Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update and New Drug Evaluation: Asthma Biologics

Date of Review: June 2022

Date of Last Review: August 2021
Dates of Literature Search: 05/01/2021 – 03/01/2022
Brand Name (Manufacturer): Tezspire (AstraZeneca/Amgen)
Dossier Received: Yes

Generic Name: Tezepelumab-ekko

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To review and evaluate the place in therapy for tezepelumab, a new monoclonal antibody approved for severe asthma, in addition to recent evidence and guideline recommendations for targeted immune modulators (TIMs) approved for the treatment of moderate-to-severe asthma and other conditions such as chronic rhinosinusitis with nasal polyps (CRSwNP).

Research Questions:
1. What is the efficacy of TIMs approved for the treatment of eosinophilic asthma including benralizumab, dupilumab, mepolizumab, and reslizumab?
2. What is the tolerability and frequency of adverse events (AEs) for benralizumab, dupilumab, mepolizumab, and reslizumab in the treatment of eosinophilic asthma?
3. What is the evidence on the benefits and harms of omalizumab for treatment of patients with moderate-to-severe allergic asthma?
4. What is the evidence on the benefits and harms of tezepelumab, a recently approved monoclonal antibody, for treatment of patients with severe asthma?
5. Are there subgroups of patients (e.g. groups defined by demographics, asthma severity, comorbidities) for which monoclonal antibodies used to treat asthma differ in efficacy or frequency of AEs?

Conclusions:
- Since the last review, one systematic review evaluating evidence for TIMs in treating chronic rhinosinusitis[1] and 4 high-quality guidelines with recommendations for the use of TIMs in treating severe asthma[2-5] were published.
- A 2021 Cochrane Review assessed the effects of dupilumab, mepolizumab, and omalizumab for the treatment of CRSwNP.[1] In patients with chronic rhinosinusitis, high-quality evidence shows dupilumab improves disease-specific, health-related quality of life (HRQoL) and moderate-quality evidence shows dupilumab may reduce disease severity compared to placebo.[1] At 16 and 52 weeks of follow-up, dupilumab may result in a reduction in serious adverse effects (SAEs) compared to placebo (low-quality evidence).[1] Mepolizumab may improve disease-related HRQoL (low-quality evidence), but it is uncertain if there is a difference in disease severity or the number of SAEs compared with placebo.[1] Omalizuamb may improve disease-related HRQoL (moderate-quality

Author: Deanna Moretz, PharmD, BCPS

evidence), but it is uncertain if there is a difference in the number of SAEs compared with placebo.[1] There is no evidence regarding the effect of omalizumab on disease severity.[1] The following limitations to the data were identified: 1) all studies were in adults, and there are no data for children; 2) there is a lack of long-term evidence, as only one study was conducted over 52 weeks; 3) sample sizes were insufficient and length of follow-up too short to comprehensively and adequately assess the risk of adverse effects.[1]

- The April 2021 Global Initiative for Asthma (GINA) guidance provides recommendations for management for severe asthma in adolescent and adult patients.[2] After referral for expert assessment and phenotyping, consider adding a monoclonal antibody for patients with exacerbations or poor symptom control on high-dose inhaled corticosteroid-long-acting beta-agonist (ICS-LABA) who have eosinophilic or allergic biomarkers, or the need for maintenance oral corticosteroids (OCS).[2] Targeted treatment should be considered using the following biomarkers: serum immunoglobulin E (IgE); baseline blood eosinophil cell counts; percentage of sputum eosinophils; or fractional exhaled nitric oxide (FeNO).[2] Frequency of asthma exacerbations and asthma that is allergy driven are additional factors to consider when adding a monoclonal antibody to asthma treatment regimens.[2]
- A clinical review of dupilumab for severe asthma was published August 2021 by the Canadian Agency for Drugs and Technologies in Health (CADTH).[3] The review summarized data from 3 randomized controlled trials (RCTs) that compared dupilumab to placebo in patients with moderate-to-severe asthma who were already receiving standard of care treatment.[3] None of the included studies had an active comparator and only 1 trial was 52 weeks in duration.[3] Based on a review of the evidence, CADTH recommended the following conditions for dupilumab utilization including: 1) inadequate asthma control despite use of high-dose inhaled ICS and one or more additional asthma controllers; 2) an eosinophil count greater than or equal to 150 cells/µL or OCS-dependent asthma; and 3) baseline assessment of asthma symptom control using a validated asthma control questionnaire prior to initiation of dupilumab treatment.[3]
- In February 2021, the National Institute for Health and Care Excellence (NICE) published guidance for the use of mepolizumab in treating severe eosinophilic asthma.[5] There is no evidence directly comparing mepolizumab with the other interleukin (IL)-5 pathway antagonists benralizumab and reslizumab.[5] Mepolizumab, as add-on therapy, is recommended as an option for treating severe refractory eosinophilic asthma, only if it is used for adults who meet the following criteria: 1) have a blood eosinophil count of 300 cells/µL or more and have had at least 3 exacerbations needing systemic corticosteroids in the previous 12 months; or 2) have had continuous OCS doses equivalent to at least prednisolone 5 mg per day over the previous 6 months; or 3) have blood eosinophil count of 400 cells/µL or more and have had at least 3 exacerbations needing systemic corticosteroids in the previous 12 months.[5]
- In December 2021, NICE published guidance for the use of dupilumab for treating severe asthma.[4] Dupilumab is recommended as add-on maintenance therapy in people 12 years and older as an option for treating inadequately controlled severe asthma with Type 2 (T2) inflammation despite maintenance therapy with high-dose ICS and another maintenance treatment only if: 1) the person has a blood eosinophil count of 150 cells/µL or more, FeNO of 25 parts per billion (ppb) or more, and has had at least 4 or more exacerbations in the previous 12 months; and 2) the person is not eligible for mepolizumab, reslizumab or benralizumab (Interleukin [IL]-5 inhibitors are the standard of care for severe asthma management in the United Kingdom [UK]), or has asthma that has not responded adequately to these therapies.[4]
- In December 2021, tezepelumab received FDA-approval as add-on maintenance treatment for patients aged 12 years and older with severe asthma.[6] Tezepelumab binds to the cytokine thymic stromal lymphopoietin (TSLP) in the upstream inflammatory cascade.[6] Clinical data from 2 studies (NAVIGATOR and PATHWAY) were submitted to the FDA to support the licensing application for tezepelumab.[7] The dose-finding, phase 2, PATHWAY trial showed the use of tezepelumab at a dose of 70 mg every 4 weeks, 210 mg every 4 weeks, and 280 mg every 2 weeks resulted in annualized asthma exacerbation rates (AAER) at week 52 of 0.27, 0.20, and 0.23, respectively, as compared with 0.72 in the placebo group.[8] Moderate-quality evidence demonstrated asthma exacerbation rates were lower in the respective tezepelumab groups than in the placebo group by 62% (90% Confidence Interval [CI], 42 to 75; P<0.001), 71% (90% CI, 54 to 82; P<0.001), and 66% (90% CI, 47 to 79; P<0.001).[8]
- The phase 3 NAVIGATOR trial enrolled adults and adolescents aged 12 to 80 years old with severe, uncontrolled asthma in a multi-center, double-blind, randomized study.[9] Subjects must have had at least 2 asthma exacerbations during the 12 months prior to study enrollment.[9] The primary objective of the study was to assess the effect of 210 mg of tezepelumab administered every 4 weeks compared with placebo on AAER over a 52-week treatment period.[9]

Moderate-quality evidence showed that for the overall population, AAER was 0.93 events per patient year with tezepelumab and 2.10 events per patient year with placebo (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P<0.001).[9] In patients with a blood eosinophil count of less than 300 cells/µL, the AAER was 1.02 events per patient year with tezepelumab and 1.73 events per patient year with placebo (rate ratio, 0.59; 95% CI, 0.46 to 0.75; P<0.001).[9] The annualized rate of asthma exacerbations was significantly lower with tezepelumab compared to placebo among adults and adolescents with severe, uncontrolled asthma, including those with low blood eosinophil counts at baseline.[9]

- In the NAVIGTOR and PATHWAY trials the frequencies and types of AEs did not differ meaningfully between tezepelumab and placebo.[8,9] In the pooled safety population, the most common adverse effects of tezepelumab (frequency 3% and greater) were pharyngitis, arthralgia, and back pain.[6] Since TSLP may be involved in the immunological response to some parasitic infections, such infections should be treated before starting tezepelumab.[6]
- The guidelines for monoclonal antibodies approved to manage eosinophilic asthma have different thresholds with respect to baseline levels of blood eosinophils. The GINA recommendations have the broadest guidance and recommend benralizumab, dupilumab, mepolizumab or reslizumab be initiated for difficult-to-treat, severe asthma when eosinophils range between 150 cells/µL and greater or 300 cells/µL and greater.[2]

Recommendations:

- Add tezepelumab injection to the Prior Authorization (PA) criteria for "Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis" and maintain as non-preferred on the Preferred Drug List (PDL).
- To align with current guidelines, revise PA criteria to reduce the threshold for blood eosinophils to 150 cells/µL for monoclonal antibodies prescribed for eosinophilic asthma, update definition of severe asthma exacerbation, and include use of OCS in asthma exacerbation criteria.
- After review of costs in executive session, no additional changes to PDL status were made.

