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PHARMACY / MEDICAL POLICY – 5.01.575

Dupixent (dupilumab)

Effective Date:	April 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	March 11, 2025	5.01.513 Xolair (omalizumab)
Replaces:	N/A	5.01.559 IL-5 Inhibitors

Select a hyperlink below to be directed to that section.

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Introduction

Atopic dermatitis (AD) is a chronic skin condition. (Chronic means the condition lasts a long time or returns again and again.) Symptoms of AD include weeping, oozing plaques, itchy skin, raised red rashes or rashes that appear to have small blisters, dry and flaky skin, and increased allergic reaction (IgE reactivity). A person with AD may also have a personal or family history of hay fever or other skin conditions. The itchy skin can be triggered by a number of situations. These include heat and perspiration, wool, emotional stress, specific foods, and house dust mites. Scratching and rubbing irritate the skin and increase inflammation, which leads to more itching. Medications called corticosteroids are often successful in treating AD. Asthma is a long-term lung condition affecting the airways of the lung. Asthma causes the airways to become inflamed. Inhaling certain substances such as tobacco smoke, pet dander, and dust mites can set off a chain reaction. The immune system produces substances called cytokines that contribute to inflammation in asthma. Dupixent is a drug that helps prevent the inflammation response in asthma by blocking cytokines. It's typically prescribed to treat moderate-to-severe asthma when symptoms aren't controlled by inhaled corticosteroids or use of oral corticosteroids. Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a condition where the sinuses and nasal passages become inflamed and contain non-cancerous growths (polyps). Symptoms of CRSwNP include mucus drainage from the nose or down the back of the throat, facial pain, pressure and/or a sensation of fullness, nasal blockage, and a reduced sense of smell. Dupixent is a drug that is prescribed as an add-on treatment for CRSwNP that isn't controlled by using an intranasal corticosteroid. Eosinophilic esophagitis (EoE) is a chronic condition that causes the esophagus to become inflamed and not function properly. Common symptoms can include difficulty

swallowing, abdominal pain, and chest pain. There is often an association with EoE and other allergic conditions such as food allergies, AD, and asthma. Prurigo nodularis (PN) is a skin condition characterized by raised and often severely itchy bumps on the arms, legs, and trunk that have a significant impact on sleep and quality of life. PN is more common in middle-aged to older adults, African American individuals, and women. This policy describes when Dupixent may be considered medically necessary to treat AD, asthma, CRSwNP, EoE, or PN.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Indication	Medical Necessity
Atopic dermatitis	**Dupixent (dupilumab) may be considered medically necessary for the treatment of moderate to severe atopic dermatitis when:** • The individual is aged 6 months or older **AND** • Has a diagnosis of atopic dermatitis involving greater than or equal to 10% of his or her body surface area (BSA) ○ **Exception**: this may be granted for extensive recalcitrant facial involvement, pustular involvement of the hands or feet, and genital involvement which interferes with normal sexual function. **AND** • For individuals aged 2 years and older, there is an inadequate response or intolerance to one topical calcineurin inhibitor medication, (e.g., pimecrolimus or tacrolimus) **AND** • For individuals aged 2 years and older, there is an inadequate response or intolerance to one topical corticosteroid medication of high potency (e.g., betamethasone dipropionate, mometasone furoate, fluocinonide, or clobetasol propionate)

Indication	Medical Necessity
	○ **Exception:** this may be granted for face or genital involvement **OR** • For individuals aged 6 months to 2 years, there is an inadequate response or intolerance to one topical prescription corticosteroid medication of any potency ○ **Exception:** this may be granted for face or genital involvement **AND** • Medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist **AND** • For adults, the maintenance dose prescribed is 300 mg given every other week **OR** • For pediatric individuals aged 6 months to 17 years, the maintenance dose prescribed is: ○ 200 mg every 4 weeks if 5 to less than 15 kg ○ 300 mg every 4 weeks if greater than or equal to 15 kg and less than 30 kg ○ 200 mg every other week if greater than or equal to 30 kg and less than 60 kg ○ 300 mg every other week if 60 kg or more
Moderate-to-severe asthma	**Dupixent (dupilumab) may be considered medically necessary for the treatment of individuals aged 6 years and older with moderate-to-severe asthma when:** • The individual has a diagnosis of moderate-to-severe asthma **AND** • Is aged 6 years or older **AND** • Is using maximum tolerated doses of an inhaled corticosteroid **AND** • Is using an inhaled long-acting beta-agonist (LABA) **AND** • Meets one of the following: ○ Two or more asthma exacerbations in the previous 12 months requiring use of oral corticosteroids

