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Subject: Dupilumab (Dupixent®) Injection

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DESCRIPTION:

Dupilumab (Dupixent) is a human monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by binding to the IL-4R alpha subunit shared by IL-4 and IL-13 receptors. This reduces IL-4 and IL-13 cytokine-induced inflammatory response such as the release of proinflammatory cytokines, chemokines, and IgE, which play roles in the development of atopic dermatitis and asthma. Dupilumab was approved in March 2017 by the US Food and Drug Administration (FDA) for "the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable". In September 2017 dupilumab was granted orphan drug designation by the FDA for the treatment of eosinophilic esophagitis. In October 2018, the indications for dupilumab were expanded when the FDA approved use "as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma." In March 2019, the moderate-to-severe atopic dermatitis indication was expanded to include adolescent patients 12 to 17 years of age. In June 2019, the indications for dupilumab were expanded again when the FDA approved use as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). Dupilumab was the first systemic agent FDA-approved for the treatment of nasal polyps. In September 2024, CRSwNP indication was expanded to include pediatric patients aged 12 years and older. In May 2020, the moderate-to-severe atopic dermatitis indication was expanded to include pediatric patients 6 to 11 years of age, making the current indication for patients aged 6 years and older. In October 2021, the moderate-to-severe asthma indication was also expanded to include pediatric patients 6 to 11 years of age, making the current indication for patients aged 6 years and older. In May 2022, the FDA approved a new indication of treatment of eosinophilic esophagitis (EoE) in adults and pediatric patients 12 years and older weighing at least 40 kilograms. Dupilumab was the first FDA-approved treatment for EoE. This indication was expanded in January 2024 to include pediatric patients down to the age of 1 year and weighing at least 15 kg. In June 2022, the moderate-to-

severe atopic dermatitis indication was again expanded to include pediatric patients 6 months of age and older. In September 2022, the FDA approved a new indication of treatment of adult patients with prurigo nodularis (PN). Dupilumab is the first FDA-approved treatment for PN. In September 2024, the FDA approved a new indication of add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype. Dupilumab is the first FDA-approved biologic therapy for COPD. In April 2025 and June 2025, the FDA approved new indications of treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment, and treatment of adult patients with bullous pemphigoid (BP), respectively. Dupilumab is the second FDA-approved biologic therapy for CSU, the first being omalizumab (Xolair) FDA-approved in 2014. Dupilumab is the first FDA-approved treatment for BP. The National Comprehensive Cancer Network (NCCN) guidelines on the Management of Immune Checkpoint Inhibitor-Related-Toxicities include dupilumab as a consideration (category 2A) for the management of the following immunotherapy-related toxicities – (1) moderate (G2) to severe (Grade 3) pruritus if no response to gabapentinoids in 1 month, (2) as additional therapy for moderate (Grade 2) or severe (Grade 3) bullous dermatitis if diagnosis of bullous pemphigoid is confirmed by biopsy or serology, (3) recommended for severe (G3) or life-threatening (G4) bullous dermatitis as a steroid-sparing measure if bullous pemphigoid is confirmed, and (4) severe (>30%) body surface area lichen planus and lichenoid diseases.

Atopic Dermatitis

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, pruritic inflammatory dermatosis affecting up to 25% of children and approximately 7% of adults. AD follows a relapsing course and is associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and/or asthma. Onset is most common between 3 and 6 months of age, with approximately 60% of patients developing the eruption in the first year of life and 90% by age 5. While the majority of affected individuals have resolution of disease by adulthood, 10 to 30% do not, and a smaller percentage first develop symptoms as adults. AD has a complex pathogenesis involving genetic, immunologic, and environmental factors, which lead to a dysfunctional skin barrier and dysregulation of the immune system. Clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification. These clinical findings vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families. Typical patterns include facial, neck and extensor involvement in infants and children, flexure involvement in any age group, with sparing of groin and axillary regions.

Goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimize therapeutics risks. Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with topical emollient/moisturizer use and conventional topical therapies (including corticosteroids and calcineurin inhibitors). Moisturizers reduce signs, symptoms, and inflammation in AD, and can improve severity while also increasing time between flares. Moisturizers are considered generally safe and are strongly recommended to be used as part of a treatment regimen for AD, either as monotherapy or as concurrent use with pharmacologic treatments.

Topical therapies remain the mainstay of treatment due to their proven track record and generally favorable safety profile. They can be utilized individually or in combination with other topical, physical,

and/or systemic treatments; as different classes of treatment have different mechanisms of action, combining therapies allows for the targeting of AD via multiple disease pathways. The American Academy of Dermatology (AAD) strongly recommends the following topical agents:

- Topical corticosteroids (TCS)
- Calcineurin inhibitors (TCIs) (e.g., tacrolimus, pimecrolimus)
- Topical PDE-4 inhibitors (e.g., crisaborole) [mild to moderate AD]
- Topical JAK inhibitors (e.g., ruxolitinib) [mild to moderate AD]

TCS are the most commonly utilized FDA-approved therapies in AD and are commonly used as first-line treatment for mild-to severe dermatitis in all skin regions. TCS target a variety of immune cells and suppress the release of proinflammatory cytokines. High to very high (super) potency TCS can be used to control flares and treat severe disease, while medium potency TCS are utilized for longer courses and as maintenance therapy. Lower potency TCS may be used, and it is important to consider the anatomical site (i.e., using lower potency agents on the face, neck, genitals, and body folds) and severity of the disease when choosing a steroid potency. Clinical trials assessing efficacy generally had a duration of 2 to 6 weeks, and response to TCS therapy should be evaluated by week 4 in clinical practice. Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient. Traditionally, TCS were stopped once AD signs and symptoms of an AD flare were controlled. Maintenance in between AD flares with once to twice weekly use of TCS is another approach.

TCIs are a safe anti-inflammatory option for mild-to-severe AD, particularly when there is concern for adverse events secondary to corticosteroid use. Both tacrolimus and pimecrolimus have been shown to be effective in treating AD, but pimecrolimus may be more appropriate for patients who have milder disease or are sensitive to local reactions. Prescribing information for pimecrolimus cream and tacrolimus ointment indicate evaluation after 6 weeks if symptoms of AD do not improve for adults and pediatrics.

When AD is more severe or refractory to topical treatment, advanced treatment with phototherapy or systemic medications can be considered. Phototherapy is conditionally recommended by the AAD as a treatment for AD based on low certainty evidence. The AAD strongly recommends the following systemic therapies:

- Monoclonal antibodies (biologics) (e.g., dupilumab, tralokinumab)
- JAK inhibitors (e.g., upadacitinib, abrocitinib, baricitinib)

In a change from the 2014 AAD AD guidelines the use of systemic antimetabolites such as methotrexate, immunosuppressants such as systemic corticosteroids, mycophenolate mofetil, azathioprine, and cyclosporine are now conditionally recommended for AD only in a small number of select patients due to low or very low certainty of evidence and need for monitoring. The most favored first-line systemic is dupilumab.

There is no clear consensus on how to operationalize a definition of the FDA indication for treatment of patients with "moderate to severe" AD. The severity of AD can vary substantially over time and, from a patient's perspective, can include a complex combination of intensity of itch, location, body surface area

(BSA) involvement, and degree of skin impairment. Given the variability of patient phenotype and lack of familiarity among clinicians with scoring systems used in clinical trials, it is advisable to create a broad clinically relevant definition inclusive of multiple specific measures of disease intensity for example:

- One of the following:
  - Affected BSA greater than or equal to 10%
  - Investigator Global Assessment (IGA) greater than or equal to 3
  - Eczema Area and Severity Index (EASI) greater than or equal to 16

OR

- One of the following:
  - Affected BSA greater than or equal to 10%
  - Involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds)
  - Severe itch that has been unresponsive to topical therapies

Efficacy

Dupilumab was FDA approved through two randomized, double-blind, placebo-controlled phase 3 trials (SOLO 1 and SOLO 2). All patients in both trials were at least 18 years old, had chronic AD (according to American Academy of Dermatology Consensus Criteria Eichenfield 2014) that had been present for at least 3 years, and had ≥10% body surface area (BSA) involvement at the screening and baseline visits. Additionally, all patients had a documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications (defined as failure to achieve and maintain remission or a low disease activity state despite treatment with a daily regimen of topical corticosteroids of medium to higher potency applied for ≥28 days or for the maximum duration recommended by the product prescribing information [e.g., 14 days for super-potent topical corticosteroids], whichever is shorter), or whom topical treatments are otherwise medically inadvisable. The primary outcome measure in both trials was proportion of patients with both IGA (Investigator Global Assessment) 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16. There were several secondary endpoints included. Some examples include proportion of patients with Eczema Area and Severity Index (EASI) -75 (≥75% improvement from baseline) at week 16, percent change from baseline to week 16 in pruritus numerical rating scale (NRS), change from baseline to week 16 in % BSA, and changes in quality of life, anxiety, and depression.

The manufacturer reports the following results from SOLO 1 and SOLO 2. In SOLO 1, the primary outcome (an IGA of 0-1 and a reduction of ≥2 points from baseline at week 16) occurred in 85 patients (38%) who received dupilumab every other week and in 83 (37%) who received dupilumab weekly, as compared with 23 (10%) who received placebo ($P<0.001$ for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 (36%) who received dupilumab weekly, as compared with 20 (8%) who received placebo ($P<0.001$ for both comparisons). In addition, in the two trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more patients who received each regimen of dupilumab than in patients who

received placebo (P<0.001 for all comparisons). Dupilumab was also associated with improvement in other clinical end points, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life.

The efficacy and safety of Dupixent monotherapy in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD and a minimum BSA involvement of ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Subjects in the Dupixent group with baseline weight of <60 kg received an initial dose of 400 mg at Week 0, followed by 200 mg Q2W for 16 weeks. Subjects with baseline weight of ≥60 kg received an initial dose of 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders. The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).

The efficacy results at Week 16 were as follows:

- IGA 0 or 1: 24% for Dupixent and 2% for placebo
- EASI-75: 42% for Dupixent and 8% for placebo
- EASI-90: 23% for Dupixent and 2% for placebo
- Peak Pruritus NRS (≥4-point improvement): 37% for Dupixent and 5% for placebo

Asthma

Asthma is a chronic inflammatory disorder of the airways. It is characterized by a history of respiratory symptoms along with variable expiratory airflow limitation, and is typically associated with bronchial hyperresponsiveness and underlying inflammation. Symptoms are variable and recurrent and include wheezing, coughing, shortness of breath, and chest tightness. Exercise, exposure to allergens and irritants, infections, and changes in the weather can be contributing factors to the variability in symptoms and airflow limitation. Guidelines recommend evaluating respiratory symptoms, medical history, physical examination, and spirometry to determine a diagnosis of asthma. Long-term goals for asthma management are to achieve control of symptoms, maintain normal activity level, and to minimize the future risk of exacerbations, decline in lung function, and medication side effects.

Different types of asthma and levels of severity exist. Moderate asthma is asthma that requires a low- or medium-dose inhaled corticosteroid (ICS) used in combination with a long-acting beta agonist (LABA) to be well controlled. Severe asthma is asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires high-dose ICS-LABA or biologic therapy to prevent it from becoming uncontrolled (e.g., asthma worsens when high-dose treatment is decreased). Severe asthma needs to be distinguished from difficult-to-treat asthma that remains symptomatic due to poor adherence, poor inhaler technique, comorbidities, and/or continued exposure to environmental agents since treatment and management differs between the two. The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines on the definition and evaluation of asthma define

uncontrolled asthma for adults and pediatric patients 6 years of age and older as a patient having at least one of the following:

- Frequent severe exacerbations (i.e., two or more bursts of systemic corticosteroids within the past 12 months)
- Serious exacerbations (i.e., at least one hospitalization, intensive care unit stay, or mechanical ventilation in the past 12 months)
- Airflow limitation (i.e., forced expiratory volume in 1 second [FEV1] less than 80% predicted)
- Asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids (or additional biologics)

The Type 2 inflammatory asthma phenotype is found in the majority of people with severe asthma. Type 2 inflammation involves a systemic allergic response and elevated levels of Type 2 inflammatory cytokines such as interleukin (IL)-4, IL-5, and IL-13. Elevated eosinophils or an increased fractional exhaled nitric oxide (FeNO) are characteristics of the eosinophilic subtype of Type 2 inflammatory asthma, while the allergic asthma subtype is additionally characterized by elevated immunoglobulin E (IgE) levels and positive skin prick testing with common environmental allergens. Type 2 inflammation typically responds well to ICS treatment and rapidly improves. However, in severe asthma, Type 2 inflammation may be relatively refractory to high-dose ICS. Maintenance oral corticosteroids (OCS) may elicit a response, but the risk of serious adverse effects with daily OCS use deters their usefulness and an alternative treatment should be sought. Type 2 inflammation is considered refractory if any of the following are found while the patient is taking high-dose ICS or daily OCS:

- Blood eosinophils greater than or equal to 150 cells/microliter
- FeNO greater than or equal to 20 ppb
- Sputum eosinophils greater than or equal to 2%
    - Note: Sputum eosinophil count is not generally available in clinical practice
- Asthma is clinically allergen-driven

The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach for managing asthma. The 2025 GINA guidelines recommend all patients 6 years of age and older with asthma receive ICS-containing medication to reduce the risk of serious exacerbation, even in patients with infrequent symptoms. It is recommended that patients with asthma symptoms most days (e.g., 4+ days per week) be started on low dose ICS-formoterol for maintenance-and-reliever therapy (MART). Patients' response to treatment should be reviewed after 2 to 3 months. If symptoms remain uncontrolled despite good adherence and correct inhaler technique, the next step up (Step 4) involves increasing MART to medium dose ICS-formoterol (ICS-LABA). Other controller options that may be added on to ICS treatment at Step 4 include a long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), or theophylline. Both LTRA and theophylline are considered less efficacious than adding on a LABA or LAMA, and also come with safety concerns. Patients with uncontrolled symptoms and/or exacerbations despite being on Step 4 treatment for 3 to 6 months should be assessed for contributory factors, have their treatment optimized, and be referred for expert assessment, phenotyping, and potential add-on therapy. Treatment optimization may include a trial of high dose ICS-LABA or add-on LAMA or LTRA

therapy, if not already trialed. Maintenance oral corticosteroids (OCS) should be used only as last resort because short-term and long-term systemic side effects are common and serious.