Summary of Prior Reviews and Current Policy:

A class update focused solely on use of monoclonal antibodies for treatment of severe asthma was presented at the August 2021 Pharmacy and Therapeutics (P & T) meeting. The August 2021 class update was informed by the February 2021 research report created by the Drug Effectiveness Review Project (DERP).[10] Recommendations from August 2021 meeting included:

- Create a PDL class entitled "Biologics for Severe Asthma" and include benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab in this PDL class.
- Modify "Monoclonal Antibodies for Severe Asthma" Prior Authorization (PA) criteria to include expanded indications for mepolizumab in treatment of HES and chronic rhinosinusitis with nasal polyps (CRSwNP) and omalizumab for treatment of nasal polyps.
- Retire dupilumab PA criteria and add dupilumab to "Monoclonal Antibodies for Severe Asthma" PA criteria.

The Oregon Health Plan (OHP) provides coverage with PA criteria for 4 monoclonal antibodies approved to manage eosinophilic asthma refractory to other asthma therapies: benralizumab, dupilumab, mepolizumab, and reslizumab. An additional biologic, omalizumab, is also part of the monoclonal antibodies for asthma PA criteria and provides coverage for patients with severe allergic asthma. Omalizuamb is also indicated for management of chronic urticaria, a diagnosis which is not currently funded according to the Health Evidence Review Commission (HERC) prioritized list. Current criteria require that auto-injectable epinephrine be co-prescribed with all asthma biologics due to the risk of delayed anaphylaxis. Prior authorization criteria for this class of drugs are outlined in **Appendix 5**. The PDL status for TIMs approved to treat moderate-to-severe asthma and atopic dermatitis is presented in **Appendix 1**. There are no preferred monoclonal antibodies for asthma on the PDL. During the fourth quarter of 2021, asthma biologic agents billed through point of sale pharmacy claims in the fee-for-service (FFS) population included 4 claims for mepolizumab and 28 claims for dupilumab. In the third quarter of 2021, provider-administered claims were submitted for mepolizumab (n=5), benralizuamb (n=2), and omalizumab (n=16).

Background:

Asthma is a heterogeneous disease, characterized by chronic airway inflammation which results in bronchial hyper-responsiveness.[2] It is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[2] The Centers for Disease Control and Prevention (CDC) estimates that 25 million Americans, including 5 million children have asthma.[11] In the United States (U.S.), asthma is more than twice as common among Black children as among White children (13.5% and 6.4% respectively), and is somewhat more common among Black adults.[11] It is estimated that severe asthma accounts for about 5 to 10% of the total asthma population, but exact prevalence is unknown due to the heterogeneous presentation of severe asthma.[12] Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with management of asthma exacerbations.[13]

The 2021 GINA guidelines introduced definitions of difficult-to-treat and severe asthma which begin with the concept of uncontrolled asthma.[2] Uncontrolled asthma includes: 1) poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma) and/or 2) frequent exacerbations (2 or more per year) requiring OCS or serious exacerbations (1 or more per year) requiring hospitalization.[2] Difficult to treat asthma is asthma that is uncontrolled despite prescribing of medium- or high-dose ICS with a second controller, usually a LABA, or with maintenance OCS, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.[2] Severe asthma is a subset of difficult-to-treat asthma.[2] It is defined as asthma that is uncontrolled despite adherence with maximal optimized high-dose ICS-LABA or that requires high-dose ICS-LABA to remain controlled.[2]

Phenotyping severe asthma based on demographic or clinical characteristics may help to effectively target treatment. The underlying pathophysiology of asthma is multi-factorial and includes several phenotypes: eosinophil predominant, neutrophil predominant, and allergic asthma. Allergic asthma is the most common phenotype, describing between 40% and 50% of cases, and can be identified through allergy testing for environmental allergens, blood immunoglobin E (IgE) levels, eosinophilia, and FeNO testing.[14] Patients with eosinophilic asthma have high levels of sputum and blood eosinophils.[2] Type 2 high inflammation asthma is characterized by the release of signature cytokines IL-4, IL-5 and IL-13 from immune system cells which contribute to mucus production, IgE synthesis, subepithelial fibrosis, bronchial remodeling and airway hyperresponsiveness.[15] Severe asthma with T2 inflammation is associated with allergy, higher risk of exacerbations, hospitalization and dependency on OCS, and increased risk of death compared to people with severe asthma without T2 inflammation.[4] The 2021 GINA guideline lists 5 criteria in its definition of severe asthma with T2 inflammation which are prognostic markers: 1) a blood eosinophil count of 150 cells/μL or more; 2) FeNO of 20 ppb or more; 3) sputum eosinophils of 2% or more; 4) asthma that is clinically allergen driven; and 5) the need for maintenance OCS.[2]

The long-term goals of asthma management are to achieve good symptom control, and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side-effects of treatment.[2] The patient's own goals regarding their asthma and its treatment should also be identified.[2] In the 2021 GINA guidelines, the options for ongoing treatment for adults and adolescents 12 years and older have been clarified by delineating 2 treatment "tracks" based on the choice of reliever consisting of 4 steps each. Treatment may be stepped up or down within a track using the same reliever at each step, or treatment may be switched between tracks, according to the individual patient's needs.[2] In Track 1, the preferred approach recommended by GINA, low-dose ICS-formoterol is the symptom reliever.[2] In Track 2, the symptom reliever is a SABA.[2] The GINA guidance recommends Step 1 and Step 2 of asthma treatment begin with as-needed low-dose ICS-formoterol (Track 1).[2] For safety, the GINA guidelines no longer recommend treatment of asthma with a short acting beta-agonist (SABA) alone in adults and adolescents; evidence has shown that using ICS-formoterol as a reliever reduces the risk of exacerbations and asthma-related mortality compared with using a SABA reliever alone.[2] However, if use of an ICS-formoterol inhaler is not possible or not preferred by a patient with no exacerbations on their current therapy, using as-needed SABA and low dose ICS together (in combination, or with the ICS taken right after the SABA) is an alternative approach (Track 2).[2] If asthma remains uncontrolled despite good adherence and proper inhaler technique, therapy can be advanced to Step 3. For adults and adolescents, the preferred Step 3 treatment in Track 1 is low-dose ICS-formoterol as both maintenance and as-needed reliever therapy (MART).[2]

Track 2 recommends a low-dose maintenance ICS-LABA with as needed SABA in Step 3.[2] The preferred Step 4 treatment for asthma varies depending on what has been tried for Step 3, but includes medium-dose ICS-formoterol or ICS-LABA as maintenance with additional controllers, including long-acting muscarinic antagonists (LAMAs) such as tiotropium and leukotriene receptor antagonists (LTRAs) such as montelukast.[2] Preferred treatment in Step 5 is referral for expert assessment, phenotyping, and add-on therapy to high-dose ICS-formoterol or high-dose ICS-LABA depending on which track is being prescribed.[2] Adding a monoclonal antibody for patients with severe asthma unresponsive to controller-drug treatments is also recommended in Step 5.[2] Low-dose azithromycin for patients older than 18 years with severe asthma has also been added to the GINA guidance after referral in Step 5.[2]

In the GINA guidance, treatment steps for children aged 6 to 11 years recommend Step 1 begin with low-dose ICS taken whenever SABA is taken.[2] Taking ICS whenever SABA is taken is preferred over daily ICS, as poor adherence is highly likely.[2] In Step 2 for children, low-dose ICS is administered daily and a daily LTRA may be added while continuing to use as needed SABA.[2] Daily ICS is preferred over taking ICS whenever SABA is taken, as there is much stronger evidence for efficacy and safety.[2] Step 3 includes MART with very-low-dose ICS-formoterol to reduce the risk of severe exacerbations.[2] Other Step 3 options include low-dose ICS-LABA or medium-dose ICS.[2] Step 4 advances therapy to medium-dose ICS-LABA or low-dose ICS-formoterol MART and referral for expert opinion.[2] In Step 5, referral for phenotypic assessment and higher dose ICS-LABA, or add-on IgE, or anti-IL-5 therapy, or low-dose OCS is recommended.[2]

Omalizumab is an anti-IgE monoclonal antibody that has been available for over a decade to manage severe allergic asthma. Three additional monoclonal antibodies; mepolizumab, reslizumab, and benralizumab, mediate the effects of IL-5 and are effective in management of eosinophilic asthma as add-on therapy. Interleukin-5 is critical for eosinophil maturation and activation. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion. The monoclonal antibodies that mediate IL-5 activity are FDA-approved to treat severe asthma in patients with an eosinophilic phenotype of asthma. Safety and efficacy of these agents have not been assessed in head-to-head trials. Dupilumab is an IL-4 receptor antagonist which modulates signaling of both the IL-4 and IL-13 pathways. Dupilumab is also indicated as add-on maintenance therapy for moderate to severe asthma. Omalizumab, dupilumab, and mepolizumab are approved for children as young as 6 years, and benralizumab is approved for people aged 12 years and older. Reslizumab is approved only for people aged 18 years and older.