Indication	Medical Necessity
	OR ○ One or more asthma exacerbations requiring hospitalization, an emergency department visit, or an urgent care visit in the previous 12 months **OR** ○ Forced expiratory volume in 1 second (FEV_1) less than 80% predicted **OR** ○ Has a dependence on oral corticosteroids of at least 5 mg per day of prednisone or equivalent **OR** ○ Has asthma with an eosinophilic phenotype and had at least ONE of the following 3 criteria: ▪ Blood eosinophil* count greater than 150 cells/mcL ▪ Sputum eosinophil* count greater than or equal to 3% ▪ Has oral corticosteroid dependent asthma and is not able to discontinue use of oral corticosteroids for blood eosinophil or sputum eosinophil tests **AND** • For adults and adolescents aged 12 years and older, the maximum maintenance dose prescribed is 300 mg given every other week **OR** • For pediatric individuals aged 6 to 11 years the maximum maintenance dose prescribed is: ○ 300 mg every four weeks for body weight 15 to less than 30 kg ○ 200 mg every other week for body weight greater than or equal to 30 kg **AND** • Dupixent (dupilumab) is not used in combination with Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab), Tezspire (tezepelumab-ekko), or Xolair (omalizumab) when the medications are being used for the treatment of asthma **AND** • Medication is prescribed by or in consultation with an allergist/immunologist or pulmonologist

Indication	Medical Necessity
	***Note:** Eosinophil count is count is a type of blood test that measures the quantity of a type of white blood cell called eosinophils. If the number in the blood or sputum is high (greater than 150 cells/mcL or 3%, respectively), this suggests that the individual is unresponsive to their regular maintenance (inhaled or oral) corticosteroid treatment

Chronic obstructive pulmonary disease (COPD)	**Dupixent (dupilumab) may be considered medically necessary as an add-on maintenance treatment in adult individuals with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype when:**
	• The individual is aged 18 years or older
	AND
	• Has been diagnosed with inadequately controlled COPD
	AND
	• Has a blood eosinophil level of greater than or equal to 300 cells/mcL within the previous 12 months
	AND
	• Has tried a combination long-acting muscarinic antagonist/long-acting beta-agonist (LAMA/LABA) product for greater than or equal to 90 days, unless the LAMA/LABA product is not tolerated, and continues to have documented symptom control issues
	AND
	• Meets ONE of the following:
	  ○ Has experienced two or more COPD exacerbations requiring treatment with a systemic corticosteroid and/or an antibiotic in the previous 12 months
	  ○ Has experienced one or more COPD exacerbations requiring a hospitalization in the previous 12 months
	AND
	• Has had signs or symptoms of chronic bronchitis (e.g., chronic productive cough) for at least 3 months in the previous 12 months
	AND
	• Medication is prescribed by or in consultation with an allergist/immunologist or pulmonologist
	AND

Indication	Medical Necessity
	• The maintenance dose prescribed is 300 mg given every other week

Chronic rhinosinusitis with nasal polyposis	**Dupixent (dupilumab) may be considered medically necessary as an add-on maintenance treatment in individuals with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP) when:**
	• The individual is aged 12 years or older
	AND
	• Has been diagnosed with inadequately controlled bilateral CRSwNP
	AND
	• Has at least two of the following are present:
	  ○ Facial pressure or pain
	  ○ Moderate to severe nasal congestion or obstruction
	  ○ Significant loss of smell
	AND
	• Has an adequate trial and failure of one intranasal corticosteroid as monotherapy
	AND
	• Has one of the following:
	  ○ Prior use of systemic corticosteroids to treat nasal polyps in the last 2 years
	  OR
	  ○ Previous surgical removal of the bilateral nasal polyps
	AND
	• Dupixent (dupilumab) is prescribed in combination with an intranasal corticosteroid
	AND
	• Medication is prescribed by or in consultation with an allergist/immunologist or otolaryngologist
	AND
	• Dupixent (dupilumab) is not used in combination with Nucala (mepolizumab) or Xolair (omalizumab) when the medications are being used for the treatment of CRSwNP
	AND
	• The maintenance dose prescribed is 300 mg given every other week