Biologic agents should be considered as add-on therapy for patients with refractory Type 2 inflammation with exacerbations and/or poor symptom control despite taking at least high dose ICS-LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS, and only after treatment has been optimized. Tezepelumab is considered a broad-acting biologic and may be considered in patients without a Type 2 inflammatory phenotype due to it binding to circulating thymic stromal lymphopoietin (TSLP), which is upstream on the inflammatory cascade. Based on efficacy results from clinical trials, the indication of use for tezepelumab is not restricted to a biomarker-defined phenotype. 2025 GINA guidelines summarize payer eligibility criteria for the use of biologics as follows:

- Anti-IgE (omalizumab) for severe allergic asthma
    - Sensitization to inhaled allergen(s) on skin prick testing for specific IgE
    - Total serum IgE and body weight within dosing range
    - Exacerbations within the last year
- Anti-IL5 (mepolizumab, reslizumab) /Anti-IL5Ra (benralizumab) for severe eosinophilic asthma
    - Blood eosinophils greater than or equal to 150 cells/microliter (or greater than or equal to 300 cells/microliter, based on locally specified level)
    - Severe exacerbations within the last year
- Anti-IL4Ra (dupilumab) for severe eosinophilic/Type 2 asthma or patients requiring maintenance OCS
    - Blood eosinophil greater than or equal to 150 cells/microliter but less than or equal to 1500 cells/microliter, or FeNO greater than or equal to 25 ppb, or taking maintenance OCS
    - Severe exacerbations within the last year
- Anti-TSLP (tezepelumab) for severe asthma
    - Severe exacerbations within the last year

Patient response to biologic therapy should be evaluated 4 months after initiating therapy, and the patient should be re-evaluated every 3 to 6 months. If response is unclear after 4 months, the trial should be extended to 6-12 months.

2025 GINA guidelines recommend the following step-down therapy process in patients responding well to targeted biologic therapy

- Re-evaluate the need for each asthma medication every 3 to 6 months, but inhaled therapy (e.g., ICS-containing therapy) should not be completely stopped
- The order of reduction of treatments should be based on observed benefit, potential side-effects, cost, and patient preference. However, minimizing the use of OCS is a very high priority.
- First, consider decreasing/stopping OCS due to their significant adverse effects. Then consider stopping other add-on asthma medications.

- Then, if asthma is well controlled for 3-6 months, consider reducing maintenance ICS dose, but do not stop maintenance ICS-containing therapy (e.g., ICS-LABA)
- Re-evaluate the need for ongoing biologic therapy, but a trial of withdrawal of the biologic should not be considered until after at least 12 months of treatment and only if asthma remains well controlled on medium-dose ICS-containing therapy
    - For allergic asthma, also confirm there is no further exposure to an allergic trigger

Efficacy

The asthma development program included three randomized, double-blind, placebo controlled, parallel-group, multi-center trials (AS Trials 1, 2, and 3) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects (12 years of age and older). Subjects enrolled in AS Trials 1 and 2 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. Subjects enrolled in AS Trial 3 required dependence on daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s). In all 3 trials, subjects were enrolled without requiring a minimum baseline blood eosinophil count. In AS Trials 2 and 3 subjects with screening blood eosinophil level of >1500 cells/mcL (<1.3%) were excluded. Dupixent was administered as add-on to background asthma treatment. Subjects continued background asthma therapy throughout the duration of the studies, except in AS Trial 3 in which OCS dose was tapered as described below.

AS Trial 1 was a 24-week dose-ranging study which included 776 subjects (18 years of age and older). Dupixent compared with placebo was evaluated in adult subjects with moderate to severe asthma on a medium or high-dose inhaled corticosteroid and a long-acting beta agonist. Subjects were randomized to receive either 200 mg (N=150) or 300 mg (N=157) Dupixent every other week (Q2W) or 200 mg (N=154) or 300 mg (N=157) Dupixent every 4 weeks following an initial dose of 400 mg, 600 mg or placebo (N=158), respectively. The primary endpoint was mean change from baseline to Week 12 in FEV1 (L) in subjects with baseline blood eosinophils ≥300 cells/mcL. Other endpoints included percent change from baseline in FEV1 and annualized rate of severe asthma exacerbation events during the 24-week placebo-controlled treatment period. Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count (≥300 cells/mcL and <300 cells/mcL. Additional secondary endpoints included responder rates in the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

AS Trial 2 was a 52-week study which included 1902 subjects (12 years of age and older). Dupixent compared with placebo was evaluated in 107 adolescents and 1795 adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid (ICS) and a minimum of one and up to two additional controller medications. Subjects were randomized to receive either 200 mg (N=631) or 300 mg (N=633) Dupixent Q2W (or matching placebo for either 200 mg [N=317] or 300 mg [N=321] Q2W) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo-controlled period and change from baseline in pre-bronchodilator FEV1 at Week 12 in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included annualized severe exacerbation rates and FEV1 in patients with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

AS Trial 3 was a 24-week oral corticosteroid-reduction study in 210 subjects with asthma who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. After optimizing the OCS dose during the screening period, subjects received 300 mg Dupixent (N=103) or placebo (N=107) once Q2W for 24 weeks following an initial dose of 600 mg or placebo. Subjects continued to receive their existing asthma medicine during the study; however, their OCS dose was reduced every 4 weeks during the OCS reduction phase (Week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction of oral corticosteroid dose at Weeks 20 to 24 compared with the baseline dose, while maintaining asthma control in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included the annualized rate of severe exacerbation events during treatment period and responder rate in the ACQ-5 and AQLQ(S) scores.

AS Trials 1 and 2 evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis population (subjects with baseline blood eosinophil count of ≥300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2), subjects receiving either Dupixent 200 mg or 300 mg Q2W had significant reductions in the rate of asthma exacerbations compared to placebo. In the overall population in AS Trial 2, the rate of severe exacerbations was 0.46 and 0.52 for Dupixent 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.87 and 0.97. The rate ratio of severe exacerbations compared to placebo was 0.52 (95% CI: 0.41, 0.66) and 0.54 (95% CI: 0.43, 0.68) for Dupixent 200 mg Q2W and 300 mg Q2W, respectively.

Prespecified subgroup analyses of AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils ≥ 150 cells/mcL. In subjects with baseline blood eosinophil count < 150 cells/mcL, similar severe exacerbation rates were observed between Dupixent and placebo.

Significant increases in pre-bronchodilator FEV1 were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of ≥ 300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV1 LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for Dupixent 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for Dupixent 200 mg Q2W and 300 mg Q2W, respectively. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils.

Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a common lung disease characterized by chronic respiratory symptoms caused by abnormalities of the airways and/or alveoli that cause persistent, and often progressive, airway obstruction. Symptoms include dyspnea, cough, wheezing, fatigue, sputum production, and/or exacerbations. The global prevalence of COPD is estimated to be 10.3% and comes with substantial economic and social burden. COPD is one of the top causes of death in the United

States and is a leading cause of morbidity and mortality worldwide, with around three million deaths globally annually.

COPD develops due to a combination of environmental exposures and patient characteristics. Smoking and air pollution are the two leading environmental exposures leading to the development of COPD. Prolonged exposure to these toxins leads to chronic inflammation which causes structural changes, narrowing of the small airways (bronchiolitis), and destruction of the lung parenchyma (emphysema).

Chronic bronchitis is a common condition in patients with COPD, and it is defined as chronic cough and sputum production (e.g., chronic productive cough) for at least 3 months per year for two consecutive years in the absence of other conditions that may be causative. Long-term inflammation and excess mucus production can lead to the formation of mucus plugs and greater airflow obstruction. Large observational studies have shown that the prevalence of chronic bronchitis ranges from 27-35% in patients with COPD, with the primary risk factor being smoking. Chronic bronchitis contributes to a worse quality of life and increased mortality.

A diagnosis of COPD is dependent on the presence of pulmonary symptoms (i.e., dyspnea, chronic cough, sputum production), patient's exposure history (e.g., current/previous smoker, history of recurrent lower respiratory tract infections), and evidence of airflow limitation. The diagnosis is confirmed by spirometry. A post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) less than 0.7 is indicative of the diagnosis.

Once a diagnosis of COPD is confirmed, it is important to determine the severity of airflow obstruction for assessment of prognosis and risk of exacerbations. Airflow obstruction severity is based on the post-bronchodilator value of FEV1. The cutoff points for each Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade of severity are as follows:

GOLD Grades	**Severity of Airflow Obstruction in COPD**	
GOLD 1	Mild	FEV1 greater than or equal to 80% predicted
GOLD 2	Moderate	FEV1 greater than or equal to 50% to less than 80% predicted
GOLD 3	Severe	FEV1 greater than or equal to 30% to less than 50% predicted
GOLD 4	Very Severe	FEV1 less than 30% predicted

Exacerbations of COPD are episodes of acute worsening of respiratory symptoms. They lead to increased dyspnea and/or cough and sputum that worsens over a less than 14-day period. They are often associated with increased airway inflammation, increased mucus production, and marked gas trapping. Symptoms of a COPD exacerbation are usually present for 7 to 10 days. They can be caused by infection, pollution, or other insult to the lungs. Moderate exacerbations are those that require treatment with a short acting bronchodilator (SABD) and oral corticosteroids, with or without an antibiotic. Severe exacerbations are associated with hospitalization or a visit to the emergency room, and may also be associated with acute respiratory failure requiring mechanical ventilation. Frequent exacerbations are

defined as having two or more exacerbations per year and typically lead to a worse health status and morbidity for patients. A previous history of exacerbations is the best predictor of having frequent exacerbations, but worsening airflow obstruction is also associated with an increased prevalence of exacerbations, hospitalization, and risk of death.

The treatment goals of COPD are to reduce symptoms and prevent disease progression and exacerbations. The GOLD "ABE" assessment tool is recommended for determining initial pharmacotherapy for the management of COPD. The tool takes into account patient symptoms and history/risk of exacerbations to assign a GOLD group (A, B, or E). Exacerbation history is broken into two sections based on the number of exacerbations per year. For patients with 0 to 1 moderate exacerbations within the past year, a formal assessment of symptoms using validated questionnaires is required to further establish the patient's GOLD grade and initial therapy. The modified Medical Research Council (mMRC) dyspnea scale assesses breathlessness, which is a key symptom for many patients with COPD. A more comprehensive questionnaire is the COPD Assessment Test (CAT), which assesses the impact of COPD on a person's health status. For group E individuals, a blood eosinophil count can guide the use of an inhaled corticosteroid (ICS) as part of pharmacological management. Studies have shown that an ICS added to regular maintenance bronchodilator treatment in patients with higher blood eosinophil counts can prevent future exacerbations.

Initial Pharmacotherapy Treatment Algorithm		
Greater than or equal to 2 moderate exacerbations, or greater than or equal to 1 exacerbation leading to hospitalization within the past year	Group E	
0 to 1 moderate exacerbations (not leading to hospitalization) within the past year	Group A	Group B
	mMRC 0-1 CAT less than 10	mMRC 2 or greater CAT 10 or greater

Treatment recommendations based on GOLD "ABE" grouping are as follows:(31)

- Group A
  - A bronchodilator
- Group B
  - LABA + LAMA
- Group E:
  - Long-acting beta agonist (LABA) + long-acting muscarinic antagonist (LAMA)
  - Consider LABA + LAMA + ICS if blood eosinophil count is 300 cells/microliter or higher
  - Use of LABA + ICS in COPD is not encouraged. If an ICS is indicated for use, ICS + LAMA + LABA has been shown to be superior to ICS + LABA

The GOLD guideline has a separate algorithm for follow up therapy, based on persistence of dyspnea and occurrence of exacerbations. Patients not responding to initial therapy should have inhaler technique, adherence, and possible interfering comorbidities addressed prior to adding or changing therapies. Follow-up recommendations are as follows:

- Dyspnea:
    - Current monotherapy with LABA or LAMA: switch to dual therapy (LABA/LAMA)
    - Current dual therapy with LABA/LAMA: consider switching inhaler devices, implement or escalate non-pharmacologic therapies, consider adding ensifentrine, or investigate other causes of dyspnea
- Exacerbations:
    - Current monotherapy (LABA or LAMA):
        - Blood eosinophil count less than 300 cells/microliter: switch to dual therapy (LABA/LAMA)
        - Blood eosinophil count greater than or equal to 300 cells/microliter: switch to triple therapy (LABA/LAMA/ICS)
    - Current dual therapy (LABA/LAMA):
        - Blood eosinophil count less than 100 cells/microliter: consider adding roflumilast (FEV1 less than 50% and chronic bronchitis) or azithromycin (preferentially in former smokers)
        - Blood eosinophil count greater than or equal to 100 cells/microliter: switch to triple therapy (LABA/LAMA/ICS)
    - Current triple therapy (LABA/LAMA/ICS):
        - Blood eosinophil count greater than or equal to 300 cells/microliter and symptoms of chronic bronchitis: consider adding dupilumab, an interleukin (IL)-4 receptor alpha antagonist biologic agent
            - Dupilumab reduces exacerbations and improves lung function and quality of life
        - Consider adding roflumilast (FEV1 less than 50% and chronic bronchitis) or azithromycin (preferentially in former smokers)
        - The ICS component should not be withdrawn unless the ICS was started inappropriately, there has been no response to the ICS, the patient experienced significant side effects, or the patient had severe or recurrent pneumonia
            - If the patient's blood eosinophil count is greater than or equal to 300 cells/microliter, de-escalation of ICS is more likely to lead to exacerbations

Efficacy

The efficacy of Dupixent as add-on maintenance treatment of adult patients with inadequately controlled COPD and an eosinophilic phenotype was evaluated in two randomized, double-blind, multicenter, parallel-group, placebo-controlled trials (BOREAS [NCT03930732] and NOTUS [NCT04456673]) of 52 weeks duration. The two trials enrolled a total of 1,874 adult subjects with COPD.