Monoclonal antibodies targeting IgE or IL-4, IL-5 and IL-13 (i.e. downstream mediators) are highly effective in reducing exacerbations and symptoms in people with severe allergic and eosinophilic asthma, respectively.[16] However, these therapies are not appropriate for 30–50% of patients with severe asthma who present with non-allergic, non-eosinophilic asthma.[16] Inflammation in these patients may be neutrophilic-prominent or present with normal levels of eosinophils and neutrophils. These patients constitute a clinical asthma phenotype, driven by distinct, yet poorly understood pathobiological mechanisms.[16] Recently developed therapies to manage severe asthma are directed at interfering with the cytokines TSLP, IL-25, and IL-33, which are released by airway epithelial cells in response to allergens, air pollutants, and viruses.[17] Thymic stromal lymphopoietin has been shown to drive various elements of asthma pathophysiology, including airway hyperresponsiveness, mucus overproduction and airway remodeling, via effects triggered downstream.[18] It has been hypothesized that interfering upstream in the inflammatory cascade might improve asthma outcomes in a broader patient population with a range of inflammatory phenotypes.[18] The efficacy of an anti-TSLP monoclonal antibody (tezepelumab), an anti-IL-33 monoclonal antibody (itepekimab), and a monoclonal antibody inhibiting the interleukin-33 receptor (astegolimab) in patients with severe asthma has been recently demonstrated in clinical trials.[17] To date, only tezepelumab has received FDA approval and will be discussed in detail later in this class update.

Although the monoclonal antibodies used to manage severe asthma are well-tolerated, serious adverse reactions have been reported. Anaphylaxis has been reported in 0.3% of patients receiving reslizumab; therefore, the drug carries an FDA boxed warning recommending observation after infusion.[19] Hypersensitivity reactions have been observed with mepolizumab and benralizumab; however neither drug has a boxed warning regarding anaphylaxis.[20,21] There are notable

differences between each biologic agent approved to treat asthma primarily related to the age of administration, route of administration, dosing regimen, and FDA-approved indication. **Table 1** summarizes significant prescribing information for the monoclonal antibodies with FDA approval to treat moderate-to-severe asthma.

Table 1. Targeted Immune Modulators FDA-Approved to Manage Moderate-to-Severe Asthma

Generic Name	Brand Name	Year Approved	Target	Asthma Indication	Administration Route	Administration Age for Asthma	Boxed Warning
Benralizumab[20]	FASENRA	2017	IL-5 Receptor	Severe asthma with an eosinophilic phenotype	SC	≥ 12 yo	No
Dupilumab[22]	DUPIXENT	2017	IL-4 Receptor	Add on maintenance treatment for moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	SC	≥ 6 yo	No
Mepolizumab[21]	NUCALA	2015	IL-5	Severe asthma with an eosinophilic phenotype	SC	≥ 6 yo	No
Omalizumab[23]	XOLAIR	2003	IgE	Moderate-to-severe persistent asthma with positive allergy testing and inadequately controlled with inhaled corticosteroids	SC	≥ 6 yo	Yes: for possible anaphylaxis
Reslizumab[19]	CINQAIR	2016	IL-5	Severe asthma with an eosinophilic phenotype	IV Infusion	≥ 18 yo	Yes: for possible anaphylaxis
Tezepelumab[6]	TEZSPIRE	2021	TSLP	Severe asthma	SC	≥ 12 yo	No

Abbreviations: FDA = Food and Drug Administration; IgE = immunoglobulin E; IL = interleukin; IU = International Units; IV = intravenous; SC = subcutaneous; TSLP = thymic stromal lymphopoietin; YO = years old

Clinically relevant outcomes to assess treatments of severe asthma include reduction in asthma exacerbations that result in: 1) decreased emergency department (ED) visits or hospitalizations; 2) decreased chronic use of OCS; 3) improved quality of life; or 4) improved symptom management. Several instruments are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma. These tests are self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users. The Asthma Control Questionnaire (ACQ-6) is a 5-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[24] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units documented as a minimal clinically important difference (MCID).[25] An ACQ score consistently greater than 1.5 indicates poor symptom control.[25] The Asthma Quality of Life Questionnaire (AQLQ-12) contains 32 items assessing disease-specific, health-related quality-of-life that include domains of activity limitations, symptoms, emotional function, and environmental stimuli in patients aged 12 years and older.[14] The scale ranges from 1 (severely impaired) to 7 (not impaired at all). Total and domain scores are calculated by taking the mean of all questions overall or for each domain.[14] The MCID for this tool is 0.5 points for each item.[14] The St. George's Respiratory Questionnaire (SGRQ) was developed to measure health in chronic health airflow limitation.[26] The questionnaire is a 50 or 76 item assessment (depending on version) that includes 2 domains: frequency and severity of symptoms and impact on activities, which can be used with a 1-month, 3-month, or 12-month recall.[14] The scale ranges from 0 (no symptoms/limitations) to 100 (severe symptoms/ limitations).[14] Scoring varies by item and item scores are converted into a domain score and an overall score, both reported on the same scale.[14] The

MCID for the SGRQ is 4 points.[14] The Asthma Control Test (ACT) contains 5 self-reported items related to symptoms and daily functioning over past 4 weeks used in patients aged 12 years and older.[14] Assessments include shortness of breath and general asthma symptoms, use of rescue medications, effect of asthma on daily functioning, and overall self-assessment of asthma control.[14] The scale ranges from 5 (poor control) to 25 (complete control) with scores of 19 and greater indicating well-controlled asthma.[14] Each item is scored on 5-point Likert scale and the sum of scores across all items yields the total score.[14] The MCID for the ACT is 3 points.[14] A summary of the outcomes commonly used in clinical trials is presented in **Table 2.** Change from baseline in forced expiratory volume is a common surrogate endpoint used in asthma treatment trials since it is highly reproducible. A decline in lung function is observed when forced expiratory volume in 1 second (FEV_1) is 60% or less of predicted values or peak expiratory flow shows a 30% or greater decrease from baseline.[14]

Table 2. Summary of Outcome Measures for Asthma Symptoms[14]

Measure	Scale	Minimal Clinically Important Difference (MCID)
Asthma Control Questionnaire (ACQ-6)	0 (totally controlled) to 6 (severely uncontrolled)	0.5
Asthma Control Test (ACT)	5 (poor control) to 25 (complete control)	3
Asthma Quality of Life Questionnaire (AQLQ-12)	1 (severely impaired) to 7 (not impaired at all)	0.5
Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	1 (severely impaired) to 7 (not impaired at all)	0.5
St. George's Respiratory Questionnaire (SGRQ)	0 (no symptoms/limitations) to 100 (severe symptoms/limitations)	4

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane: Monoclonal Antibodies for Chronic Rhinosinusitis

A 2021 Cochrane Review assessed the effects of 3 monoclonal antibodies; dupilumab, mepolizumab, and omalizumab, for the treatment of chronic rhinosinusitis.[1] Literature was searched through September 2020. Ten studies with an overall low risk-of-bias met inclusion criteria.[1] All of the studies were sponsored or supported by industry.[1] Of 1,262 adult participants, 1,260 had severe CRSwNP and were using topical nasal steroids to manage symptoms; 43% to 100% also had asthma.[1] Primary outcomes were disease-specific HRQoL, disease severity and serious adverse events (SAEs).[1]

Three RCTs evaluated dupilumab versus placebo (n=784).[1] Disease-specific HRQoL was measured with the Sino-Nasal Outcome Test-22 (SNOT-22), a 22-item questionnaire, with a score range of 0 to 110; MCID 8.9 points.[1] At 24 weeks, dupilumab results in a large reduction (improvement) in the SNOT-22 score (mean difference [MD] -19.61, 95% CI -22.54 to -16.69; 3 studies; high certainty).[1] At between 16 and 52 weeks of follow-up, dupilumab probably results in a large reduction in disease severity, as measured by a 0- to 10-point visual analog scale (MD -3.00, 95% CI -3.47 to -2.53; 3 studies; moderate certainty).[1] This is a global symptom score, including all aspects of chronic rhinosinusitis symptoms. At 16 and 52 weeks of follow-up, dupilumab may result in a reduction in SAEs compared to placebo (5.9% versus 12.5%, risk ratio (RR) 0.47, 95% CI 0.29 to 0.76; 3 studies, 782 participants; low certainty).[1]

