 2020.
76 Tezspire [package insert]. Thousand Oaks, CA; Amgen; December 2021.
77 Fasenra [package insert]. Wilmington, DE; AstraZeneca; February 2021.
78 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
79 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
80 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.

81 Cinqair [package insert]. West Chester, PA; Teva Respiratory; February 2020.
82 Tezspire [package insert]. Thousand Oaks, CA; Amgen; December 2021.
83 Xolair [communication letter]. South San Francisco, CA; Genentech; April 2020. Available at: https://www.gene.com/download/pdf/Xolair_DHCP_important-prescribing-information_04-16-20.pdf. Accessed July 12, 2022.
84 Bleeker ER, Fitzgerald JM, Chanez P, et al for the SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2115-2127. DOI: 10.1016/S0140-6736(16)31324-1.
85 Fitzgerald JM, Bleeker ER, Nair P, et al for the CALIMA study investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2128-2141. DOI: 10.1016/S0140-6736(16)31322-8.
86 Nair P, Wenzel S, Rabe KF, et al for the Zonda trial investigators. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med. 2017;376(25):2448-2458. DOI: 10.1056/NEJMoa1703501.
87 Ferguson GT, Fitzgerald JM, Bleecker ER, et al for the BISE study investigators. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2017;5(7):568-576. DOI: 10.1016/S2213-2600(17)30190-X.
88 Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018;378:2486-96. DOI: 10.1056/NEJMoa1804092.
89 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
90 Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018;378:2475-85. DOI: 10.1056/NEJMoa1804093.
91 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
92 Bacharier LB, Maspero JF, Katelaris CH, et al. Dupilumab in children with uncontrolled moderate-to-severe asthma. N Engl J Med 2021;385:2230-40. DOI: 10.1056/NEJMoa2106567.
93 Dupixent [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
94 Ortega HG, Liu MC, Pavord ID, Brusselle GG. Mepolizumab treatment in patients with severe eosinophilic asthma. NEJM. 2014 25;371(13):1198-207. DOI: 10.1056/NEJMoa1403290.
95 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
96 Bel EH, Wenzel SE, Thompson PJ, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. NEJM. 2014; 371:1189-1197. DOI: 10.1056/NEJMoa1403291.
97 Khurana S, Brusselle GG, Bel EH, et al. Long-term safety and clinical benefit of mepolizumab in patients with the most severe eosinophilic asthma: the COSMEX study. Clin Ther. 2019;41(10):2041-2056.e5. DOI: 10.1016/j.clinthera.2019.07.007.
98 Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med. 2017 May;5(5):390-400. DOI: 10.1016/S2213-2600(17)30125-X.
99 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
100 Gupta A, Pouliquen I, Austin D, et al. Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. Pediatr Pulmonol. 2019;54(12):1957-1967. DOI: 10.1002/ppul.24508.
101 Gupta A, Ikeda M, Geng B, et al. Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. J Allergy Clin Immunol. 2019;144(5):1336-1342.e7. DOI: 10.1016/j.jaci.2019.08.005.
102 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
103 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
104 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
105 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
106 Cinqair [package insert]. West Chester, PA; Teva Respiratory; February 2020.
107 Food and Drug Administration – Cinqair Medical Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761033Orig1s000MedR.pdf. Accessed July 12, 2022.
108 Bernstein JA, Virchow JC, Murphy K, et al. Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials. Lancet Respir Med. 2020;8(5):461-474. DOI: 10.1016/S2213-2600(19)30372-8.
109 Cinqair [package insert]. West Chester, PA; Teva Respiratory; February 2020.
110 Food and Drug Administration – Cinqair Medical Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761033Orig1s000MedR.pdf. Accessed July 12, 2022.
111 Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01270464?term=reslizumab&rank=11. Accessed July 22, 2021.
112 Bernstein JA, Virchow JC, Murphy K, et al. Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials. Lancet Respir Med. 2020;8(5):461-474. DOI: 10.1016/S2213-2600(19)30372-8.
113 Cinqair [package insert]. West Chester, PA; Teva Respiratory; February 2020.
114 Center for Drug Evaluation and Research Medical Review – Cinqair. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761033Orig1s000MedR.pdf. Accessed July 12, 2022.
115 Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01508936?sect=X70156&term=reslizumab&rank=4#outcome1. Accessed July 12, 2022.
116 Bernstein JA, Virchow JC, Murphy K, et al. Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials. Lancet Respir Med. 2020;8(5):461-474. DOI: 10.1016/S2213-2600(19)30372-8.
117 Murphy K, Jacobs J, Bjermer L, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. J Allergy Clin Immunol Pract. 2017;5(6):1572–81.

118 Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021; 384:1800-1809. DOI: 10.1056/NEJMoa2034975.
119 Wechsler ME, Menzies-Gow A, Brightling CE, et al. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled phase 3 study. Lancet Respir Med. 2022; 10: 650-660. DOI: 10.1016/S2213-2600(21)00537-3.
120 Xolair [package insert]. South San Francisco, CA; Genentech; July 2021.
121 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
122 Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. NEJM. 2017;18;376(20):1921-1932. DOI: 10.1056/NEJMoa1702079
123 Nucala [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2022.
124 Roufosse F, Kahn JE, Rothenberg ME; et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020:148(6): 1397-1405. DOI: 10.1016/j.jaci.2020.08.037.
125 Nachef Z, Krishnan A, Mashtare T, et al. Omalizumab versus Mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: A network meta-analysis. J Asthma. 2017;1:1-12. DOI: 10.1080/02770903.2017.1306548.
126 Farne HA, Wilson A, Powell C, et al. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev. 2017; 21;9:CD010834. DOI: 10.1002/14651858.CD010834.pub3.
127 Edris A, De Feyter S, Maes T, et al. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. Respir Res. 2019 Aug 8;20(1):179. DOI: 10.1186/s12931-019-1138-3.
128 Ya K, Balijepalli C, Sharma R, et al. Reslizumab and mepolizumab for moderate-to-severe poorly controlled asthma: an indirect comparison meta-analysis. Immunotherapy. 2019;11(17):1491-1505. DOI: 10.2217/imt-2019-0113.
129 Iftikhar IH, Schimmel M, Bender W, et al. Comparative efficacy of anti-IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis. Lung. 2018;196(5):517-530. DOI: 10.1007/s00408-018-0151-5.
130 He LLL, Zhang L, Jiang L, et al. Efficacy and safety of anti-interleukin-5 therapy in patients with asthma: A pairwise and Bayesian network meta-analysis. Int Immunopharmacol. 2018;64:223-231. DOI: 10.1016/j.intimp.2018.08.031.
131 Ando K, Fukuda Y, Tanaka A, et al. Comparative efficacy and safety of tezepelumab and other biologics in patients with inadequately controlled asthma according to thresholds of type 2 inflammatory biomarkers: a systematic review and network meta-analysis. Cells. 2022; 11(5):819. DOI: 10.3390/cells11050819.