Both trials enrolled subjects with a diagnosis of COPD with moderate to severe airflow limitation (post-bronchodilator FEV1/FVC ratio less than 0.7 and post-bronchodilator FEV1 of 30% to 70% predicted) and

a minimum blood eosinophil count of 300 cells/mcL at screening. Patients had to have been receiving maintenance triple therapy consisting of a long-acting muscarinic antagonist (LAMA), long-acting beta agonist (LABA), and inhaled corticosteroid (ICS) for at least 3 months before randomization; LAMA/LABA dual therapy was allowed if ICS use was contraindicated. Trial enrollment required an exacerbation history of at least 2 moderate or 1 severe exacerbation(s) in the previous year despite receiving maintenance therapy, and symptoms of chronic productive cough for at least 3 months in the past year. Exacerbations of COPD were defined as clinically significant worsening of COPD symptoms including increases in dyspnea, wheezing, cough, sputum volume, and/or increase in sputum purulence. Exacerbation severity was further defined as moderate if treatment with systemic corticosteroids and/or antibiotics was required, or severe if they resulted in hospitalization or observation for over 24 hours in an emergency department or urgent care facility. One of the two required moderate exacerbations had to require the use of systemic corticosteroids. Greater than or equal to 95% of subjects in each trial had chronic bronchitis. Subjects also had a Medical Research Council (MRC) dyspnea score greater than or equal to 2 (range 0-4). In both trials, subjects were randomized to receive Dupixent 300 mg subcutaneously every two weeks (Q2W) or placebo in addition to their background maintenance therapy for 52 weeks.

The primary endpoint for BOREAS and NOTUS trials was the annualized rate of moderate or severe COPD exacerbations during the 52-week treatment period. In both trials, Dupixent demonstrated a significant reduction in the annualized rate of moderate or severe COPD exacerbations compared to placebo when added to background maintenance therapy. In the BOREAS trial, the annualized rate of moderate or severe exacerbations of COPD was 0.78 (95% confidence interval [CI], 0.64 to 0.93) in the dupilumab group and 1.10 (95% CI, 0.93 to 1.30) in the placebo group (rate ratio, 0.70; 95% CI, 0.58 to 0.86; P value less than 0.001). In the NOTUS trial, the annualized rate of moderate or severe exacerbations of COPD was lower in the dupilumab group (0.86; 95% CI, 0.70 to 1.06) than in the placebo group (1.30; 95% CI, 1.05 to 1.60), resulting in a rate ratio of 0.66 (95% CI, 0.54 to 0.82; P value less than 0.001). Treatment with Dupixent decreased the risk of a moderate to severe COPD exacerbation as measured by time to first exacerbation when compared with placebo in BOREAS (HR: 0.80; 95% CI: 0.66, 0.98) and NOTUS (HR: 0.71; 95% CI: 0.57, 0.89).

In both trials (BOREAS and NOTUS), Dupixent demonstrated numerical improvement in post-bronchodilator FEV1 at Weeks 12 and 52 compared to placebo when added to background maintenance therapy. Significant improvements of similar magnitude were observed in change from baseline in pre-bronchodilator FEV1 at Weeks 12 and 52 in subjects treated with Dupixent compared to placebo across both trials. In both trials (BOREAS and NOTUS), the St. George's Respiratory Questionnaire (SGRQ) total score responder rate (defined as the proportion of subjects with SGRQ improvement from baseline of at least 4 points) at Week 52 was evaluated. SGRQ is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation and scores range from 0 to 100, with lower scores indicating a better quality of life. In BOREAS, the responder rate was 51% for subjects treated with Dupixent versus 43% for placebo (N=939, odds ratio: 1.44; 95% CI: 1.10, 1.89). In NOTUS, the responder rate was 51% for subjects treated with Dupixent versus 47% for placebo (N=721, odds ratio: 1.16; 95% CI: 0.86, 1.58).

Bullous Pemphigoid (BP)

Bullous pemphigoid (BP) is a chronic autoimmune disease that causes subepidermal blistering of the skin and mucous membranes. It is characterized by bullous lesions that can be localized or widespread, and is accompanied by intense itch. BP most commonly affects patients older than 70 years of age, has high morbidity, and can have severe impacts on quality of life. It is associated with autoantibodies against BP antigen 180 (BP180) and BP antigen 230 (BP230).

The diagnosis of BP involves a clinical examination to obtain a patient history of the disease, and to assess signs and symptoms. A detailed drug history of medications the patient has received within the 6 months prior to the development of symptoms is needed due to the potential of drug-induced BP. Drugs associated with the development of BP include diuretics, dipeptidyl peptidase-4 inhibitors (DPP-4; "gliptins"), nonsteroidal anti-inflammatory drugs (NSAIDs), amoxicillin, and programmed death-1 (PD-1) inhibitors. At this time, there is no clear recommendation to either stop or continue the drug(s) that are probable or plausible to be inducing BP. This is due to a lack of knowledge and contradictory results from studies. However, if a culprit drug can be stopped or substituted with no harm it should be considered.

When clinical findings are suggestive of BP, laboratory assessment is required to confirm the diagnosis. A biopsy of lesional tissue is needed for histopathologic examination, and a biopsy of perilesional tissue is needed for direct immunofluorescence (DIF). A positive DIF finding is essential to correctly diagnose BP, with very few exceptions. The proper classification of BP requires immune serological tests to detect circulating anti-basement membrane zone autoantibodies. Indirect immunofluorescence (IIF) microscopy is supportive of the diagnosis if findings consist of antibodies localized to the epidermal side (roof) of the split on human skin. An enzyme-linked immunosorbent assay (ELISA) is supportive of the diagnosis with detection of antibodies to the NC16A domain of BP180 and/or BP230 antibodies. Overall, the diagnosis of BP generally requires suggestive clinical features, a positive DIF, and the presence of serum antibodies indicative of the disease.

The BP Disease Area Index (BPDAI) is a scoring tool used to determine the extent and severity of the disease. The score ranges from 0 to 360 with the following severity cutoffs: mild (less than or equal to 19), moderate (20 to 56), and severe (greater than or equal to 57). The BPDAI can be used to guide treatment decisions and monitor disease activity.

Goals of BP treatment include reducing skin eruption and itch, improving quality of life, and limiting side effects. Topical and systemic corticosteroids are the mainstays of treatment for BP, and their use is based on the extent of the disease and severity. Super-potent topical corticosteroids (TCS), such as clobetasol propionate, are typically used in localized BP of less than 20% body surface area. High-dose systemic corticosteroids, such as prednisone at a dose of 0.5 to 1 mg/kg/day, are used for extensive disease. A starting dose of 0.5mg prednisone/kg/day is recommended in patients with mild to severe BP, and doses lower than this have not been validated or shown to be effective. Once control of disease activity has been achieved, corticosteroids (topical and/or systemic) should be tapered and potentially discontinued in patients in remission.

The European Academy of Dermatology & Venerology (EADV) guidelines for the management of BP recommend the following treatments based on disease severity/BPDAI score:

Mild and moderate BP

- Localized (presence of lesions involving one body site):
    - Apply super-potent TCS on lesions only (e.g., 10 g/day of clobetasol propionate). Continue treatment until 15 days after control of disease activity has been achieved, followed by a progressive tapering of doses over 4 months.
- Non-localized:
    - Super-potent TCS on the whole body, except the face (e.g., 20 to 30 g/day of clobetasol propionate), or
    - Oral corticosteroids at an initial dose of 0.5 mg/kg/day of prednisone or prednisolone

Severe BP

- Super-potent TCS on the whole body, except the face (e.g., 30 to 40 g/day of clobetasol propionate), or
- Oral corticosteroids at an initial dose of 0.5 mg/kg/day of prednisone or prednisolone
    - In patients who do not achieve disease control within 3 weeks, two options may be considered:
        - Increase the dose of prednisone up to 0.75 mg/kg/day
        - Add super-potent TCS

Relapsing BP

- Topical corticosteroids:
    - In patients who relapse during the dose reduction period, it is recommended to increase the dose to the previous level.
    - In patients who experience a relapse after treatment withdrawal, it is recommended to treat using the following doses of clobetasol propionate: 10 g/day for patients with localized relapse; 20 g/day for patients with mild disease; 30 to 40 g/day for patients with moderate to extensive relapse.
- Oral corticosteroids: In the case of a relapse during the dose reduction period, it is recommended to increase the dose to the previous level.

In patients with corticosteroid-dependent, relapsing, treatment-recalcitrant, or resistant BP, conventional immunosuppressants or other alternative agents may be added or introduced to the treatment regimen. They may also be used if contraindications to corticosteroids are present or in patients with extensive BP. However, evidence of their efficacy is lacking, and there is no positive evidence supporting their use as a first-line treatment option. Immunosuppressant options include methotrexate, azathioprine, and mycophenolate. Other options include doxycycline or dapsone.

Biologics, such as dupilumab, may be considered in difficult-to-treat cases of BP based on clinical features and response to topical/oral corticosteroid therapy. This includes patients who remain below the controllable level despite several weeks of intensive therapy with corticosteroids.

Treatment failure is defined as the development of new non-transient lesions, continued extension of old lesions, failure of established lesions to begin to heal, or daily pruritus despite certain strengths of corticosteroids with or without higher doses of adjuvant therapies. Systemic corticosteroids should be

trialed for a minimum of 3 weeks, and topical corticosteroids for at least 4 weeks, before determining treatment failure.

Efficacy

The efficacy of Dupixent in adults with bullous pemphigoid (BP) was evaluated in a 52-week randomized, double-blind, parallel-group, multicenter, placebo-controlled trial (ADEPT; NCT04206553). This trial enrolled 106 adult subjects with a Bullous Pemphigoid Disease Area Index (BPDAI) activity score of greater than or equal to 24 on a scale of 0-360 and a weekly average Peak Pruritus NRS score of greater than or equal to 4 on a scale of 0-10. Patients also had clinical features of BP, such as urticarial or eczematous or erythematous plaques, bullae, pruritus. At baseline, 63% of subjects had prior systemic corticosteroid use for BP, and the mean age was 71.3 years. The mean Peak Pruritus NRS score was 7.5 at baseline.

In this trial, subjects were randomized to receive either subcutaneous Dupixent 600 mg (two 300 mg injections) on Day 1, followed by 300 mg every other week (Q2W), or matching placebo for 52 weeks. All subjects were also initiated on a standard regimen of oral corticosteroids (prednisone or prednisolone; 0.5 or 0.75 mg/kg/day) on Day 1. After achieving control of disease activity for 2 weeks, oral corticosteroids (OCS) were tapered with the objective to taper them off no later than Week 16 as long as the control of disease activity was maintained. Subjects who experienced a loss of control of disease activity (new lesions form and existing lesions cease to heal) during OCS taper, or who relapsed post-taper, or who used rescue medications were considered treatment failures. During the OCS taper, subjects were permitted to increase their OCS once, with any subsequent increases being considered rescue therapy. Subjects could be rescued during the trial with topical or oral corticosteroids, non-steroidal immunosuppressive medications, or immunomodulating biologics. Subjects were allowed to continue trial treatment if rescued with topical or oral corticosteroids.

The primary endpoint was the proportion of subjects achieving sustained remission at Week 36. Sustained remission was defined as the achievement of complete remission and off OCS no later than Week 16, absence of disease relapse from the time of completion of the corticosteroid taper to Week 36, and absence of rescue therapy during the 36-week double-blind treatment period. Secondary endpoints included total cumulative dose of OCS and proportion of subjects with a reduction in itch defined as at least a 4-point improvement (reduction) in the Peak Pruritus NRS.

The efficacy results at Week 36 are presented in the table below.

	Dupixent 300 mg Q2W + OCS (N=53)	**Placebo + OCS (N=53)**	**Difference (95% CI) for Dupixent vs. Placebo**
Proportion of subjects achieving sustained remission	18.3%	6.1%	12.2% (-0.8, 26.1)
Proportion of subjects with improvement (reduction) of greater than or equal to 4 points in Peak Pruritus NRS from baseline	38.3%	10.5%	27.8% (11.6, 43.4)

The proportion of subjects that received rescue therapy during the 36-week treatment period was 53% in the Dupixent group and 79% in the placebo group. The median (min, max) cumulative dose of OCS at Week 36 was 2.8 g (1.2, 22.7) in the Dupixent group compared to 4.1 g (1.5, 23.3) in the placebo group.

Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory condition affecting the paranasal sinuses and nasal cavity. The International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR-RS) indicates that the diagnostic criteria for CRSwNP consist of ALL the following:

- Symptoms for greater than or equal to 12 weeks
- Two of the following symptoms:
    - Nasal discharge (rhinorrhea or post-nasal drainage)
    - Nasal obstruction or congestion
    - Hyposmia (loss or decreased sense of smell)
    - Facial pressure or pain
    - Cough (in pediatric patients)
- One or more of the following objective findings:
    - Evidence of inflammation on nasal endoscopy or computed tomography (CT)
    - Evidence of purulence coming from paranasal sinuses or ostiomeatal complex
- Presence of nasal polyps

The objective confirmation of CRSwNP through documentation of sinonasal inflammation and nasal polyps can be accomplished via direct visualization by anterior rhinoscopy or nasal endoscopy, or via imaging by CT scanning. Anterior rhinoscopy allows visualization of the anterior one-third of the nasal cavity and is sufficient at detecting large polyps or gross purulence. Nasal endoscopy also allows visualization of the anterior nasal cavity, in addition to the posterior nasal cavity, nasopharynx, and sinus drainage pathway. Anterior rhinoscopy has the least cost and risk associated with it, but nasal endoscopy and CT scanning have a higher diagnostic accuracy. CT scanning also comes with the risk of radiation exposure. Serum biomarkers (e.g., elevated eosinophils, IL-5, IL-5, IgE) are emerging as a potential diagnosis tool, but their role is still not clearly defined. Currently, biomarkers are used to distinguish types of CRS and prognosis.

Topical saline irrigation and intranasal corticosteroids (INCS) are recommended as initial treatment for CRSwNP. Nasal saline irrigation, used as adjunct treatment with other therapies, improves symptoms and quality of life (QoL) outcomes and is considered an important aspect of the management of CRSwNP. Saline irrigation can improve nasal mucosa function through the mechanical clearance of thick mucus and inflammatory mediators, including eosinophilic mucin. Saline irrigation should not be confused with saline spray since irrigation is more effective in clearing secretions and improving QoL.