Two RCTs evaluated mepolizumab versus placebo (n=135).[1] Disease-specific HRQoL was measured with the SNOT-22. At 25 weeks, the SNOT-22 score may be reduced (improved) in participants receiving mepolizumab (MD -13.26 points, 95% CI -22.08 to -4.44; 1 study; 105 participants; low certainty; MCID 8.9).[1] It is very uncertain whether there is a difference in disease severity at 25 weeks: on a 0- to 10-point VAS, disease severity was -2.03 lower in those receiving mepolizumab (95% CI -3.65 to -0.41; 1 study; 72 participants; very low certainty).[1] It is very uncertain if there is a difference in the number of SAEs between mepolizumab and placebo at 25 to 40 weeks (1.4% versus 0%; RR 1.57, 95% CI 0.07 to 35.46; 2 studies; 135 participants, very low certainty).[1]

Five studies compared omalizumab to placebo (n=329).[1] Disease-specific HRQL was measured with the SNOT-22. At 24 weeks omalizumab probably results in a large reduction in SNOT-22 score (MD -15.62, 95% CI -19.79 to -11.45; 2 studies; 265 participants; moderate certainty; MCID 8.9).[1] No evidence was identified for overall disease severity.[1] It is very uncertain whether omalizumab affects the number of SEAs compared to placebo, with follow-up between 20 and 26 weeks (0.8% versus 2.5%, RR 0.32, 95% CI 0.05 to 2.00; 5 studies; 329 participants; very low certainty).[1]

In summary, in patients with chronic rhinosinusitis, dupilumab improves disease-specific HRQoL and may reduce disease severity compared to placebo.[1] At 16 and 52 weeks of follow-up, dupilumab may result in a reduction in SAEs compared to placebo.[1] Mepolizumab may improve disease-related HRQoL, it is uncertain if there is a difference in disease severity or the number of SAEs, compared with placebo.[1] Omalizuamb may improve disease-related HRQoL, but it is uncertain if there is a difference in the number of SAEs compared with placebo.[1] There is no evidence regarding the effect of omalizumab on disease severity.[1] Cochrane reviewers identified the following limitations to the data: 1) all studies were in adults, there are no data for children; 2) there is a lack of long-term evidence, and only one study had a 52-week follow-up; 3) sample sizes were insufficient and length of follow-up too short to comprehensively and adequately assess the risk of adverse effects.[1]

After review, 4 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[27-30]

New Guidelines:

High Quality Guidelines:

<u>Global Initiative for Asthma: Difficult-to-Treat and Severe Asthma</u>

The April 2021 GINA guidance provides recommendations for management for difficult-to-treat and severe asthma in adolescent and adult patients.[2] For patients with exacerbations or poor symptom control on high-dose ICS-LABA who have eosinophilic or allergic biomarkers, consider adding a monoclonal antibody or maintenance OCS.[2] Targeted treatment should be considered using the parameters described below.

A. Anti-IgE for severe allergic asthma:
    i. Sensitization on skin prick testing or specific IgE challenge
    ii. Total serum IgE and weight

iii. Number of exacerbations in the past year
iv. Factors that may predict good asthma response to anti-IgE monoclonal antibody treatment include: blood eosinophils ≥ 260 cells/µL, FeNO ≥ 20 ppb, allergen-driven symptoms, and childhood-onset asthma.[2]

B. Anti-IL-5/Anti-IL-5 Receptors for severe eosinophilic asthma:
   i. Number of exacerbations in the last year
   ii. Blood eosinophils (e.g. ≥ 150 cells/µL or ≥ 300 cells/µL: depending on which medication is selected)
   iii. Factors that may predict good asthma response to anti-IL5 monoclonal antibody treatment include: higher blood eosinophils, more exacerbations in previous year, adult-onset asthma, and nasal polyposis.[2]

C. Anti-IL-4 Receptors for severe eosinophilic or T2 asthma:
   i. Number of exacerbations in the last year
   ii. Blood eosinophils ≥ 150 cells/µL or FeNO ≥ 25 ppb
   iii. Need for maintenance OCS
   iv. Factors that may predict good asthma response to anti-IL-4 monoclonal antibody treatment include: higher blood eosinophils and higher FeNO.[2]

Choose one agent if patient meets eligibility and trial for at least 4 months and assess response.[31] If good response, continue targeted therapy and re-evaluate every 3 to 6 months.[2] If response is unclear, extend trial 6 to 12 months.[2] If no response, consider switching to a different targeted therapy, if patient meets eligibility parameters.[2]

<u>Canadian Agency for Drugs and Technologies in Health: Dupilumab for Type 2 or Eosinophilic Asthma</u>

A clinical review of dupilumab for severe asthma was published August 2021 by CADTH.[3] The review summarized data from 3 RCTs that compared dupilumab to placebo in patients with moderate-to-severe asthma who were already receiving standard of care treatment.[3] Both the 200 mg and 300 mg doses of dupilumab reduced the annualized rate of severe asthma exacerbations compared to placebo.[3] In a population with severe OCS-dependent asthma, dupilumab 300 mg every 2 weeks reduced the daily OCS dose requirement versus placebo.[3] There was no clear or consistent indication of serious safety or tolerability issues with dupilumab in the included studies.[3] None of the included studies had an active comparator and only 1 trial was 52 weeks in duration.[3] Overall, the studies were unlikely to be of sufficient duration to assess the longer term safety and efficacy of dupilumab.[3] Based on a review of the evidence, CADTH implemented the following conditions for dupilumab utilization:

1. Patient is inadequately controlled with high-dose ICS, defined as at least 500 mcg of fluticasone propionate or equivalent daily, and 1 or more additional asthma controller(s) (e.g., LABAs).[3]
2. Patient must have an eosinophil count ≥ 150 cells/µL or have OCS-dependent asthma.[3]
3. A baseline assessment of asthma symptom control using a validated asthma control questionnaire must be completed prior to initiation of dupilumab treatment.[3]
4. Dupilumab should not be used in combination with other biologics used to treat asthma.[3]
5. Patients should be managed by a physician with expertise in treating asthma.[3]
6. The effects of treatment should be assessed every 12 months to determine whether reimbursement should continue.[3] Dupilumab should be discontinued if any of the following occur:
   a. the 12-month asthma control questionnaire score has not improved from baseline, when baseline represents the initiation of treatment or
   b. the asthma control questionnaire score achieved after the first 12 months of therapy has not been maintained subsequently or
   c. the number of clinically significant asthma exacerbations has increased within the previous 12 months or

d. in patients on maintenance treatment with OCS, there has been no decrease in the OCS dose in the first 12 months of treatment or
e. in patients on maintenance treatment with OCS, the reduction in the dose of OCS achieved after the first 12 months of treatment is not maintained or improved subsequently.[3]

National Institute for Health and Care Excellence: Mepolizumab For Treating Severe Eosinophilic Asthma

In February 2021, NICE published guidance for the use of mepolizumab in treating severe eosinophilic asthma.[5] There is no evidence directly comparing mepolizumab with benralizumab and reslizumab.[5] However, an indirect comparison suggests that it works as well as benralizumab and reslizumab for people with a blood eosinophil count of 400 cells/µL or more.[5] Mepolizumab, as an add-on therapy, is recommended as an option for treating severe refractory eosinophilic asthma, only if it is used for adults who have agreed to and followed the optimized standard treatment plan **and** the patient meets at least one of the following criteria:

- the blood eosinophil count has been recorded as 300 cells/µL or more and the person has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, **or**
- the patient has had continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous 6 months **or**
- the blood eosinophil count has been recorded as 400 cells/µL or more and the person has had at least 3 exacerbations needing systemic corticosteroids in the previous 12 months.[5]

At 12 months mepolizumab should be discontinued if asthma has not responded adequately.[5] An adequate response is defined as: a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or a clinically significant reduction in continuous OCS use while maintaining or improving asthma control.[5]

National Institute for Health and Care Excellence: Dupilumab For Treating Severe Asthma

In December 2021, NICE published guidance for the use of dupilumab for treating severe asthma with T2 inflammmation.[4] Some aspects of the guidance were based on proprietary real-world observational evidence submitted by the manufacturer and responses from stakeholders.[4] Clinical trial results show that adding dupilumab to standard asthma treatment is more effective than placebo plus standard treatment at reducing the frequency of severe exacerbations, and the use of OCS in people with severe asthma with T2 inflammation.[4] Dupilumab as add-on maintenance therapy is recommended as an option for treating severe asthma with T2 inflammation that is inadequately controlled in people 12 years and older, despite maintenance therapy with high-dose ICS and another maintenance treatment, only if:

- the dosage used is 400 mg initially and then 200 mg subcutaneously every other week **and**
- the person has agreed to and follows an optimized standard treatment plan **and**
- the person has a blood eosinophil count of 150 cells/µL or more and FeNO of 25 ppb or more, and has had at least 4 or more exacerbations in the previous 12 months **and**
- the person is not eligible for mepolizumab, reslizumab or benralizumab (IL-5 inhibitors are the standard of care for severe asthma in the UK), or has asthma that has not responded adequately to these biological therapies).[4]

Stop dupilumab if the rate of severe asthma exacerbations has not been reduced by at least 50% after 12 months.[4]

After review, no guidelines were excluded due to poor quality.