Indication	Medical Necessity

Eosinophilic esophagitis	**Dupixent (dupilumab) may be considered medically necessary for the treatment of adult and pediatric individuals 1 year of age and older with eosinophilic esophagitis when:**
	• The individual is aged 1 year or older
	AND
	• Weighs greater than or equal to 15 kg
	AND
	• Has been diagnosed with eosinophilic esophagitis as confirmed by an esophageal biopsy demonstrating greater than or equal to 15 intraepithelial eosinophils per high-power field (HPF) (or 60 eosinophils per mm^2)
	AND
	• Has received greater than or equal to 8 weeks of therapy with a proton pump inhibitor (e.g., esomeprazole, lansoprazole, omeprazole)
	AND
	• Meets one of the following:
	  ○ Has tried dietary modifications to treat/manage eosinophilic esophagitis (e.g., elemental diet or an elimination diet)
	  OR
	  ○ The provider has determined that the individual is not an appropriate candidate for dietary modifications
	AND
	• Medication is prescribed by or in consultation with an allergist/immunologist or gastroenterologist
	AND
	• Maintenance dose prescribed is limited to 300 mg every week

Prurigo nodularis	**Dupixent (dupilumab) may be considered medically necessary for the treatment of adult individuals with prurigo nodularis (PN) when:** • The individual is aged 18 years or older **AND** • Has greater than or equal to 20 identifiable nodular lesions in total **AND** • Has experienced pruritus for greater than or equal to 6 weeks

Indication	Medical Necessity
	AND • Has tried at least one high- or super-high-potency prescription topical corticosteroid for greater than or equal to 14 consecutive days **AND** • Medication is prescribed by or in consultation with an allergist/immunologist or dermatologist **AND** • Maintenance dose prescribed is 300 mg given every other week

Drug	Investigational
Dupixent (dupilumab)	**The medication listed in this policy is subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **Use of Dupixent (dupilumab) in individuals aged less than 6 months is considered investigational.** **All other uses of Dupixent (dupilumab) for conditions not outlined in the Medical Necessity section above are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for Dupixent (dupilumab) may be approved up to 12 months.** **All other reviews for Dupixent (dupilumab) may be approved up to 6 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for Dupixent (dupilumab) may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by the following for each diagnosis:**

Length of Approval	
Approval	**Criteria**
	Atopic dermatitis • Decrease in the body surface area (BSA) involvement **AND** • Amelioration of the associated symptoms (i.e., pruritus, inflammation, redness, etc.) **Moderate-to-severe asthma** • Decrease in requirements for oral steroids, exacerbation frequency, ER and urgent care visits, hospitalizations **OR** • Decrease in frequency and severity of asthma symptoms **OR** • Increase in quality of life measures and ability to perform activities of daily living **Chronic rhinosinusitis with nasal polyposis** • Decrease from baseline of nasal polyp size unless previous surgical removal of nasal polyps **AND** • Decrease from baseline of nasal congestion/obstruction **AND** • Improvement from baseline of sense of smell **Eosinophilic esophagitis** • Reduced intraepithelial eosinophil count **OR** • Decreased dysphagia/pain upon swallowing **OR** • Reduced frequency/severity of food impaction **Prurigo nodularis** • Reduced nodular lesion count **OR** • Decreased pruritus **OR**

Length of Approval	
Approval	**Criteria**
	• Reduced nodular lesion size

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:
• Office visit notes that contain the diagnosis, relevant history, physical evaluation, lab results and medication history

Coding

Code	Description
HCPCS	
J3590	Unclassified biologics (use to report: Dupixent)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Disease Background (Pathophysiology and Treatment Alternatives)

Atopic Dermatitis

In 1998, the prevalence of AD in the US was found to be 6%, of which 30% reported mild disease, 53% moderate disease, and 18% severe disease in a population-based survey.[10] Disease onset is typically in early childhood, with approximately 45% of individuals developing skin manifestations by 6 months of age, 60% by one year of age, and 85% by five years of age. Approximately one third of those who develop AD in childhood, one third will continue to have the disease in adulthood.