INCS can improve symptoms, reduce nasal polyp size, and improve sense of smell through their anti-inflammatory properties. INCS are well tolerated and long term treatment is effective and safe. Many different corticosteroids have been used in the treatment of CRSwNP, including triamcinolone,

mometasone, fluticasone, and budesonide, and different dosage forms are also available, including intranasal sprays and steroid-eluding stents. However, no specific corticosteroid or formulation is recommended as being superior to the others.

Oral systemic corticosteroids (OCS) should be considered in patients with an inadequate response to INCS after 3 months of therapy. A short course (1-3 weeks) can result in a significant reduction in symptoms and nasal polyps for up to three months after the start of treatment. Up to 2 courses per year, taken in addition to INCS, can be useful for patients with partially or uncontrolled disease. Long term use of OCS should be avoided due to the increased risk of adverse effects.

Endoscopic sinus surgery (ESS) is aimed at improving symptoms and creating better conditions for local treatment. Sinus surgery should be considered when disease is refractory and remains symptomatic despite trial of primary medical therapy (e.g., nasal sinus irrigation, INCS, oral corticosteroids). Based on current evidence, delaying surgical intervention can be detrimental to symptom improvement and outcomes. After surgery, patients need to continue other treatments, such as saline irrigation and INCS, due to the chronic nature of the disease and nasal polyps potentially reoccurring. INCS can help to prevent nasal polyp recurrence post-surgery.

Biologics can be considered as add-on therapy in patients where their disease remains uncontrolled despite appropriate medical treatment and/or sinus surgery, or when surgery is not a viable option. For patients that continue to have high disease burden despite using INCS for at least 4 weeks, biologics may be considered and preferred over other medical treatment choices. Biologics vary in their magnitude of benefits, harms, and certainty of evidence across outcomes. Based on network analyses, dupilumab and omalizumab have shown to be the most beneficial for the most patient-important outcomes when compared to other biologics, followed by mepolizumab. Response to biologic treatment should initially be evaluated 6 months after initiation of therapy. Response can be defined as reduced nasal polyp size, reduced need for systemic oral corticosteroids, improved QoL, improved sense of smell, and/or reduced impact of comorbidities. Patients with no response should have the current biologic drug discontinued and/or switched, or a revision surgery can be considered. Patients with partial response may continue the current biologic therapy and be re-evaluated at 12 months since some biologics need more than 6 months to reach their full potential. Patients with partial response may also switch to a different biologic, consider salvage surgery, or complete an additional short course of OCS.

Efficacy

Two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) evaluated Dupixent in CRSwNP. There were 724 subjects aged 18 years and older on background intranasal corticosteroids (INCS) included in the trials. These studies included subjects with CRSwNP despite prior sinonasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Patients with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion. In CSNP Trial 1, a total of 276 subjects were randomized to receive either 300 mg Dupixent (N=143) or placebo (N=133) every other week for 24 weeks. In CSNP Trial 2, 448 subjects were randomized to receive either 300 mg Dupixent (N=150) every other week for 52 weeks, 300 mg Dupixent (N=145) every other week until week 24 followed by 300 mg Dupixent every 4 weeks until week 52, or placebo (N=153). All subjects had evidence of sinus opacification on the Lund Mackay (LMK) sinus CT scan and 73% to 90% of subjects had opacification of

all sinuses. Subjects were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). A total of 63% of subjects reported previous sinus surgery, with a mean number of 2.0 prior surgeries, 74% used systemic corticosteroids in the previous 2 years with a mean number of 1.6 systemic corticosteroid courses in the previous 2 years, 59% had co-morbid asthma, and 28% had NSAID-ERD.

The co-primary efficacy endpoints were change from baseline to Week 24 in bilateral endoscopic nasal polyps score (NPS; 0-8 scale) as graded by central blinded readers and change from baseline to Week 24 in nasal congestion/obstruction score averaged over 28 days (NC; 0-3 scale), as determined by subjects using a daily diary. In both studies, key secondary end-points at Week 24 included change from baseline in: LMK sinus CT scan score, daily loss of smell, and 22-item sinonasal outcome test (SNOT-22). In the pooled efficacy results, the reduction in the proportion of subjects rescued with systemic corticosteroids and/or sinonasal surgery (up to Week 52) were evaluated.

Statistically significant efficacy was observed in CSNP Trial 2 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52. Similar results were seen in CSNP Trial 1 at Week 24. In the post-treatment period when subjects were off Dupixent, the treatment effect diminished over time. In both studies, significant improvements in nasal congestion were observed as early as the first assessment at Week 4. A significant decrease in the LMK sinus CT scan score was observed. Dupilumab significantly improved the loss of smell compared to placebo. In both studies, significant improvements in daily loss of smell severity were observed as early as the first assessment at Week 4. Dupilumab significantly decreased sinonasal symptoms as measured by SNOT-22 compared to placebo.

In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with Dupixent resulted in significant reduction of systemic corticosteroid use and need for sinonasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35). The proportion of subjects who required systemic corticosteroids was reduced by 74% (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The proportion of subjects who required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46).

The effects of Dupixent on the primary endpoints of NPS and nasal congestion and the key secondary endpoint of LMK sinus CT scan score were consistent in patients with prior surgery and without prior surgery.

Chronic Spontaneous Urticaria (CSU)

Chronic spontaneous urticaria (CSU) can be a debilitating condition that can significantly affect a patient's quality of life. Routine diagnostic work-up for CSU is limited to blood tests for complete blood count and inflammatory markers, such as C-reactive protein and/or erythrocyte sedimentation rate, mostly to rule out other potential diseases. Skin prick testing, typically used to identify specific allergens, is not useful for CSU as the condition is rarely caused by type 1 allergy. CSU is), also referred to as chronic urticaria (CU) or chronic idiopathic urticaria (CIU), is a mast cell-mediated condition that involves the recurrent spontaneous occurrence of urticaria and/or angioedema. Urticaria is characterized by the development of wheals (hives), angioedema, or both. CSU is defined by the presence of urticaria for more than 6 weeks with no definite eliciting factor involved. Signs and symptoms may occur daily or follow an intermittent/recurrent course. Routine diagnostic tests (e.g., blood tests for complete blood

count and inflammatory markers, skin prick test) are mainly used to rule out other potential diseases and not to confirm the diagnosis. Medication that is suspected to worsen the disease (e.g., NSAIDs) should be discontinued or substituted by another class of agents to reduce disease exacerbations. CSU can be a debilitating condition that significantly impairs a patient's quality of life, and treatment goals include symptom control and normalization of quality of life for the patient.

The international European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology Forum (EDF)/Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) guideline recommends the following algorithm for the treatment of CSU:

- First-line treatment: Second-generation H1-antihistamine at standard dosing, dosed daily (e.g., cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine)
- Second-line treatment: If inadequate control at standard dosing, increase the daily dose of the second-generation H1-antihistamine to up to 4 times the standard dosing before other treatments are considered
- Third-line treatment: If inadequate control after 2-4 weeks of therapy with a high dose second-generation H1-antihistamine, add on omalizumab

High dose second-generation H1-antihistamine therapy has been suggested in guidelines since the year 2000, and no serious adverse events or side effects from long-term use or potential accumulation have been reported. Treatment for CSU should be evaluated every 3 to 6 months to assess disease activity, impact, and control. The severity of urticaria can fluctuate, including the possibility of spontaneous remission. In addition, patients should be assessed for any side effects of treatment. If an adjustment to treatment is warranted, it may include stepping up therapy, changing medication due to side effects, or stepping down treatment if the patient has been symptom free for 3 to 6 months.

Omalizumab was approved for the treatment of CSU in 2014 and has since received placement in treatment guidelines. However, for some patients omalizumab provides partial or no improvement in their signs and symptoms. Current guidelines support using cyclosporine as add-on therapy for patients with severe disease and an incomplete response to omalizumab and an antihistamine used in combination, but it is not recommended as standard treatment due to the risk and incidence of adverse effects. Dupilumab has been shown to be an effective treatment for CSU per the LIBERTY CUPID CSU studies, but its place in treatment guidelines has yet to be established. The LIBERTY CSU CUPID-B trial was designed to determine if dupilumab is an effective alternative in patients with a lack of response to omalizumab, incomplete control of their CSU while taking omalizumab, or an inability to tolerate the use of omalizumab. The dupilumab group in this study did not meet statistical significance for reduction in the primary endpoint of change from baseline in itch severity score over 7 days (ISS7) at Week 24.

Efficacy

The efficacy of Dupixent for the treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria who remain symptomatic despite H1 antihistamine treatment was evaluated in a master protocol clinical trial (CUPID [NCT04180488]) that included three 24-week, randomized, double-blind, parallel-group, multicenter, placebo-controlled trials (CUPID Study A, Study B, and Study C), followed by 12-week blinded safety follow-up periods. CUPID Study A and Study C included subjects who remained symptomatic despite H1 antihistamine treatment and were anti-IgE treatment

naïve, while CUPID Study B included patients who remained symptomatic despite H1 antihistamine and anti-IgE treatments. The efficacy of Dupixent was based only on CUPID Study A and Study C; Study B did not meet the primary endpoint.

CUPID Study A and Study C enrolled a total of 284 adult and pediatric patients 12 years of age and older with CSU (Itch Severity Score over 7 days [ISS7] greater than or equal to 8 on a scale of 0 to 21 and Urticaria Activity Score over 7 days [UAS7] greater than or equal to 16 on a scale of 0 to 42) who were symptomatic despite the use of H1 antihistamines, but who were anti-IgE treatment naïve. In the Dupixent group, adults and pediatric subjects (12 years of age and older) weighing greater than or equal to 60 kg received a subcutaneous dose of Dupixent 600 mg on Day 1, followed by 300 mg every 2 weeks (Q2W), while pediatric subjects (12 years of age and older) weighing 30 kg to less than 60 kg received a subcutaneous dose of Dupixent 400 mg on Day 1, followed by 200 mg Q2W.

The primary endpoint was change from baseline in itch severity score over 7 days (ISS7) at Week 24. The ISS7 score was defined as the sum of the daily itch severity scores (ISS), from 0 to 3, recorded at the same time of the day for a 7-day period, ranging from 0 to 21. The key secondary endpoint was change from baseline in urticaria activity score over 7 days (UAS7) at Week 24. The UAS7 (range 0 to 42) was a composite of the weekly itch severity score (ISS7, range 0 to 21) and the weekly hive count score (HSS7, range 0 to 21). The results for primary and secondary endpoints in CUPID Study A and Study C are presented in the table below.

	CUPID Study A			**CUPID Study C**		
	Dupixent (N=68)	Placebo (N=68)	Dupixent vs. Placebo (95% CI)	Dupixent (N=73)	Placebo (N=75)	Dupixent vs. Placebo (95% CI)
Change from baseline in ISS7 at Week 24*	-10.44 (0.92)	-6.02 (0.94)	-4.42 (-6.84, -2.01)^	-8.50 (1.39)	-6.13 (1.38)	-2.37 (-4.48, -0.27)^
Change from baseline in UAS7 at Week 24*	-20.99 (1.77)	-11.95 (1.81)	-9.04 (-13.68, -4.40)^	-15.61 (2.62)	-11.27 (2.61)	-4.34 (-8.31. -0.36)^

**Values presented are LS mean change from baseline (SE) for continuous variables and number and percent of responders for binary variables*
^Values presented are LS mean differences

In CUPID Study A and Study C, improvements in ISS7 and UAS7 at Week 24 were consistent regardless of the patients' baseline IgE level.

Eosinophilic Esophagitis (EoE)

Eosinophilic esophagitis (EoE) is a chronic allergen/immune-mediated disease characterized by esophageal dysfunction and marked eosinophilic inflammation of the esophageal mucosa in the absence of secondary causes. EoE is characterized histologically with eosinophil-predominant inflammation confined to the esophagus. EoE is a progressive disease if left untreated, and the chronic inflammation can lead to tissue fibrosis and strictures in the esophagus. Atopic and allergic inflammatory conditions (e.g., asthma, atopic dermatitis, food/seasonal allergy) commonly occur concomitantly with EoE.

The symptoms of EoE are age dependent. Young children and infants may refuse to eat or have abdominal pain, trouble swallowing, or vomiting. In addition, persistent feeding difficulties may lead to weight loss or a failure to thrive. Older children and adults most commonly present with dysphagia to solid food, but may also have symptoms of chest pain or heartburn. Food impaction is a common cause for emergency room visits in these patients.

The diagnosis of EoE is suspected on the basis of chronic symptoms such as dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia, abdominal pain, and malnutrition. Due to the wide range of chronic symptoms, the diagnosis should be highly considered in the presence of concomitant atopic conditions and if there are endoscopic findings. Endoscopic findings associated with EoE include esophageal rings, longitudinal furrows, exudates, edema, strictures, or narrow caliber esophagus. When a patient's clinical presentation is suggestive of EoE, an esophageal biopsy should be performed. Patients with esophageal eosinophilia of greater than or equal to 15 eosinophils (eos) per high-power field (hpf) would be considered to have clinically suspected EoE. The eosinophilic infiltration should be isolated to the esophagus. It should be brought into consideration that diet and medications, including those used to treat EoE, may lead to a falsely negative result on esophageal biopsy, and an endoscopy would ideally be performed while on no treatment to maximize diagnostic sensitivity. The diagnosis is then finalized after evaluation shows that there are no significant other causes of symptoms and/or esophageal eosinophilia.

A summary of the EoE diagnostic criteria is as follows:

1. Symptoms of esophageal dysfunction and a clinical presentation suggestive of EoE
   [Next step: perform esophageal biopsy]
2. Esophageal eosinophilia of greater than or equal to 15 eos/hpf
   [Next step: evaluate for the presence of non-EoE disorders that cause or potentially contribute to esophageal eosinophilia]
3. Other causes of symptoms and/or esophageal eosinophilia have been excluded

Nonpharmacological treatment of EoE includes esophageal dilation and diet. Esophageal dilation is used to treat strictures and luminal narrowing and is conditionally recommended only for patients with dysphagia associated with strictures, noting that the dilation does not address the underlying inflammation or pathogenesis. Both elemental and elimination diets have been shown to be effective, however, barriers of adherence and cost make this treatment modality feasible only for select patients.

Proton pump inhibitors (PPIs) are a first line treatment option for patients with EoE, and PPI monotherapy is widely used in practice. PPIs have a longstanding safety profile and have shown to be effective based on symptom response and histological remission. In EoE, PPIs can provide benefit beyond acid suppression by decreasing expression of eotaxin-3 (the main cytokine that recruits eosinophils to the esophagus), improving esophageal barrier function, and helping to maintain esophageal epithelial transcriptional homeostasis.