Randomized Controlled Trials:
A total of 189 citations were manually reviewed from the initial literature search. After further review, 189 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts[32]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Dupilumab	DUPIXENT	10/2021	Warnings and Precautions	Hypersensitivity reactions including erythema multiforme were reported in less than 1% of subjects who received dupilumab in clinical trials. Adverse reactions of helminth infections (5 cases of enterobiasis and 1 case of ascariasis) were reported in pediatric patients 6 to 11 years old who participated in the pediatric asthma development program.
Dupilumab	DUPIXENT	12/2021	Adverse Reactions: Postmarketing Experience	Immune system disorders: angioedema Skin and subcutaneous tissue disorders: Facial skin reactions, including erythema, rash, scaling, edema, papules, pruritus, burning, and pain

NEW DRUG EVALUATION: Tezepelumab
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Tezepelumab is FDA-approved as add-on maintenance treatment for patients aged 12 years and older with severe asthma.[6] Tezepelumab binds to TSLP in the upstream inflammatory cascade.[6] FDA granted tezepelumab "breakthrough therapy designation" for the treatment of severe asthma without an eosinophilic phenotype.[7] Tezepelumab is administered by a healthcare provider via subcutaneous injection every 4 weeks.[6]

Clinical Efficacy:
Clinical data from 2 studies (NAVIGATOR and PATHWAY) were submitted to the FDA to support the licensing application for tezepelumab.[7] The PATHWAY trial was a dose-finding, placebo-controlled, phase 2 trial which evaluated 3 doses (70 mg every 4 weeks, 210 mg every 4 weeks, and 280 mg every 2 weeks) of tezepelumab on asthma exacerbation rates in adults (n=550) with inadequately controlled, severe asthma.[8] Patients had documented history of at least 2 asthma exacerbation events or at least 1 severe asthma exacerbation resulting in hospitalization (admission to the hospital for at least 24 hours) within the 12 months prior to study enrollment.[8] The primary efficacy end point was the AAER (events per patient-year) at week 52.[8] An asthma exacerbation was defined as a worsening of asthma symptoms that led to any of the following: the use of systemic glucocorticoids (oral or injectable) or, in the case of a stable maintenance regimen of oral glucocorticoids, a doubling of the dose for 3 or more days; an emergency department visit due to asthma that led to systemic glucocorticoid

treatment; or an inpatient hospitalization due to asthma[8] Secondary end points included the changes from baseline in the pre-bronchodilator FEV_1, ACQ-6 score, and AQLQ score.[8] The efficacy analyses were based on the intention-to-treat (ITT) population, which consisted of patients who underwent randomization and received at least one dose of tezepelumab or placebo.[8]

The use of tezepelumab at a dose of 70 mg every 4 weeks (low-dose), 210 mg every 4 weeks (medium-dose) or 280 mg every 2 weeks (high-dose), resulted in AAER at week 52 of 0.27, 0.20, and 0.23 per patient-year, respectively, as compared with 0.72 per patient-year in the placebo group.[8] Asthma exacerbation rates were lower in the respective tezepelumab groups than in the placebo group by 62% (90% CI, 42 to 75; P<0.001), 71% (90% CI, 54 to 82; P<0.001), and 66% (90% CI, 47 to 79; P<0.001).[8] The change from baseline at week 52 in the prebronchodilator FEV_1 was greater in the low-dose, medium-dose, and high-dose tezepelumab groups than in the placebo group by 0.12 liters (95% CI, 0.02 to 0.22; P = 0.015), 0.13 liters (95% CI, 0.03 to 0.23; P=0.009), and 0.15 liters (95% CI, 0.05 to 0.25; P = 0.002).[8]

The NAVIGATOR trial enrolled adults and adolescents aged 12 to 80 years old with severe, uncontrolled asthma in a phase 3, multi-center, double-blind, randomized study.[9] A total of 1061 patients were randomized from 294 study sites in 18 countries; 82 (8%) of these patients were adolescents.[9] The proportion of participants who were enrolled in the U.S. (18%) was higher than those in any of the other international study sites. To be eligible for the study, patients must have been receiving medium- to high-dose ICS for at least 3 months before screening, and must have been taking at least one additional controller medication with or without OCS in the 3 months before the date of informed consent.[9] In addition, subjects must have had at least 2 asthma exacerbations during the 12 months prior to study enrollment.[9] The adult study population included similar proportions of patients with an eosinophil count of less than 300 cells/µL and patients with at least 300 cells/µL. Approximately 25% of patients had an eosinophil count of less than 150 cells/µL or of greater than 450 cells/µL.[9] Adolescents were excluded from assessing target eosinophil counts. Add-on therapy with tezepelumab, at a dose of 210 mg administered subcutaneously every 4 weeks, was compared to placebo administered via the same route and dosing interval. During the trial, all the patients continued to receive their previously prescribed ICS plus additional controller medications, with or without OCS, without change. Patients were permitted to use SABAs for symptom relief as needed.

The primary objective of the NAVIGATOR study was to assess the effect of tezepelumab compared with placebo on AAER (events per patient-year) over the 52-week treatment period.[9] Prior to enrollment, 60% of subjects experienced 2 asthma exacerbations in the previous 12 months, while 40% of subjects experienced more than 2 asthma exacerbations. The definition of an asthma exacerbation was a worsening of asthma that led to any of the following: 1) use of systemic corticosteroids for at least 3 consecutive days; 2) an emergency room or urgent care visit that required systemic corticosteroids for at least 3 days; or 3) an inpatient hospitalization due to asthma. For patients receiving maintenance oral glucocorticoids, a temporary doubling of the stable existing maintenance dose for at least three days qualified for the definition of asthma exacerbation. In addition to the overall population, the primary objective was assessed a priori in a subgroup of patients with blood eosinophil counts less than 300 cells/µL. Key secondary objectives included assessment of the effect of tezepelumab compared with placebo on pulmonary function (pre-bronchodilator FEV_1) and on patient-reported outcomes, including health-related quality of life (HRQoL) using the AQLQ-12 and asthma control (using the ACQ-6).[9]

The annualized rate of asthma exacerbations was lower with tezepelumab than with placebo among adults and adolescents with severe, uncontrolled asthma, including those with low blood eosinophil counts at baseline.[9] Moderate-quality evidence showed that for the overall population, AAER was 0.93 events per patient year with tezepelumab and 2.10 events per patient year with placebo (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P<0.001).[9] In patients with a blood eosinophil count of less than 300 cells/µL, the AAER was 1.02 events per patient year with tezepelumab and 1.73 events per patient year with placebo (rate ratio, 0.59; 95% CI, 0.46 to 0.75; P<0.001).[9] At week 52, improvements were greater with tezepelumab than with placebo with respect to the prebronchodilator FEV_1 (0.23 vs. 0.09 liters; difference, 0.13 liters; 95% CI, 0.08 to 0.18; P<0.001) and scores on the ACQ-6 (−1.55 vs. −1.22; difference, −0.33; 95% CI, −0.46 to

−0.20; P<0.001; MCID = 0.5), and AQLQ-12 (1.49 vs. 1.15; difference, 0.34; 95% CI, 0.20 to 0.47; P<0.001; MCID = 0.5).[9] Although symptom scores on the ACQ-6 and AQLQ-12 improved, they did not meet the MICD of 0.5. Additional safety and efficacy data from the PATHWAY and NAVIGATOR trials are described and evaluated in **Table 6**.

A randomized, double-blind trial (SOURCE) was conducted in 150 adults with severe asthma who were receiving OCS, in addition to standard treatment.[33] The primary objective for this RCT was to evaluate the efficacy of tezepelumab in reducing OCS use in adults with OCS-dependent asthma.[33] Data from this trial has not yet been published. The FDA analysis indicated in this trial, subcutaneous administration of tezepelumab 210 mg every 4 weeks did not result in a statistically significant reduction in the maintenance dose of OCS at 48 weeks compared to placebo.[7]

Trial Limitations:
The phase 2 PATHWAY trial was conducted in primarily white, female adults, which limits extrapolation of data to ethnically diverse populations.[8] In the NAVIGATOR trial, although the adolescent subpopulation was not powered to demonstrate statistical significance, numerical reductions in asthma exacerbations and improvements in lung function were observed compared to placebo.[7] Partial extrapolation of efficacy in adults was used to support FDA approval in the adolescent subgroup, as the pathophysiology of asthma is similar in adults and adolescents.[7] All of the subjects met the criteria of severe asthma but some sub-populations including smokers were excluded from the clinical trial. Long-term safety data is not available, although a long-term extension study is currently underway.