Swallowed topical corticosteroids (STCs) are also a first line treatment option for patients with EoE. Both the American Gastroenterological Association (AGA) and the American College of Gastroenterology (ACG) strongly recommend their use. STCs have demonstrated histologic efficacy, a reduction in symptoms (including dysphagia), and improvement in endoscopic disease activity. In short term use of 3

months or less, STCs have a favorable safety profile, and studies have shown no increased risk of adverse events compared to placebo outside of candidal infection. Options for STCs include fluticasone propionate or budesonide. Fluticasone propionate is swallowed using commercially available metered dose inhalers (MDIs) and budesonide is consumed via an oral slurry using aqueous budesonide respules mixed with sucralose, honey, or maple syrup. An oral budesonide suspension is also commercially available for the treatment of EoE. Off-label use of asthma preparations of corticosteroids adapted for esophageal delivery have comparable histologic efficacy with preparations designed for esophageal delivery. A trial comparing fluticasone to budesonide showed similar efficacy between the two drugs, and either one is a reasonable choice for initial treatment based on patient/provider preference.

Diet, PPIs, and STCs work by treating the inflammatory component of the disease and can also lead to benefit in esophageal caliber. A single anti-inflammatory therapy should be used for initial treatment of EoE and should be selected based on disease characteristics and patient preference. Combination therapy with multiple anti-inflammatory drug therapies is not recommended due to a current lack of data. Treatment response should be assessed by clinical, endoscopic, and histologic disease activity 8 to 12 weeks after starting the new therapy. Assessing clinical symptom improvement alone is not sufficient since there is only a modest correlation between symptomatic improvement and histologic remission or endoscopic response. If adequate response is achieved, the current medication can be continued, noting that a decrease in dose may be warranted and desired for maintenance therapy. If a patient has non-response with initial treatment, a change in medication, dose, or formulation may be considered prior to stepping up to therapy with a biologic agent.

Maintenance therapy is needed for the treatment of EoE due to the chronic relapsing nature of the disease and the current understanding that it is a lifelong condition. When EoE treatment is stopped, regardless of the treatment used, disease activity and flares almost always recur. Fibrostenotic progression also occurs in most patients. Data supports the long-term efficacy of PPIs and dietary elimination for maintenance therapy, but STCs may also be used. Using STCs for maintenance therapy comes with the risk of long-term adverse effects (such as candidal infection or adrenal insufficiency), and they may also have a loss of response over time. If using STCs long-term, the lowest effective dose should be used. Studies involving the discontinuation of STCs following initial therapy have shown that the median time to symptom relapse after stopping treatment is about 3 months. Patients with rapid symptomatic/histologic relapse following STC initial therapy should consider reinitiating STC therapy based on shared decision-making. Patients with severe dysphagia, food impaction, or high-grade esophageal stricture may also consider reinitiation or maintenance therapy with a STC.

A biologic agent may be considered as a step-up therapy option in patients who do not respond to initial pharmacologic treatment, especially PPI non-responders. Dupilumab, an interleukin (IL)-4 receptor alpha antagonist, has been shown to decrease dysphagia symptoms and improve endoscopic and histologic severity in patients with EoE. Response should be assessed between 12 and 24 weeks after therapy is initiated. Data supports maintenance therapy with a biologic agent, and dupilumab demonstrated continued histologic, endoscopic, and symptom efficacy in patients treated for 52 weeks, with some patients having a higher response rate after 52 weeks than at 24 weeks.

The treatment algorithm for pediatric patients aligns with how the disease is managed in adults. This includes the use of biologic agents (e.g., dupilumab) for difficult-to-treat patients that do not respond to, or are intolerant of, alternative treatments.

Efficacy

A single randomized, double-blind, parallel-group, multicenter, placebo-controlled trial, including two 24-week treatment periods (Parts A and B), was conducted in adult and pediatric subjects 12 to 17 years of age, weighing at least 40 kg, with EoE (NCT03633617). In both parts, subjects were randomized to receive 300 mg Dupixent every week or placebo. Eligible subjects had greater than or equal to 15 intraepithelial eosinophils per high-power field (eos/hpf) following a treatment course of a proton pump inhibitor (PPI) either prior to or during the screening period and symptoms of dysphagia as measured by the Dysphagia Symptom Questionnaire (DSQ). At baseline, 43% of subjects in Part A and 37% of subjects in Part B had a history of prior esophageal dilations.

The coprimary efficacy endpoints in Parts A and B were the (1) proportion of subjects achieving histological remission defined as peak esophageal intraepithelial eosinophil count of less than or equal to 6 eos/hpf at week 24; and (2) the absolute change in the subject reported DSQ score from baseline to week 24.

In Parts A and B, a greater proportion of subjects randomized to Dupixent achieved histological remission (peak esophageal intraepithelial eosinophil count less than or equal to 6 eos/hpf) compared to placebo (Part A: 25% vs 2%; Part B: 47% vs 5%). Treatment with Dupixent also resulted in a significant improvement in LS mean change in DSQ score compared to placebo at week 24 (Part A: -21.9 vs -9.6; Part B -23.8 vs -13.9). The results of the anchor-based analyses that incorporated the subjects' perspectives indicated that the observed improvement in dysphagia from Parts A and B is representative of a clinically meaningful within-subject improvement.

Prurigo Nodularis (PN)

Prurigo nodularis (PN) is a skin disorder that is defined by the presence of chronic pruritus and multiple elevated, firm, and nodular lesions. PN is more common in older adults but can occur in children. The underlying cause of PN is unknown, but it appears neural and immunologic processes both play a role in its development. The nodules form in a subset of patients that have chronic pruritus, with the nodules forming in areas with continuous scratching over prolonged periods of time. There is significant disease burden associated with PN including sleep disruption, anxiety, and depression. The nodules are typically firm, dome-shaped, and itchy and range in size from millimeters to several centimeters. The nodules can range in color from flesh tones to brown/black and can range in number from a few to hundreds. The pruritis associated with PN can range from sporadic to continuous and generally the underlying cause is unknown. There are a number of conditions, both dermatologic and other diseases, that are associated with PN, such as atopic dermatitis, kidney disease, diabetes, and HIV.

The diagnosis of PN is generally one of exclusion. The American Academy of Dermatology (AAD) indicates that the diagnostic workup should include a clinical examination with a complete review of systems and assessment of PN severity, which should include both disease burden (e.g., quality of life, sleep disturbances) and pruritis intensity. The ADD notes three core features associated with PN:

- Presence of firm, nodular lesions
- Pruritus that lasts for at least 6 weeks
- History and/or signs of repeated scratching, picking, or rubbing

Management requires a multifaceted approach with a focus on reducing pruritis, interrupting the itch-scratch cycle, and healing lesions. General measures that should be used at baseline include gentle skin care, moisturizers, and antipruritic emollients. Treatment may need to address both the neural and immunologic components of pruritis based on patient signs and symptoms, and often involves the use of topical and systemic therapies. Most therapies for PN have not been adequately studied, and their evidence for use is based on small clinical trials, observational studies, and case reports.

Topical therapies are the initial treatment for limited disease. Topical corticosteroids (TCS) target the immunologic component of PN. The International Forum for the Study of Itch (IFSI) 2020 guideline on chronic prurigo including prurigo nodularis strongly recommends moderate to very potent topical corticosteroids on lesional skin. Intralesional corticosteroids may be directly injected into thicker lesions where required, but use should be limited to patients with less than 10 lesions. Topical calcineurin inhibitors and topical calcipotriol have also been used in patients who failed TCS therapy and a prolonged course of a topical immunomodulator is desired. Topical capsaicin, which targets the neural component of PN, has limited clinical evidence and tends to have short term efficacy.

Systemic therapies are used for widespread disease or disease refractory to topical therapy. Phototherapy is reasonably tolerated and addresses both the immunologic and neural components of PN. However, phototherapy combined with topical therapy will not be adequate for most patients, and the majority will require supplemental systemic therapy. Oral immunosuppressants, such as methotrexate and cyclosporine, have shown to reduce pruritis and heal lesions per limited data available. Methotrexate is generally preferred due to its more favorable side effect profile in comparison to cyclosporine, and cyclosporine should only be considered in more severe cases. Other systemic therapies that have shown to be less efficacious and treat the neural component of PN include thalidomide, gabapentin, pregabalin, antidepressants, aprepitant, and naltrexone. Since PN is a nonhistaminergic condition, antihistamines are unlikely to be effective and are not recommended.

Biologic agents are the first therapies to gain approval from the US Food and Drug Administration (FDA) for the treatment of PN. These immunomodulating drugs are believed to target molecules expressed by specific cell types that release a variety of itching mediators that directly or indirectly stimulate receptors on nerve endings in the skin. Biologic agents disrupt this cycle and have been proven to alleviate both pruritus and PN lesions.

Efficacy

The prurigo nodularis (PN) development program included two 24-week randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (PRIME [NCT04183335] and PRIME 2 [NCT04202679]) in 311 adult subjects 18 years of age and older with pruritus (WINRS greater than or equal to 7 on a scale of 0 to 10) and greater than or equal to 20 nodular lesions. PRIME and PRIME 2 assessed the effect of Dupixent on pruritus improvement as well as its effect on PN lesions. In these two trials, subjects received either subcutaneous Dupixent 600 mg (two 300 mg injections) on day 1, followed by 300 mg once every other week (Q2W) for 24 weeks, or matching placebo.

At baseline, the mean Worst Itch-Numeric Rating Scale (WI-NRS) was 8.5, 66% had 20 to 100 nodules (moderate), and 34% had greater than 100 nodules (severe). Patients were required to have failed at least a 2-week trial of a medium to super potent topical corticosteroid or topical corticosteroids were not medically advised. The WI-NRS is comprised of a single item, rated on a scale from 0 (no itch) to 10

(worst imaginable itch). Subjects were asked to rate the intensity of their worst pruritus (itch) over the past 24 hours using this scale. The Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA PN-S) is a scale that measures the approximate number of nodules using a 5-point scale from 0 (clear) to 4 (severe).

Efficacy was assessed with the proportion of subjects with improvement (reduction) in WI-NRS by greater than or equal to 4 points, the proportion of subjects with IGA PN-S 0 or 1 (the equivalent of 0-5 nodules), and the proportion of subjects who achieved a response in both WI-NRS and IGA PN-S per the criteria described above. Overall, patients treated with Dupixent saw improvement in all endpoints over placebo.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of dupilumab (Dupixent) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "11"):

1. **ONE** of the following ("a", "b", or "c"):
    a. The member has been treated with dupilumab (starting on samples is not approvable) within the past 90 days
    b. The prescriber states the member has been treated with dupilumab (starting on samples is not approvable) within the past 90 days **AND** is at risk if therapy is changed
    c. **BOTH** of the following ('i" and "ii"):
        i. Dupilumab will be used for the treatment of an indication listed in the Table, and **ALL** of the indication-specific criteria are met
        ii. **EITHER** of the following if the member has an FDA-approved indication ("I" or "II"):
            I. The member's age is within FDA labeling for the requested indication for dupilumab
            II. The prescriber has provided information in support of using dupilumab for the member's age for the requested indication
2. If the member has a diagnosis of moderate-to-severe atopic dermatitis (AD), then **BOTH** of the following ("a" and "b"):
    a. The member is currently treated with topical emollients and practicing good skin care
    b. The member will continue the use of topical emollients and good skin care practices in combination with the requested agent
3. If the member has a diagnosis of bullous pemphigoid (BP), then **ONE** of the following ("a", "b", or "c"):

a. The member will be using a tapering course of an oral corticosteroid started at a dose of at least 0.5 mg prednisone/kg/day (or an equivalent) in combination with dupilumab

b. The member has an intolerance, hypersensitivity, or FDA labeled contraindication to **ALL** oral corticosteroids used in the treatment of BP

c. The member is currently treated with dupilumab **AND** after achieving initial control of disease activity, concurrent oral corticosteroids were tapered and discontinued

4. If the member has a diagnosis of chronic obstructive pulmonary disease (COPD), then **ALL** of the following:

   a. **ONE** of the following:

      i. The member is currently treated with an inhaled corticosteroid (ICS) for at least 3 months **AND** has been adherent for 90 days within the past 120 days

      ii. The member has an intolerance or hypersensitivity to **ONE** inhaled corticosteroid

      iii. The member has an FDA labeled contraindication to **ALL** inhaled corticosteroids

   b. **ONE** of the following:

      i. The member is currently treated with a long-acting muscarinic antagonist (LAMA) **AND** a long-acting beta-2 agonist (LABA) used in combination for at least 3 months **AND** has been adherent for 90 days within the past 120 days

      ii. The member has an intolerance or hypersensitivity to therapy with a LAMA **AND** a LABA used in combination

      iii. The member has an FDA labeled contraindication to **ALL** long-acting muscarinic antagonists (LAMA) AND long-acting beta-2 agonists (LABA)

   c. The member will continue COPD inhaled maintenance therapy (e.g., ICS/LAMA/LABA triple therapy, LAMA/LABA) in combination with the requested agent

5. If the member has a diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP), then **BOTH** of the following ("a" and "b'):

   a. The member is currently treated with standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids [e.g., fluticasone nasal spray, mometasone nasal spray, Sinuva])

   b. The member will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids [e.g., fluticasone nasal spray, mometasone nasal spray, Sinuva]) in combination with dupilumab

6. If the member has a diagnosis of chronic spontaneous urticaria (CSU) [otherwise known as chronic idiopathic urticaria [CIU]], then **ONE** of the following ("a" or "b"):

   a. **BOTH** of the following:

      i. The member is currently treated with second-generation H1-antihistamine therapy (e.g., cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine)

      ii. The member will continue second-generation H1-antihistamine therapy in combination with dupilumab

   b. The member has an intolerance, hypersensitivity, or FDA labeled contraindication to **ALL** second-generation H1-antihistamines