Clinical Safety:
In the NAVIGATOR trial, the frequencies and types of AEs did not differ meaningfully between tezepelumab and placebo.[9] The most frequently reported AEs with tezepelumab compared with placebo in the NAVIGATOR trial included nasopharyngitis (21.4% vs. 21.5%); upper respiratory tract infection (11.2% vs. 16.4%); headache (8.1% vs. 8.5%); bronchitis (4.7% vs. 6.2%); back pain (4.0% vs. 2.8%); and arthralgia (3.8% vs. 2.4%).[9] In the pooled safety population from the PATHWAY, NAVIGATOR and SOURCE trials, the most common adverse effects observed with tezepelumab were pharyngitis, arthralgia, and back pain.[6] The incidence rates of adverse effects observed with tezepelumab compared with placebo in the pooled safety population are presented in **Table 4**. Thymic stromal lymphopoietin may be involved in the immunological response to some parasitic infections; such infections should be treated before starting tezepelumab.[6] No episodes of anaphylaxis or increases in serious infections were reported during clinical trials.[7]

Table 4. Adverse Reactions With Tezepelumab With Incidence Greater Than 3% And More Common Than Placebo In Pooled Safety Population[6]

Adverse Reaction	Tezepelumab (n=665)	Placebo (n=669)
Pharyngitis	4%	3%
Arthralgia	4%	3%
Back Pain	4%	3%

Look-alike / Sound-alike Error Risk Potential: No drugs identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Annualized rate of asthma exacerbations
2) Improved pulmonary function
3) Asthma control and symptoms
4) Health related quality of life
5) Asthma-related morbidity or mortality
6) Serious AEs
7) Study withdrawal due to an AE

Primary Study Endpoint:
1) Annualized rate of asthma exacerbations

Table 5. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	Blocks thymic stromal lymphopoietin, an upstream modulator of inflammation
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Volume of Distribution: 3.9 liters; No data on protein binding
Elimination	Tezepelumab is eliminated by intracellular catabolism and there is no evidence of target-mediated clearance.
Half-Life	26 days
Metabolism	Tezepelumab is degraded by proteolytic enzymes widely distributed in the body and not metabolized by hepatic enzymes.

Table 6. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Corren J. et al[8] PATHWAY Phase 2, MC, DB, PC, PG, RCT	1. Tezepelumab 70 mg SC every 4 weeks 2. Tezepelumab 210 mg SC every 4 weeks 3. Tezepelumab 280 mg SC every 2 weeks 4. Placebo SC every 2 weeks 52 weeks	Demographics: 1. Mean age: 50 yo 2. Male: 35% 3. Race - White: 90% Asian: 3% Black: 3% 4. Baseline ACQ-6 score: 2.7 5. Baseline AQLQ score: 4 6. Mean baseline eosinophil level ≤ 250 cells/µL: 56% 7. Baseline exacerbations in previous 12 months: 1 or 2 exacerbations: 80% More than 2 exacerbations: 20% Key Inclusion Criteria: 1.Aged 18-75 yo 2. Severe, uncontrolled asthma 3. Medium- or high-dose ICS use 4. ACQ-6 ≥ 1.5 5. History of ≥ 2 asthma exacerbations leading to OCS treatment or 1 exacerbation leading to hospitalization in previous 12 mos 6. Mean baseline FEV_1 40-80% Key Exclusion Criteria: 1. Any pulmonary disease associated with high eosinophil counts, excluding asthma 2. Any significant infection requiring antibiotic or antiviral treatment 2 weeks prior to randomization 3. History of HIV, cancer, or hepatitis B or C 4. Current smoker or smoking history ≥ 10 pack years 5. Use of biologic agent 30 days prior to randomization or	ITT: 1. 138 2. 137 3. 137 4. 138 Attrition: 1. 8 (5.7%) 2. 11 (8%) 3. 15 (11%) 4. 22 (16%)	Primary Endpoint: AAER over 52 weeks 1. 0.27 events per patient-year 2. 0.20 events per patient-year 3. 0.23 events per patient-year 4. 0.72 events per patient-year **1 vs. 4**: Relative reduction: 62% 90% CI 42 to 75 P<0.001 **2 vs. 4**: Relative reduction: 71% 90% CI 54 to 82 P<0.001 **3 vs. 4:** Relative reduction: 66% 90% CI 47 to 79 P<0.001 Secondary Endpoints: LS mean change from baseline in pre-bronchodilator FEV_1 at week 52 1. 0.07 L 2. 0.08 L 3. 0.10 L 4. -0.06 L **1 vs. 4:** Difference: 0.12 L 95% CI 0.02 to 0.22 P=0.015 **2 vs. 4**: Difference: 0.13 L 95% CI 0.03 to 0.23 P=0.009 **3 vs. 4**: Difference: 0.15 L 95% CI 0.05 to 0.25 P=0.002 LS mean change from baseline in ACQ-6 at week 52 1. -1.17 2. -1.20 3. -1.22 4. -0.91 **1 vs. 4**: Difference: -0.26 95% CI -0.52 to 0.01	NA NA NA NA	AEs 1. 67.4% (n=93) 2. 65.7% (n=90) 3. 65% (n=89) 4. 65.9% (n=91) SAEs 1. 12.3% (n=17) 2. 9.5% (n=13) 3. 13.1% (n=18) 4. 13% (n=18) Discontinuation due to AE 1. 0% 2. 1.5% (n=2) 3. 2.2% (n=3) 4. 0.7% (n=1)	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1:1 via IVRS. Patients stratified by geographic region, blood eosinophil count (≥ 250 cells/µL or < 250 cells/µL), and ICS dose (medium vs. high). Baseline characteristics balanced between groups. Performance Bias: Low. Trial agents were similar in appearance. Injections administered by staff at study site who were unaware of trial-group assignments. Detection Bias: Low. Patients and providers blinded to treatment. Patients recorded ACQ-6 and AQLQ scores in an electronic device. Attrition Bias: Low. Higher attrition in the placebo arm, primarily due to withdrawal by the patient (16%). Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Funded by MedImmune (a member of the AstraZeneca group) and Amgen. Sponsors developed the protocol and conducted data analysis. **Applicability**: Patient: Higher proportion of females compared to males (65% vs. 35%) and White (90%) subjects compared to Black (3%) and Asian races (3%) were enrolled. Intervention: Dose finding Phase 2 trial. Comparator: Placebo comparator is appropriate. Outcomes: Annualized rates of asthma exacerbations were used in other monoclonal antibody trials for severe asthma. Setting: 108 sites in 12 countries.

		immunosuppressive drug 12 weeks prior to randomization		P=0.059 **2 vs. 4:** Difference: -0.29 95% CI -0.56 to -0.01 P=0.039 **3 vs. 4**: Difference: -0.31 95% CI -0.58 to -0.04 P=0.024 LS mean change from baseline in AQLQ-12 at week 52 1. 1.12 2. 1.17 3. 1.32 4. 0.97 **1 vs. 4**: Difference: 0.14 95% CI -0.13 to 0.42 P=.309 **2 vs. 4:** Difference: 0.20 95% CI -0.09 to 0.48 P=0.185 **3 vs. 4**: Difference: 0.34 95% CI 0.06 to 0.63 P=0.017	NA			
1. Menzie-Gow A., et al[9] NAVIGATOR Phase 3, MC, DB, PC, PG, RCT	1. Tezepelumab 210 mg SC every 4 weeks 2. Placebo SC every 4 weeks 52 weeks	<u>Demographics</u>: 1. Mean age: 49 yo 2. Male: 37% 3. Race - White: 63% Asian: 28% Black: 6% 4. Baseline high-dose ICS use:75% 5. Baseline OCS use: 9% 6. Mean baseline FEV_1 : 63% 7. Mean baseline ACQ-6 score: 2.8 8. Mean baseline AQLQ score: 4 9. Mean baseline eosinophil level ≤ 300 cells/µL: 58.4% 10. Baseline exacerbations in previous 12 months: 2 exacerbations: 60% More than 2 exacerbations: 40% <u>Key Inclusion Criteria</u>: 1. Age 12-80 yo	<u>ITT</u>: 1. 528 2. 531 <u>Attrition</u>: 1. 36 (6.8%) 2. 57 (10.7%)	<u>Primary Endpoint</u>: AAER over 52 weeks for overall population 1. 0.93 events per patient-year 2. 2.10 events per patient-year Rate ratio: 0.44 95% CI 0.37 to 0.53 P<0.0001 AAER over 52 weeks in patients with eosinophil < 300 cells/µL 1. 1.02 events per patient-year (n=309) 2. 1.73 events per patient-year (n=309) Rate ratio: 0.59 95% CI 0.46 to 0.75 P<0.001 <u>Secondary Endpoints</u>: LS mean change from baseline in pre-bronchodilator FEV_1 at week 52	NA NA NA	<u>AEs</u> 1. 77.1% (n=407) 2. 80.8% (n=429) <u>SAEs</u> 1. 9.8% (n=52) 2. 13.7% (n=73) <u>Discontinuation due to AE</u> 1. 2.1% (n=11) 2. 3.6% (n=19)	NA NA NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: Low. Randomized 1:1 via IVRS. Patients stratified by geographic region and age. Baseline characteristics balanced between groups. <u>Performance Bias</u>: Low. Placebo was matched to active drug in volume, appearance, and packaging. Injections administered by HCP at study site. <u>Detection Bias</u>: Low. Patients and providers blinded to treatment. Independent adjudication committee assessed blinded data. Asthma exacerbation defined in study protocol (use of OCS, ER admit, or inpatient admission). <u>Attrition Bias</u>: Low. Higher attrition in the placebo arm, primarily due to withdrawal by the patient (4.9%). Data post-withdrawal from the study were assumed to be missing at random and were not imputed into the primary analysis. <u>Reporting Bias</u>: Low. Protocol available online. According to FDA, 195 subjects had 1 important protocol deviation, but none of the deviations impacted the study quality or overall interpretation of the results.