7. If the member has a diagnosis of moderate-to-severe asthma, then **ALL** of the following ("a", "b", and "c"):
    a. **ONE** of the following ("i", "ii", "iii", or "iv"):
        i. The member is **NOT** currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including dupilumab) **AND** is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days
        ii. The member is currently being treated with a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma (including dupilumab), **AND ONE** of the following:
            - The member is currently treated with an inhaled corticosteroid for at least 3 months that is adequately dosed to control symptoms **AND** has been adherent for 90 days within the past 120 days
            - The member Is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **AND** has been adherent for 90 days within the past 120 days
        iii. The member has an intolerance or hypersensitivity to **ONE** inhaled corticosteroid
        iv. The member has an FDA labeled contraindication to **ALL** inhaled corticosteroids
    b. **ONE** of the following ("i", "ii", or "iii"):
        i. The member is currently being treated for at least 3 months **AND** has been adherent for 90 days within the past 120 days with **ONE** of the following:
            - A long-acting beta-2 agonist (LABA)
            - Long-acting muscarinic antagonist (LAMA)
            - A leukotriene receptor antagonist (LTRA)
            - Theophylline
        ii. The member has an intolerance or hypersensitivity to **ONE** long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonist (LTRA), or theophylline
        iii. The member has an FDA labeled contraindication to **ALL** long-acting beta-2 agonists (LABA) **AND** long-acting muscarinic antagonists (LAMA)
    c. The member will continue asthma control therapy (e.g., ICS, ICS/LABA, LTRA, LAMA, theophylline) in combination with dupilumab
8. The prescriber is a specialist in the area of the member's diagnosis (e.g., atopic dermatitis, BP, CSU, or prurigo nodularis - dermatologist, allergist, immunologist; asthma or COPD - allergist, immunologist, pulmonologist; CRSwNP -otolaryngologist, allergist, pulmonologist; EoE - allergist, immunologist, gastroenterologist), **OR** the prescriber has consulted with a specialist in the area of the member's diagnosis
9. The member does **NOT** have any FDA labeled contraindications to Dupixent
10. The member will **NOT** be using dupilumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi

(deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq/Rinvoq LQ (upadacitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast); Rhapsido (remibrutinib), Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]

11. **ONE** of the following ("a", "b", or "c"):
    a. The requested quantity (dose) does **NOT** exceed the following based on indication and the member's age and weight:
        i. Atopic dermatitis
            - Adults (18 years of age and older)
                - Loading dose: 600 mg [two 300 mg injections] as a single dose (Week 0)
                - Subsequent doses: 300 mg every two weeks starting at Week 2
                    - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
                    - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days
            - Pediatric members (6 months to 17 years of age)
                - Weight of 5 kg to less than 15 kg: 200 mg every four weeks (no loading dose)
                    - QL: 200 mg/1.14 mL pre-filled syringe - 1 syringe (1.14 mL) per 28 days
                    - QL: 200 mg/1.14 mL pre-filled pen injector - 1 pen (1.14 mL) per 28 days
                - Weight of 15 kg to less than 30 kg (6 months to 5 years of age): 300 mg every four weeks (no loading dose)
                    - QL: 300 mg/2 mL pre-filled syringe - 1 syringe (2 mL) per 28 days
                    - QL: 300 mg/2 mL pre-filled pen injector - 1 pen (2 mL) per 28 days
                - Weight of 15 kg to less than 30 kg (6 to 17 years of age)
                    - Loading dose: 600 mg [two 300 mg injections] as a single dose (Week 0)
                    - Subsequent doses: 300 mg every four weeks starting at Week 4
                        - QL: 300 mg/2 mL pre-filled syringe - 1 syringe (2 mL) per 28 days
                        - QL: 300 mg/2 mL pre-filled pen injector - 1 pen (2 mL) per 28 days
                - Weight of 30 kg to less than 60 kg
                    - Loading dose: 400 mg [two 200 mg injections] as a single dose (Week 0)
                    - Subsequent doses: 200 mg every two weeks starting at Week 2
                        - QL: 200 mg/1.14 mL pre-filled syringe - 2 syringes (2.28 mL) per 28 days
                        - QL: 200 mg/1.14 mL pre-filled pen injector - 2 pens (2.28 mL) per 28 days
                - Weight of 60 kg or more
                    - Loading dose: 600 mg [two 300 mg injections] as a single dose (Week 0)
                    - Subsequent doses: 300 mg every two weeks starting at Week 2
                        - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days

- QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

ii. Bullous pemphigoid
- Loading dose: 600 mg [two 300 mg injections] as a single dose (Week 0)
- Subsequent doses: 300 mg every two weeks starting at Week 2
  - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
  - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

iii. Chronic rhinosinusitis with nasal polyposis and COPD - 300 mg every two weeks (no loading dose)
- QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
- QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

iv. Chronic spontaneous urticaria
- Adults (18 years of age and older):
  - Loading dose: 600 mg [two 300 mg injections] as a single dose (Week 0)
  - Subsequent doses: 300 mg every two weeks starting at Week 2
    - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days
- Pediatric members (12 to 17 years of age)
  - Weight of 30 kg to less than 60 kg:
    - Loading dose: 400 mg [two 200 mg injections] as a single dose (Week 0)
    - Subsequent doses: 200 mg every two weeks starting at Week 2
      - QL: 200 mg/1.14 mL pre-filled syringe - 2 syringes (2.28 mL) per 28 days
      - QL: 200 mg/1.14 mL pre-filled pen injector - 2 pens (2.28 mL) per 28 days
  - Weight of 60 kg or more:
    - Loading dose: 600 mg [two 300 mg injections] as a single dose (Week 0)
    - Subsequent doses: 300 mg every two weeks starting at Week 2
      - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
      - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

v. Eosinophilic esophagitis
- Weight of 15 kg to less than 30 kg - 200 mg every two weeks (no loading dose)
  - QL: 200 mg/1.14 mL pre-filled syringe - 2 syringes (2.28 mL) per 28 days
  - QL: 200 mg/1.14 mL pre-filled pen injector - 2 pens (2.28 mL) per 28 days
- Weight of 30 kg to less than 40 kg - 300 mg every two weeks (no loading dose)
  - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days

- QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

- Weight of 40 kg or more - 300 mg every week (no loading dose)
  - QL: 300 mg/2 mL pre-filled syringe - 4 syringes (8 mL) per 28 days
  - QL: 300 mg/2 mL pre-filled pen injector - 4 pens (8 mL) per 28 days

vi. Moderate-to-severe asthma

- 12 years of age and older:
  - Loading dose: 600 mg as a single dose (Week 0)
  - Subsequent doses: 300 mg every two weeks starting at Week 2
    - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled pen injector – 2 pens (4 mL) per 28 days
- 6 to 11 years of age (no loading dose):
  - Weight of 15 kg to less than 30 kg: 100 mg every other week, **OR** 300 mg every four weeks
    - QL: 100 mg/0.67 mL pre-filled syringe - 2 syringes (1.34 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled syringe - 1 syringe (2 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled pen injector – 1 pen (2 mL) per 28 days
  - Weight of 30 kg or greater: 200 mg every other week
    - QL: 200 mg/1.14 mL pre-filled syringe - 2 syringes (2.28 mL) per 28 days
    - QL: 200 mg/1.14 mL pre-filled pen injector - 2 pens (2.28 mL) per 28 days

vii. Prurigo nodularis

- Loading dose: 600 mg [two 300 mg injections] as a single dose (Week 0)
- Subsequent doses: 300 mg every two weeks starting at Week 2
  - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
  - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

OR

b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** there is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does **NOT** exceed the program quantity limit

OR

c. The requested indication does **NOT** have a maximum FDA labeled dose, **AND** there is support for therapy with a higher dose for the requested indication

Table 1

Indications and Specific Criteria	
Indication	**Specific Criteria**
Moderate-to-severe atopic dermatitis (AD)	When **BOTH** of the following are met ("1" and "2"): 1. **ONE** of the following ("a", "b", "c", or "d"): a. The member has at least 10% body surface area involvement **OR** b. The member has involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) **OR** c. The member has an Eczema Area and Severity Index (EASI) score of greater than or equal to 16 **OR** d. The member has an Investigator Global Assessment (IGA) score of greater than or equal to 3 **AND** 2. **EITHER** of the following ("a" or "b"): a. **BOTH** of the following ("i" and "ii"): i. **ONE** of the following: • The member has tried and had an inadequate response to **ONE** at least medium-potency topical corticosteroid used in the treatment of AD after at least a 4-week duration of therapy **OR** • The member has an intolerance or hypersensitivity to **ONE** at least medium-potency topical corticosteroid used in the treatment of AD **OR** • The member has an FDA labeled contraindication to **ALL** medium-, high-, and super-potency topical corticosteroids used in the treatment of AD **AND** ii. **ONE** of the following:

	• The member has tried and had an inadequate response to **ONE** topical calcineurin inhibitor (e.g., Elidel/pimecrolimus, Protopic/tacrolimus) used in the treatment of AD after at least a 6-week duration of therapy **OR** • The member has an intolerance or hypersensitivity to **ONE** topical calcineurin inhibitor in the treatment of AD **OR** • The member has an FDA labeled contraindication to **ALL** topical calcineurin inhibitors used in the treatment of AD **OR** b. The member's medication history indicates use of another biologic immunomodulator agent with an FDA-approved indication for AD **OR** supported in DrugDex with 1 or 2a level of evidence or AHFS for AD
Moderate-to-severe asthma	When **BOTH** of the following are met ("1" and "2"): 1. **ONE** of the following ("a" or "b"): a. The member has eosinophilic type asthma, **AND** the diagnosis has been confirmed by **ONE** of the following: i. The member has a baseline (prior to therapy with dupilumab) blood eosinophilic count of 150 cells/microliter or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids **OR** ii. The member has a fraction of exhaled nitric oxide (FeNO) of 20 parts per billion or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids **OR** iii. The member has sputum eosinophils 2% or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids **OR** b. The member has oral corticosteroid dependent type asthma **AND** 2. **EITHER** of the following ("a" or "b"): a. The member has a history of uncontrolled asthma while on asthma control therapy (e.g., inhaled corticosteroid [ICS]/long-acting beta-2

	agonist [LABA] combination therapy) as demonstrated by **ONE** of the following: • Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months **OR** • Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months **OR** • Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered **OR** • Baseline (prior to therapy with dupilumab) Forced Expiratory Volume (FEV1) that is less than 80% of predicted **OR** b. The member's medication history indicates use of a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of asthma within the past 12 months (treatment on samples is not approvable)
Bullous pemphigoid (BP)	When **ALL** of the following are met ("1" and "4"): 1. The member has clinical features of BP (e.g., urticarial or eczematous or erythematous plaques, bullae, pruritus) **AND** 2. The member's diagnosis was confirmed by histopathologic, immunopathologic, and serologic assessment **AND** 3. The member has a baseline (prior to therapy with dupilumab) Bullous Pemphigoid Disease Area Index (BPDAI) activity score of greater than or equal to 24 **AND** 4. The member has **ONE** of the following: a. Tried and had an inadequate response to **ONE** super-potent topical corticosteroid (e.g., clobetasol propionate) used in the treatment of BP after at least a 4-week duration of therapy **OR**

	b. Tried and had an inadequate response to **ONE** oral corticosteroid started at a dose of at least 0.5 mg prednisone/kg/day (or an equivalent) used in the treatment of BP after at least a 3-week duration of therapy (**NOTE**: tapering of the dose within the 3-week duration is approvable) **OR** c. An intolerance or hypersensitivity to **ONE** super-potent topical corticosteroid or oral corticosteroid used in the treatment of BP **OR** d. An FDA labeled contraindication to **ALL** super-potent topical corticosteroids **AND** oral corticosteroids used in the treatment of BP
Chronic obstructive pulmonary disease (COPD)	When **ALL** of the following are met ("1", "2" and "3"): 1. The member's diagnosis was confirmed by spirometry with a post-bronchodilator FEV1/FVC ratio less than 0.7 **AND** 2. The member has an eosinophilic phenotype defined by a baseline (prior to therapy with dupilumab) blood eosinophil count of 300 cells/microliter or higher **AND** 3. **EITHER** of the following ("a" or "b"): a. The member has a history of inadequately controlled COPD while on COPD inhaled maintenance therapy as demonstrated by **EITHER** of the following ("i" or "ii"): i. Frequent COPD exacerbations (i.e., 2 or more moderate exacerbations) requiring one or more courses of systemic corticosteroids within the past 12 months **OR** ii. A severe COPD exacerbation requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months **OR** b. The member's medication history indicates use of a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of COPD within the past 12 months (treatment on samples is not approvable)

Chronic rhinosinusitis with nasal polyposis (CRSwNP)	When **ALL** of the following are met ("1" to "4"): 1. The member has at least **TWO** of the following symptoms consistent with chronic rhinosinusitis (CRS): a. Nasal discharge (rhinorrhea or post-nasal drainage) b. Nasal obstruction or congestion c. Loss or decreased sense of smell (hyposmia) d. Facial pressure or pain **AND** 2. The member has had symptoms consistent with CRS for at least 12 consecutive weeks **AND** 3. The member's diagnosis was confirmed by **ONE** of the following ("a", "b", or "c"): a. Anterior rhinoscopy **OR** b. Nasal endoscopy **OR** c. Computed tomography (CT) of the sinuses **AND** 4. **ONE** of the following ("a", "b", or "c"): a. The member has tried and had an inadequate response to **ONE** intranasal corticosteroid (e.g., fluticasone nasal spray, mometasone nasal spray, Sinuva) after at least a 4-week duration of therapy **OR** b. The member has an intolerance or hypersensitivity to **ONE** intranasal corticosteroid (e.g., fluticasone nasal spray, mometasone nasal spray, Sinuva) **OR** c. The member has an FDA labeled contraindication to **ALL** intranasal corticosteroids
Chronic spontaneous urticaria (CSU)	When **ALL** of the following are met ("1" to "3"): 1. The member has had hives and itching for more than 6 weeks **AND**