		2. Severe, uncontrolled asthma 3. Medium- or high-dose ICS use plus 1 additional controller (LABA, LAMA, theophylline, LTRA) with or without OCS 4. ACQ-6 ≥ 1.5 5. History of ≥ 2 asthma exacerbations in previous 12 mos Key Exclusion Criteria: 1. Any pulmonary disease associated with high eosinophil counts, excluding asthma 2. Any significant infection requiring antibiotic or antiviral treatment 2 weeks prior to randomization 3. Helminth or parasitic infection diagnosed 6 mos before randomization that had been treated or was unresponsive to SOC treatment 4. History of HIV, cancer, or hepatitis B or C 5. Current smoker or smoking history ≥ 10 pack years 6. Use of biologic agent 4 mos prior to randomization or immunosuppressive drug 12 weeks prior to randomization		1. 0.23 L 2. 0.09 L LS mean difference: 0.13 L 95% CI 0.08 to 0.18 P<0.001 LS mean change from baseline in ACQ-6 at week 52 1. -1.55 2. -1.22 LS mean difference: -0.33 95% CI -0.46 to -0.20 P<0.001 LS mean change from baseline in AQLQ-12 at week 52 1. 1.49 2. 1.15 LS mean difference: 0.34 95% CI 0.20 to 0.47 P<0.001	NA NA			Other Bias: Unclear. Sponsored by AstraZeneca and Amgen. Five investigators reported conflict of interest due to support from various manufacturers including AstraZeneca and Amgen. **Applicability**: Patient: Relevant patient groups (e.g. smokers) were excluded and percentage of included adolescents was small (8%). Higher proportion of females compared to males (63% vs. 37%) and White subjects (63%) compared to Asian (28%) Black (6%) races were enrolled. All patients met GINA criteria for severe asthma and had at least 2 exacerbations in the prior 12 months. Intervention: Dosing evaluated in a phase 2 RCT and showed reduction in AAER. Comparator: Placebo comparator is appropriate. Outcomes: Annualized rates of asthma exacerbations were used in other monoclonal antibody trials for severe asthma. Setting: 294 sites in 18 countries. 18% of sites were in the US, which was the highest percentage of all participating countries.

Abbreviations : ACQ = Asthma Control Questionnaire; AAER = annualized asthma exacerbation rate; AQLQ = Asthma Quality of Life Questionnaire; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; ER = Emergency Room; FDA = Food and Drug Administration; FEV_1 = forced expiratory volume in 1 second; GINA = Global Initiative for Asthma; HCP = health care professional; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICS = inhaled corticosteroid; ITT = intention to treat; IVRS = interactive voice response system; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic agent; L = liters; LS = least squares; LTRA = leukotriene receptor antagonist; MC = multi-center; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OCS = oral corticosteroids; PC = placebo-controlled; PG = parallel-group; PP = per protocol; RCT = randomized controlled trial; SC = subcutaneous; SOC = standard of care; US = United States; yo = years old

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21. NUCALA (mepolizumab) Subcutaneous Injection. Prescribing Information. Philadelphia, PA; GlaxoSmithKline. January 2022.
22. DUPIXENT (dupilumab) Subutaneous Injection. Prescribing Information. Tarrytown, NJ; Regneron Pharmaceuticals and Bridgewater, NJ; Sanofi Genzyme. December 2021.
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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL	Atopic Dermatitis Indication
abrocitinib	CIBINQO	TABLET	ORAL	N	Y
benralizumab	FASENRA PEN	AUTO INJCT	SUBCUT	N	
benralizumab	FASENRA	SYRINGE	SUBCUT	N	
dupilumab	DUPIXENT PEN	PEN INJCTR	SUBCUT	N	Y
dupilumab	DUPIXENT SYRINGE	SYRINGE	SUBCUT	N	Y
mepolizumab	NUCALA	AUTO INJCT	SUBCUT	N	
mepolizumab	NUCALA	SYRINGE	SUBCUT	N	
mepolizumab	NUCALA	VIAL	SUBCUT	N	
omalizumab	XOLAIR	SYRINGE	SUBCUT	N	
omalizumab	XOLAIR	VIAL	SUBCUT	N	
reslizumab	CINQAIR	VIAL	INTRAVEN	N	
tezepelumab-ekko	TEZSPIRE	SYRINGE	SUBCUT	N	
tralokinumab-ldrm	ADBRY	SYRINGE	SUBCUT	N	Y

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1946 to February Week 3, 2022, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 03, 2022

1.	benralizumab.mp	538
2.	mepolizumab.mp	1064
3.	exp Omalizumab/	2078
4.	reslizumab.mp	335
5.	dupilumab.mp	1521
6.	tezpelumab.mp	76
7.	anti-asthmatic agents	12512
8.	severe asthma.mp	9053
9.	1 or 2 or 3 or 4 or 5 or 6 or 7	16030
10.	8 and 9	1923
11.	limit 10 to (english language and humans and yr=”2021-current”)	189

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TEZSPIRE safely and effectively. See full prescribing information for TEZSPIRE.

TEZSPIRE™ (tezepelumab-ekko) injection, for subcutaneous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

TEZSPIRE is a thymic stromal lymphopoietin (TSLP) blocker, human monoclonal antibody (IgG2λ), indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. (1)

Limitations of Use:

- Not for relief of acute bronchospasm or status asthmaticus. (1)

DOSAGE AND ADMINISTRATION

- Administer by subcutaneous injection. (2)
- Recommended dosage is 210 mg administered once every 4 weeks. (2)

DOSAGE FORMS AND STRENGTHS

Injection:

- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose glass vial. (3)
- 210 mg/1.91 mL (110 mg/mL) solution in a single-dose pre-filled syringe. (3)

CONTRAINDICATIONS

Known hypersensitivity to tezepelumab-ekko or excipients. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Hypersensitivity reactions (e.g., rash, allergic conjunctivitis) can occur after administration of TEZSPIRE. Initiate appropriate treatment as clinically indicated in the event of a hypersensitivity reaction. (5.1)
- Risk Associated with Abrupt Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with TEZSPIRE. Decrease corticosteroids gradually, if appropriate. (5.3)
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with TEZSPIRE. If patients become infected while receiving TEZSPIRE and do not respond to anti-helminth treatment, discontinue TEZSPIRE until the parasitic infection resolves. (5.4)
- Vaccination: Avoid use of live attenuated vaccines. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 3%) are pharyngitis, arthralgia, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2021

Appendix 4: Key Inclusion Criteria

Population	Adults and children with asthma or chronic rhinosinusitis
Intervention	Biological maintenance treatments for asthma or chronic rhinosinusitis
Comparator	Placebo or active therapies
Outcomes	Mortality, exacerbations, hospitalizations
Timing	As needed
Setting	Outpatient

Targeted Immune Modulators for Severe Asthma and Severe Atopic Dermatitis

Goal(s):

- Restrict use of targeted immune modulators to patients with severe asthma requiring chronic systemic corticosteroid use or with history of asthma exacerbations in the past year that required an Emergency Department visit or hospitalization or for patients with severe atopic dermatitis.
- Restrict use for conditions not funded by the OHP (e.g., chronic urticaria, mild-to-moderate atopic dermatitis).