[otherwise known as chronic idiopathic urticaria (CIU)]	2. The prescriber has evaluated the member to determine if the member is currently treated with medications known to cause or worsen urticaria (e.g., NSAIDs) in order to reduce urticaria risk **AND** 3. The member has **ONE** of the following ("a", "b", or "c"): a. Has tried and had an inadequate response to the FDA-labeled maximum dose of **ONE** second-generation H-1 antihistamine (e.g., cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine) after at least a 2-week duration of therapy, **AND ONE** of the following: i. The member has tried and had an inadequate response to a maximally tolerated dose of **ONE** second-generation H1-antihistamine titrated up to 4 times above the FDA labeled maximum dose after at least a 2-week duration of therapy **OR** ii. There is support that the member cannot be treated with a second-generation H-1 antihistamine at a dose above the FDA labeled maximum dose **OR** b. An intolerance or hypersensitivity to therapy with **ONE** second-generation H-1 antihistamine **OR** c. An FDA labeled contraindication to **ALL** second-generation H-1 antihistamines
Eosinophilic esophagitis (EoE)	When **ALL** of the following are met ("1", "2", and "3"): 1. The member's diagnosis has been confirmed by **ALL** of the following: a. Chronic symptoms of esophageal dysfunction **AND** b. Greater than or equal to 15 eosinophils per high-power field on esophageal biopsy **AND** c. Other causes that may be responsible for or contributing to symptoms and esophageal eosinophilia have been ruled out **AND** 2. **ONE** of the following: a. The member has tried and had an inadequate response to **ONE** standard corticosteroid therapy (i.e., budesonide oral suspension,

	swallowed budesonide nebulizer solution, swallowed fluticasone from a metered dose inhaler [MDI]) used in the treatment of EoE after at least an 8-week duration of therapy **OR** b. The member has an intolerance or hypersensitivity to **ONE** standard corticosteroid therapy used in the treatment of EoE **OR** c. The member has an FDA-labeled contraindication to **ALL** standard corticosteroid therapy used in the treatment of EoE **OR** d. The member has tried and had an inadequate response to **ONE** proton pump inhibitor (PPI) used in the treatment of EoE after at least an 8-week duration of therapy **OR** e. The member has an intolerance or hypersensitivity to **ONE** PPI used in the treatment of EoE **OR** f. The member has an FDA labeled contraindication to **ALL** PPI therapies used in the treatment of EoE **AND** 3. The member weighs 15 kg (33 lbs) or greater
Prurigo nodularis (PN)	When **BOTH** of the following are met ("1" and "2"): 1. The member has **ALL** of the following features associated with PN: a. Presence of greater than or equal to 20 firm, nodular lesions **AND** b. Pruritus that has lasted for at least 6 weeks **AND** c. History and/or signs of repeated scratching, picking, or rubbing **AND** 2. **ONE** of the following: a. The member has tried and had an inadequate response to **ONE** at least medium-potency topical corticosteroid used in the treatment of PN after at least a 2-week duration of therapy **OR**

	b. The member has an intolerance or hypersensitivity to **ONE** at least medium-potency topical corticosteroid used in the treatment of PN **OR** c. The member has an FDA-labeled contraindication to **ALL** medium-, high-, and super-potency topical steroids used in the treatment of PN **OR** **d.** The member's medication history indicates use of a biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of PN
Other indications	The member has another FDA-approved indication for subcutaneous dupilumab **OR** an indication supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium 1 or 2a recommended use for subcutaneous dupilumab
Approval duration*: 6 months for moderate-to-severe AD, moderate-to-severe asthma, CRSwNP, CSU, EoE, and PN; 9 months for BP; 12 months for COPD and all other indications *Please approve initial loading dose for asthma (age 12 years and older), atopic dermatitis (age 5 years and older), BP, CSU, and PN **ONLY**	

Continuation of dupilumab (Dupixent) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to 11"):

1. An authorization or reauthorization for dupilumab has been previously approved by Florida Blue [Note: members not previously approved for the requested agent will require initial evaluation review]
2. The member has had clinical benefit with dupilumab
3. If the member has a diagnosis of moderate-to-severe atopic dermatitis (AD), then the member will continue standard maintenance therapies (e.g., topical emollients, good skin care practices) in combination with dupilumab
4. If the member has a diagnosis of moderate to severe asthma, then the member is currently treated within the past 90 days and is compliant with asthma control therapy [e.g., inhaled corticosteroids (ICI), ICS/long-acting beta-2 agonist (LABA), leukotriene receptor antagonist (LTRA), long-acting muscarinic antagonist (LAMA), theophylline]
5. If the member has a diagnosis of chronic obstructive pulmonary disease (COPD), then the member is currently treated within the past 90 days and is compliant with COPD inhaled maintenance therapy (i.e., inhaled corticosteroid [ICS]/long-acting muscarinic antagonist [LAMA]/long-acting beta-2 agonist [LABA] triple therapy, LAMA/LABA dual therapy)
6. If the member has a diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP), then the member will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids [e.g., fluticasone nasal spray, mometasone nasal spray, Sinuva]) in combination with dupilumab

7. If the member has a diagnosis of chronic spontaneous urticaria (CSU) [otherwise known as chronic idiopathic urticaria [CIU]], then **ONE** of the following ("a" or "b"):
    a. The member will continue second-generation H1-antihistamine therapy (e.g., cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine) in combination with dupilumab
    b. The member has an intolerance, hypersensitivity, or FDA labeled contraindication to ALL second-generation H1-antihistamines
8. The prescriber is a specialist in the area of the member's diagnosis (e.g., atopic dermatitis, BP, CSU, or prurigo nodularis - dermatologist, allergist, immunologist; asthma or COPD - allergist, immunologist, pulmonologist; CRSwNP - otolaryngologist, allergist, pulmonologist; EoE - allergist, immunologist, gastroenterologist), **OR** the prescriber has consulted with a specialist in the area of the member's diagnosis
9. The member does **NOT** have any FDA-labeled contraindications to Dupixent
10. The member will **NOT** be using dupilumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq/Rinvoq LQ (upadacitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast); Rhapsido (remibrutinib), Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
11. **ONE** of the following ("a", "b", or "c"):
    a. The requested quantity (dose) does **NOT** exceed the following based on indication and the member's age and weight:
        i. Atopic dermatitis
            - Adults (18 years of age and older): 300 mg every two weeks starting at Week 2
                - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
                - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days
            - Pediatric members (6 months to 17 years of age)
                - Weight of 5 kg to less than 15 kg: 200 mg every four weeks (no loading dose)
                    - QL: 200 mg/1.14 mL pre-filled syringe - 1 syringe (1.14 mL) per 28 days
                    - QL: 200 mg/1.14 mL pre-filled pen injector - 1 pen (1.14 mL) per 28 days
                - Weight of 15 kg to less than 30 kg (6 months to 5 years of age): 300 mg every four weeks (no loading dose)
                    - QL: 300 mg/2 mL pre-filled syringe - 1 syringe (2 mL) per 28 days
                    - QL: 300 mg/2 mL pre-filled pen injector - 1 pen (2 mL) per 28 days
                - Weight of 15 kg to less than 30 kg (6 to 17 years of age): 300 mg every four weeks starting at Week 4
                    - QL: 300 mg/2 mL pre-filled syringe - 1 syringe (2mL) per 28 days
                    - QL: 300 mg/2 mL pre-filled pen injector - 1 pen (2 mL) per 28 days
                - Weight of 30 kg to less than 60 kg: 200 mg every two weeks starting at Week 2

        - QL: 200 mg/1.14 mL pre-filled syringe - 2 syringes (2.28 mL) per 28 days
        - QL: 200 mg/1.14 mL pre-filled pen injector - 2 pens (2.28 mL) per 28 days
    - Weight of 60 kg or more: 300 mg every two weeks starting at Week 2
        - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
        - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

ii. Bullous pemphigoid - 300 mg every two weeks starting at Week 2
- QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
- QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

iii. Chronic rhinosinusitis with nasal polyposis and COPD - 300 mg every two weeks
- QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
- QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

iv. Chronic spontaneous urticaria
- Adults (18 years of age and older): 300 mg every two weeks starting at Week 2
    - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days
- Pediatric members (12 to 17 years of age)
    - Weight of 30 kg to less than 60 kg: 200 mg every two weeks starting at Week 2
        - QL: 200 mg/1.14 mL pre-filled syringe - 2 syringes (2.28 mL) per 28 days
        - QL: 200 mg/1.14 mL pre-filled pen injector - 2 pens (2.28 mL) per 28 days
    - Weight of 60 kg or more: 300 mg every two weeks starting at Week 2
        - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
        - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

v. Eosinophilic esophagitis
- Weight of 15 kg to less than 30 kg - 200 mg every two weeks (no loading dose)
    - QL: 200 mg/1.14 mL pre-filled syringe - 2 syringes (2.28 mL) per 28 days
    - QL: 200 mg/1.14 mL pre-filled pen injector - 2 pens (2.28 mL) per 28 days
- Weight of 30 kg to less than 40 kg - 300 mg every two weeks (no loading dose)
    - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days
- Weight of 40 kg or more - 300 mg every week (no loading dose)
    - QL: 300 mg/2 mL pre-filled syringe - 4 syringes (8 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled pen injector - 4 pens (8 mL) per 28 days

vi. Moderate-to-severe asthma

- 12 years of age and older: 300 mg every two weeks starting at Week 2
    - QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled pen injector – 2 pens (4 mL) per 28 days
- 6 to 11 years of age
- Weight of 15 kg to less than 30 kg: 100 mg every other week, **OR** 300 mg every four weeks
    - QL: 100 mg/0.67 mL pre-filled syringe - 2 syringes (1.34 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled syringe - 1 syringe (2 mL) per 28 days
    - QL: 300 mg/2 mL pre-filled pen injector – 1 pen (2 mL) per 28 days
- Weight of 30 kg or greater: 200 mg every other week
    - QL: 200 mg/1.14 mL pre-filled syringe - 2 syringes (2.28 mL) per 28 days
    - QL: 200 mg/1.14 mL pre-filled pen injector - 2 pens (2.28 mL) per 28 days

vii. Prurigo nodularis - 300 mg every two weeks starting at Week 2

- QL: 300 mg/2 mL pre-filled syringe - 2 syringes (4 mL) per 28 days
- QL: 300 mg/2 mL pre-filled pen injector - 2 pens (4 mL) per 28 days

OR

b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** there is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does **NOT** exceed the program quantity limit

OR

c. The requested indication does **NOT** have a maximum FDA labeled dose, **AND** there is support for therapy with a higher dose for the requested indication

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Atopic dermatitis

- For the treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids. Dupilumab is administered by subcutaneous injection. A member may self-inject after training in subcutaneous injection technique using the pre-filled syringe or pre-filled pen. The pre-filled

pen is only for use in adults and adolescents aged 12 years and older. In adolescents 12 years of age and older, it is recommended that dupilumab be given by or under the supervision of an adult. Dupixent pre-filled syringe should be given by a caregiver in pediatric patients 6 months to 11 years of age. Before injection, the pre-filled syringe or pen should be removed from the refrigerator and allowed to reach room temperature (45 minutes for 300 mg and 30 min for 200 mg).

- The recommended dose in adults (18 years of age and older) is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (every 2 weeks). The recommended dose in pediatric and adolescent patients (6 to 17 years of age) is based on weight. For weight of 15 kg to less than 30 kg, the recommended dose is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every four weeks. For weight of 30 kg to less than 60 kg, the recommended dose is an initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week (every 2 weeks). For weight of 60 kg or more, the recommended dose is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (every 2 weeks). The recommended dose in patients 6 months to 5 years of age is also based on weight. For weight of 5 kg to less than 15 kg, the recommended dose is 200 mg given every four weeks. For weight of 15 kg to less than 30 kg, the recommended dose is 300 mg given every four weeks. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Asthma

- Indicated as an add-on maintenance treatment in patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. The package label includes the following “Limitation of Use” statement - “Dupixent is not indicated for the relief of acute bronchospasm or status asthmaticus”. Dupilumab is administered by subcutaneous injection. A member may self-inject after training in subcutaneous injection technique using the pre-filled syringe or pre-filled pen. The pre-filled pen is only for use in adults and adolescents aged 12 years and older. In adolescents 12 years of age and older, it is recommended that dupilumab be given by or under the supervision of an adult. Dupixent pre-filled syringe should be given by a caregiver in children 6 to 11 years of age. Before injection, the pre-filled syringe or pen should be removed from the refrigerator and allowed to reach room temperature (45 minutes for 300 mg and 30 min for 100 and 200 mg).
- The recommended dose for adults and adolescents (12 years of age and older) is:
    - An initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week (every 2 weeks), **OR**
    - An initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week (every 2 weeks).
    - For patients with oral corticosteroids-dependent asthma, or with co-morbid moderate-to-severe atopic dermatitis, start with an initial dose of 600 mg followed by 300 mg given every other week (every 2 weeks).
- The recommended dose for pediatric patients (6 to 11 years of age) is:
    - 15 to less than 30 kg - 100 mg every other week (every 2 weeks), **OR** 300 mg every four weeks
    - 30 kg or greater - 200 mg every other week (every 2 weeks).
    - No initial loading dose is recommended
    - For pediatric patients with asthma **AND** co-morbid moderate-to-severe atopic dermatitis, follow the recommended dosage for atopic dermatitis which includes an initial loading dose

Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)

- Indicated as an add-on maintenance treatment in adult and pediatric patients aged 12 years and older with inadequately controlled chronic rhinosinusitis with nasal polyposis.
- The recommended dose for adult patients and pediatric patients 12 years of age and older is 300 mg given every other week (every 2 weeks).

Eosinophilic esophagitis (EoE)

- Indicated for the treatment of adult and pediatric patients aged 1 year and older, weighing at least 15 kg, with eosinophilic esophagitis.
- The recommended dosage is:
  - 15 to less than 30 kg - 200 mg every other week (every 2 weeks)
  - 30 to less than 40 kg - 300 mg every other week (every 2 weeks)
  - 40 kg or greater - 300 mg every week
  - No initial loading dose is recommended.

Prurigo Nodularis (PN)

- Indicated for the treatment of adult patients with prurigo nodularis.
- The recommended dose for adult patients is an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week (every 2 weeks)

Chronic Obstructive Pulmonary Disease (COPD)

- Indicated as an add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype. Limitations of Use (per the package insert): Dupixent is not indicated for the relief of acute bronchospasm.
- The recommended dose for adult patients is 300 mg given every other week (every 2 weeks).