Length of Authorization:

- Up to 12 months

Requires PA:

- Targeted immune modulators with indications for severe asthma or severe atopic dermatitis (see **Table 2** below) (pharmacy and provider-administered claims)
- This PA does not apply to topical agents for inflammatory skin conditions which are subject to separate clinical PA criteria.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Maximum Adult Doses for Inhaled Corticosteroids

High Dose Corticosteroids:	**Maximum Dose**
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Armonair (fluticasone propionate)	232 mcg BID
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID

AirDuo Digihaler (fluticasone/salmeterol)	232/14 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	232/14 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 2. FDA-approved Indications and Ages

Generic Name/ BRAND NAME	Eosinophilic Asthma	Moderate to Severe Allergic Asthma	Difficult To Treat, Severe Asthma*	Hypereosinophilic Syndrome (HES)	Eosinophilic Granulomatosis with Polyangiitis (EGPA)	Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	Atopic Dermatitis (AD)
Abrocitinib CIBINQO							≥18 years
Benralizumab FASENRA	≥12 years						
Dupilumab DUPIXENT	≥6 years (or with oral corticosteroid dependent asthma)					≥18 years	≥6 years
Mepolizumab NUCALA	≥6 years			≥ 12 years	≥18 years	≥18 years	
Omalizumab XOLAIR		≥6 years				≥18 years	
Reslizumab CINQAIR	≥18 years						
Tezepelumab TEZSPIRE			≥ 12 years				
Tralokinumab ADBRY							≥18 years

*Difficult to treat, severe asthma is defined as asthma with poor symptom control on high-dose inhaled corticosteroid-long acting beta agonist (ICS-LABA) or maintenance oral corticosteroids (OCS)

Table 3. FDA-Approved Abrocitinib Dosing for Atopic Dermatitis

Assessment	Recommended Dose
CYP2C19 Poor Metabolizer	50 mg once daily
GFR 30 to 60 mL/min	50 mg once daily
GFR < 30 mL/min	Use is not recommended
Severe hepatic impairment (Child-Pugh Class C)	Use is not recommended
Abbreviations: GFR=glomerular filtration rate; mL=milliliters; min=minutes	

Table 4. FDA-Approved Dosing for Monoclonal Antibodies Used to Treat Severe Asthma Phenotypes

Generic Name	Brand Name	Asthma Indication	Initial Dose and Administration Route	Maintenance Dose and Administration Route
Benralizumab	FASENRA	Severe asthma with an eosinophilic phenotype	30 mg SC every 4 weeks for the first 3 doses	30 mg SC every 8 weeks
Dupilumab	DUPIXENT	Add on maintenance treatment for moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	Pediatrics (ages 6 – 11 yo)**:** An initial loading dose is not necessary Adults and Adolescents ≥ 12 yo : 400 mg to 600 mg SC x 1 dose	Ages 6 – 11 yo (weight 15 to 30 kg) 100 mg SC every 2 weeks OR 300 mg SC every 4 weeks Adults and Adolescents ≥ 12 yo: 200 to 300 mg SC every 2 weeks
Mepolizumab	NUCALA	Severe asthma with an eosinophilic phenotype	N/A	Ages ≥ 6 – 11 yo: 40 mg SC every 4 weeks Ages ≥ 12 yo: 100 mg SC every 4 weeks
Omalizumab	XOLAIR	Moderate to severe persistent asthma and positive allergy testing	N/A	75 to 375 mg SC every 2 to 4 weeks based on weight and serum IgE levels
Reslizumab	CINQAIR	Severe asthma with an eosinophilic phenotype	N/A	3 mg/kg IV infusion every 4 weeks
Tezepelumab	TEZSPIRE	Severe asthma	N/A	210 mg SC every 4 weeks
Abbreviations: IgE = immunoglobulin E; IV = intravenous; kg = kilogram; mg = milligram; N/A = Not Applicable; SC = subcutaneous; yo = years old				

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP-funded diagnosis? Note: chronic idiopathic urticaria and mild-to-moderate atopic dermatitis are not OHP-funded conditions	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
3. Is the request for an FDA-approved indication and age (**Table 2**)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Does the patient have a concurrent prescription for EpiPen® or equivalent to enable management of possible delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the diagnosis Severe Atopic Dermatitis (AD)? Severe disease is defined as:[1] • Having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involved, or • Hand, foot, face, or mucous membrane involvement	**Yes:** Go to #7	**No:** Go to #14
7. Is the medication being prescribed by or in consultation with a dermatologist, allergist, or a provider who specializes in care of atopic dermatitis?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for abrocitinib?	**Yes:** Go to #9	**No:** Go to # 13

Approval Criteria		
9. Are baseline labs (platelets, lymphocytes, lipids) documented? *Note: Abrocitinib therapy should not be initiated if platelet count is < 50,000/mm^3, absolute lymphocyte count is < 500/mm^3, absolute neutrophil count (ANC) is < 1,000/mm^3, or hemoglobin is < 8 g/dL	**Yes:** Go to # 10 Document Lab and Date Obtained: Platelets:_____ Lymphocytes:_____ Lipids:_____ Hemoglobin:	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the patient currently taking other targeted immune modulators or oral immunosuppressants?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
11. If the patient has renal or hepatic impairment has the dose been adjusted as described in Table 3?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. If the patient is taking a strong CYP2C19 inhibitor (e.g., fluvoxamine, fluoxetine), or CYP2C9 inhibitor (e.g., fluconazole, amiodarone) or CYP2C9 inducer (e.g,rifampin, phenobarbital), or CYP2C19 inducer (carbamazepine) or antiplatelet agent has the abrocitinib dose been adjusted as described in Table 3 or has the interacting drug been discontinued if necessary? *Note: agents with antiplatelet properties (NSAIDs, SSRIs, etc.) should not be used during the first 3 months of abrocitinib therapy. Do not use aspirin at doses ≥ 81 mg/day with abrocitinib during the first 3 months of therapy.	**Yes:** Go to # 13	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
1. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
2. Is the request for eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #15
3. Is the request for the treatment of a patient with hypereosinophilic syndrome (HES) with a duration of 6 months or greater without an identifiable non-hematologic secondary cause?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #16
4. Is the request for treatment of nasal polyps?	**Yes:** Go to # 17	**No:** Go to #19
5. Is the prescriber an otolaryngologist, or allergist who specializes in treatment of chronic rhinosinusitis with nasal polyps?	**Yes:** Go to # 18	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
18. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
19. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #20	**No:** Pass to RPh. Deny; medical appropriateness.
20. Has the patient experienced one of the following: • at least 4 asthma exacerbations requiring systemic corticosteroids in the previous 12 months OR • taking continuous oral corticosteroids at least the equivalent of prednisolone 5 mg per day for the previous 6 months OR • at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	**Yes:** Go to #21 Document number asthma exacerbations over the previous 12 months or oral corticosteroid dose over the previous 6 months or number of hospitalizations or ED visits in the past 12 months_____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
21. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #22	**No:** Pass to RPh. Deny; medical appropriateness.
22. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, or tezepelumab, etc.)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #23
23. Is the request for tezepelumab?	**Yes:** Approve for up to 12 months.	No: Go to # 24

Approval Criteria		
24. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	**Yes:** Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	**No:** Go to #25
25. If the request is for asthma with an eosinophilic phenotype, can the prescriber provide documentation of one of the following biomarkers: • severe eosinophilic asthma, confirmed by blood eosinophil count ≥150 cells/µL OR • fractional exhaled nitric oxide (FeNO)≥ 25 ppb in the past 12 months?	**Yes:** Approve up to 12 months, based on dosing outlined in Table 4. Document eosinophil count or FeNO (date):_____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew therapy for EGPA, nasal polyps, or HES?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #4	**No:** Go to #5

Renewal Criteria		
4. Have the patient's symptoms improved with targeted immune modulator therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started OR • at least a 2 point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the number of ED visits, hospitalizations, or asthma exacerbations requiring oral corticosteroids in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

1. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed March 1, 2022.*
2. National Institute for Health and Care Excellence (NICE) Guidance. Mepolizumab for Treating Severe Eosinophilic Asthma. https://www.nice.org.uk/guidance/ta671 February 2021.
3. National Institute for Health and Care Excellence (NICE) Guidance. Dupilumab for Treating Severe Asthma with Type 2 Inflammation. https://www.nice.org.uk/guidance/ta751 December 2021
4. Global Initiative for Asthma. Global strategy for asthma management and prevention (2021 update). 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf

P&T Review: *6/22 (DM); 8/21); 10/20; 7/19; 7/18; 7/16*
Implementation: *7/1/22; 1/1/22; 9/1/21; 8/19/19, 8/15/18, 8/16*