Chronic Spontaneous Urticaria (CSU)

- Indicated for the treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria who remain symptomatic despite H1 antihistamine treatment. Limitations of Use (per the package insert): Dupixent is not indicated for treatment of other forms of urticaria.
- The recommended dosage is based on age and weight:
  - Adults (18 years and older) - initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every 2 weeks
  - Ages 12 to 17 years:
    - 30 to less than 60 kg - initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every 2 weeks
    - 60 kg or more - initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every 2 weeks

Bullous Pemphigoid (BP)

- Indicated for the treatment of adult patients with bullous pemphigoid.
- The recommended dosage for adult patients is an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every 2 weeks
- Use in combination with a tapering course of oral corticosteroids. Once disease control has occurred, gradually taper corticosteroids after which continue Dupixent as monotherapy. In case of relapse, corticosteroids may be added if medically advisable.

Dose Adjustments

- No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of dupilumab was conducted

Drug Availability

- Carton containing two single-dose, pre-filled pens (300 mg/2 mL)
- Carton containing two single-dose, pre-filled syringes (300 mg/2 mL) with needle shield
- Carton containing two single-dose, pre-filled pens (200 mg/1.14 mL)
- Carton containing two single-dose, pre-filled syringes (200 mg/1.14 mL) with needle shield
- Carton containing two single-dose, pre-filled syringes (100 mg/0.67 mL) with needle shield
- Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. If necessary, dupilumab may be kept at room temperature up to 77°F (25°C) for a maximum of 14 days.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Known hypersensitivity to dupilumab or any of its excipients

Precautions/Warnings

- **Hypersensitivity** - Hypersensitivity reactions, including anaphylaxis, acute generalized exanthematous pustulosis (AGEP), serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme have been reported. A case of AGEP was reported in an adult subject who participated in the bullous pemphigoid development program. If a clinically significant hypersensitivity reaction occurs, discontinue dupilumab immediately and initiate appropriate therapy.
- **Conjunctivitis and Keratitis** - Conjunctivitis and keratitis adverse reactions have been reported in clinical trials. Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received dupilumab. Among asthma subjects the frequency of conjunctivitis was similar to placebo. In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the dupilumab group vs. 1% in the placebo group in the 24-week safety pool; these subjects recovered. There were no cases of keratitis

reported in the CRSwNP development program. Among subjects with EoE, there were no reports of conjunctivitis and keratitis in the dupilumab group in placebo-controlled trials. In subjects with PN, the frequency of conjunctivitis was 4% in the dupilumab group compared to 1% in the placebo group; these subjects recovered or were recovering during the treatment period. There were no cases of keratitis reported in the PN development program. Among subjects with COPD, the frequency of conjunctivitis and keratitis was 1.4% and 0.1% in the dupilumab group and 1% and 0% in the placebo group, respectively. In subjects with CSU, the frequency of conjunctivitis was similar between dupilumab and placebo. There were no cases of keratitis reported in the CSU development program. Among subjects with BP, the frequency of conjunctivitis and keratitis was 7.5% and 3.8% in the dupilumab group and 0% and 0% in the placebo group, respectively. Advise patient or their caregiver to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination for patients who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis, as appropriate.

- **Eosinophilic Conditions** – Patients being treated for asthma may present with clinical features of eosinophilic pneumonia or eosinophilic granulomatosis with polyangiitis (EGPA). These events may be associated with the reduction of oral corticosteroid therapy. Healthcare providers should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, kidney injury, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adults who participated in the asthma development program. Cases of EGPA have been reported in adults who participated in the asthma development program as well as in adults with co-morbid asthma in the CRSwNP development program. Advise patients to report signs of eosinophilic pneumonia and EGPA to their healthcare provider. Consider withholding dupilumab if eosinophilic pneumonia or EGPA are suspected.
- **Acute Symptoms of Asthma or Chronic Obstructive Pulmonary Disease or Acute Deteriorating Disease** - Dupilumab should not be used to treat acute symptoms or acute exacerbations of asthma or COPD. Do not use to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma or COPD remains uncontrolled or worsens after initiation of treatment.
- **Reduction of Corticosteroid Dosage** - Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with dupilumab. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.
- **Patients with Comorbid Asthma** - Advise atopic dermatitis or CRSwNP patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.
- **Psoriasis** - Advise patients to report new-onset psoriasis symptoms to their healthcare provider. If symptoms persist or worsen, consider dermatologic evaluation and/or discontinuation of dupilumab.
- **Arthralgia and Psoriatic Arthritis** - Arthralgia has been reported with some patients reporting gait disturbances or decreased mobility associated with joint symptoms; some cases resulted in hospitalization. Cases of new-onset psoriatic arthritis requiring systemic treatment have been reported. Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation.

- **Parasitic (Helminth) Infections** – Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if dupilumab will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with dupilumab. If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, discontinue treatment with dupilumab until the infection resolves.
- **Vaccinations** - Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with dupilumab. Avoid use of live vaccines in patients treated with dupilumab.
- **Interactions with CYP450 Substrates** - The formation of CYP450 enzymes can be altered by increased levels of certain cytokines; therefore, dupilumab could modulate the formation of CYP450 enzymes. Upon initiation or discontinuation of dupilumab in members receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.
- **Immunogenicity** - Approximately 6% of subjects with atopic dermatitis or asthma who received dupilumab for 52 weeks developed antibodies to dupilumab; approximately 2% exhibited persistent responses, and approximately 2% had neutralizing antibodies. Approximately 9% of subjects with asthma who received dupilumab for 52 weeks developed antibodies to dupilumab; approximately 4% exhibited persistent responses, and approximately 4% had neutralizing antibodies.
- **Pregnancy -** There are no available data on dupilumab use in pregnant women to inform any drug associated risk. Refer to the product label for more information.
- **Lactation** – There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Refer to the product label for more information.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J33.0 – J33.9	Nasal polyp
J42	Unspecified chronic bronchitis
J43.0 – J43.9	Emphysema
J44.0 – J44.9	Other chronic obstructive pulmonary disease
J45.40 – J45.42	Moderate persistent asthma
J45.50 – J45.52	Severe persistent asthma
J82.83	Eosinophilic asthma
K20.0	Eosinophilic esophagitis
L12.0	Bullous pemphigoid
L20.0	Besnier's prurigo
L20.81	Atopic neurodermatitis
L20.82	Flexural eczema
L20.84	Intrinsic (allergic) eczema
L20.89	Other atopic dermatitis

L20.9	Atopic dermatitis, unspecified
L28.1	Prurigo nodularis
L29.8	Other pruritus [for immunotherapy-related pruritus ONLY]
L29.9	Pruritus, unspecified [for immunotherapy-related pruritus ONLY]
L50.8	Other urticaria

ICD-10 Diagnosis Codes That Support Medical Necessity

J3590	Unclassified biologics

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

Eczema Area Severity Index score (EASI) - assesses severity (severity score) and body surface area affected by erythema, induration/papulation/edema, excoriations, and lichenification (area score), which are graded systematically for each of 4 anatomical regions (head and neck, trunk, upper limbs, lower limbs) and assembled in a composite score, with a score range of 0 to 72.

- EASI 50 - a percentage improvement of EASI score from baseline that is ≥50%
- EASI 75 - a percentage improvement of EASI score from baseline that is ≥75%
- EASI 90 - a percentage improvement of EASI score from baseline that is ≥90%

Eosinophilic esophagitis – a chronic, immune-mediated disease of the esophagus in which white blood cells called eosinophils build up in the esophagus. This causes damage and inflammation, which can cause pain and may lead to trouble swallowing.

FEV1 – forced expiratory volume in 1 second

FVC – forced vital capacity

Helper T cells (a.k.a., CD4+ T cells) – a type of lymphocyte or white blood cell (WBC) that matures in the thymus and play an important role in cell-mediated immunity. T helper cells assist other WBCs in immunologic processes by releasing T cell cytokines. Different types of T helper cells secrete different cytokines (e.g., type 2 release IL-4, IL-5, IL-9, IL-10 and IL-13)

Intertriginous area – an area where two skin areas may touch or rub together (e.g., axilla of the arm, the anogenital region, skin folds of the breasts, between digits)

Lichenified - skin that has become thickened and leathery. This often results from continuously rubbing or scratching the skin.

Patient-Oriented Eczema Measure (POEM) – a validated questionnaire, examining seven items (scored 0 to 4 based on frequency of event), used in clinical settings to assess time spent with symptoms and the impact of symptoms on sleep, with a score range of 0 to 28.

PEF – peak expiratory flow

Pruritus – itching

Scoring Atopic Dermatitis (SCORAD) - the extent and severity of AD over the body area and the severity of 6 specific symptoms (erythema, edema/papulation, excoriations, lichenification, oozing/crusts, and dryness) are assessed and scored by the investigator. Subjective assessment of itch and sleeplessness is scored by the patient. The SCORAD score is a combined score of body area affected, and investigator and patient symptom scoring, with a score range of 0 to103.

RELATED GUIDELINES:

Abrocitinib (Cibinqo), 09-J4000-27
Benralizumab (Fasenra), 09-J2000-92
Lebrikizumab-lbkz (Ebglyss) Injection, 09-J5000-00
Mepolizumab (Nucala), 09-J2000-54
Nemolizumab-ilto (Nemluvio) Injection, 09-J4000-99
Omalizumab (Xolair), 09-J0000-44
Psoralens with Ultraviolet A (PUVA), 02-10000-16
Reslizumab (Cinqair) IV infusion, 09-J2000-63
Tezepelumab-ekko (Tezspire), 9-J4000-13
Tralokinumab-ldrm (Adbry), 09-J4000-20
Upadacitinib (Rinvoq), 09-J3000-51

OTHER:

NOTE: The list of biologic immunomodulator agents not permitted as concomitant therapy can be found at Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.

Mild Intermittent Asthma

- < or = to 2 times a week

- and normal PEF between exacerbations
- brief (from a few hours to a few days); intensity may vary
- symptoms < or = to 2 times a month
- or PEF > or = to 80% predicted
- variability < 20%

Mild Persistent Asthma

- > 2 times a week but < 1 time a day
- may affect activity
- symptoms > 2 times a month
- or PEF > or = to 80% predicted
- variability 20 to 30 %

Moderate Persistent Asthma

- symptoms
- symptoms > one time a week
- use of inhaled short-acting beta2-agonist
- may affect activity
- > or = to 2 times a week; may last days
- or PEF > 60% but less than 80% predicted
- variability > 30%

Severe Persistent Asthma

- symptoms (i.e., coughing, dyspnea, wheezing)
- physical activity
- exacerbations
- nighttime symptoms
- or PEF < or = 60% predicted
- variability > 30%

Table 2: Definitions of Low, Medium, and High Daily Dose of Various Inhaled Corticosteroids in Adults and Adolescents (12 years of age and older)

Drug	Daily Dose (mcg)		
	Low	Medium	High
Beclomethasone dipropionate (CFC)	200 - 500	>500 – 1,000	>1,000
Beclomethasone dipropionate (HFA)	100 - 200	>200 - 400	>400
Budesonide DPI	200 - 400	>400 - 800	>800
Ciclesonide (HFA)	80 - 160	>160 - 320	>320
Fluticasone furoate (DPI)	100	N/A	200
Fluticasone propionate (DPI)	100 - 250	>250 - 500	>500
Fluticasone propionate (HFA)	100 - 250	>250 - 500	>500
Mometasone furoate	110 - 220	>220 - 440	>440
Triamcinolone acetonide	400 – 1,000	>1,000 – 2,000	>2,000

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/11/25.

GUIDELINE UPDATE INFORMATION:

06/15/17	New Medical Coverage Guideline.

01/15/18	Revision to the guideline consisting of updating the position statement in regard to the prerequisite requirements for members receiving systemic immunosuppressant therapy or phototherapy.
10/15/18	Review and revision to guideline consisting of updating the position statement, definitions, and references.
12/15/18	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, coding/billing, related guidelines, and references based on the new FDA-approved indication for moderate to-severe asthma.
04/15/19	Revision to the guideline consisting of updating the description section, position statement, dosage/administration, and references based on the new FDA-approved indication for atopic dermatitis in adolescents.
05/15/19	Revision to guideline consisting of updating the description section, position statement, and references.
09/15/19	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, coding/billing, and references.
02/15/20	Revision to guideline consisting of updating the position statement.
07/15/20	Revision to guideline consisting of updating the description section, position statement, dosage/administration, and references based on a new FDA-approved expanded age for atopic dermatitis (ages 6 to 11 years).
10/01/20	Revision to guideline consisting of updating the position statement and billing/coding.
01/01/21	Review and revision to guideline consisting of updating the references.
02/15/21	Revision to guideline consisting of updating the position statement.
01/01/22	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, billing/coding, and references.
02/15/22	Revision to guideline consisting of updating the description, position statement, other section, and references.
09/15/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, related guidelines, and references based on a new FDA-approved indication for EoE and expanded age for atopic dermatitis (ages 6 months to 5 years).
10/15/22	Revision to guideline consisting of updating the position statement to include PPI therapy as a qualifying prerequisite treatment for EoE.
01/01/23	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, billing/codling, and references based on the new FDA-approved indication of prurigo nodularis (PN). New drugs were added to the list of drugs that are not permitted for use in combination.
04/15/23	New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/23	Revision to guideline consisting of updating the other section. Humira biosimilar products added to list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
01/01/24	Review and revision to guideline consisting of updating the description (asthma, atopic dermatitis, and NCCN info), position statement, billing/coding, other section, and references. Added additional parameters for diagnosis of “moderate-to-severe” atopic dermatitis and new parameter for diagnosis of CRSwNP. Clarified that standard of care

	requirements for asthma and CRSwNP apply to all members continuing treatment. Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
04/01/24	Revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, and references. Updated with expanded FDA-approved age for the treatment of eosinophilic esophagitis (EoE) and removal of the step requirement of a systemic immunosuppressant for AD (based on new AD guidelines).
04/25/24	Update to Position Statement.
07/01/24	Revision to guideline consisting of updating the position statement and other section. Drugs added to the list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
01/01/25	Review and revision to guideline consisting of updating the position statement, other section, and references. New FDA-approved indication for COPD. New drugs were added to the list of drugs that are not permitted for use in combination.
10/01/25	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding, and references. New FDA-approved indications for chronic spontaneous urticaria and bullous pemphigoid.
01/01/26	Review and revision to guideline consisting of updating the description, position statement, and references. Clarified requirements for chronic spontaneous urticaria.