Asthma is a high-cost disease in terms of both human suffering and dollars in the US Approximately 8.7% of Americans have asthma, with a higher prevalence in women and those of mixed race and African Americans. Direct costs are around $56 billion annually due in part to 8.9 million office visits, 1.9 million emergency department visits, and nearly half a million hospitalizations annually. The cost of asthma medications is out of reach for 25% of African Americans and 20% of Hispanics, the very populations more at risk. In addition, asthma sufferers miss 24.7 million days per year of school or work. The cost of care increases with severity of disease due to higher levels healthcare utilization, especially emergency and individual care, and prescription medications. Of note locally, Washingtonians are half as likely to be hospitalized for asthma compared to the national average (73.2 vs. 144 per hundred thousand, respectively).

There are several factors that can predispose individuals to the development of AD. These factors include climate, infection, genetics, environmental aeroallergens, and food. The initial mechanisms that trigger inflammatory changes in the skin in individuals with AD, however, are unknown.[9] Neuropeptides, irritation, or pruritus-induced scratching that may cause the release of proinflammatory cytokines from keratinocytes may be a potential mechanism. Alternatively, allergens in the epidermal barrier or in food may cause T-cell mediated but IgE-independent reactions. Microbial colonization of pathologic organisms may further complicate the disease and increase susceptibility for skin infections. Skin barrier dysfunction and loss of function mutations or deficiencies in the skin structural protein play a critical role in the development of AD. Antimicrobial peptides (AMP) are normally involved in forming a chemical shield on the surface of the skin and a reduction in these peptides results in a diminished antimicrobial barrier, which correlates with increased susceptibility to infection and superinfections seen in these individuals.

Successful management of AD includes not only clearance of skin lesions, control of itch, minimizing or eliminating triggers, minimizing or preventing adverse events from medications, and providing adequate social and psychological support for the individual, family, and caregivers.

An important nonpharmacological standard of care is the use of moisturizers. Adequate skin hydration is a fundamental part of managing AD. The application of moisturizers should be an integral part of the treatment of individuals and there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention.[12] Currently, topical corticosteroids are recommended for the management of moderate-to-severe AD and if approved, dupilumab will be the first biologic on the market for the treatment of AD.

Topical corticosteroids are recommended for the treatment of AD by the American Academy of Dermatology in AD individuals who have failed to respond to good skin care and regular use of emollients alone.[9] The choice of corticosteroid depends on a variety of factors, such as individual

age, areas of body to which the medication will be applied, and other individual factors such as degree of xerosis, individual preference, and cost of medication. Low-potency corticosteroids, are suitable for the face, and medium-potency corticosteroids may be used for the body. Mid-strength and high-potency corticosteroids should be used for short-term management of exacerbations. Ultrahigh- and high-potency corticosteroids are typically reserved for short-term treatment of lichenified areas in adults. It is important to note that altering local environment through hydration and/or occlusion as well as changing the vehicle may alter absorption and effectiveness of the topical corticosteroid.

Topical calcineurin inhibitors are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with AD, and are particularly useful in recalcitrance to steroids, sensitive areas, steroid-induced atrophy, and long-term uninterrupted topical steroid use. Tacrolimus and pimecrolimus, both drugs are recommended for use as second-line treatments in AD due to concerns of skin-burning and pruritus, especially when applied to acutely inflamed skin. Concomitant use of topical corticosteroid with a topical calcineurin inhibitor may be recommended for the treatment of AD.

Topical antimicrobials and topical antiseptics have been shown to be clinically helpful in individuals with AD, however, it is not routinely recommended. In individuals with moderate to severe AD and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity.

Phototherapy is recommended when the disease is not controlled by tacrolimus or pimecrolimus ointment. Phototherapy may help prevent secondary bacterial skin infections, however, in a few individuals, phototherapy may worsen the AD and is not recommended in individuals whose disease flares up when exposed to sunlight.

Systemic immunomodulatory agents are indicated for individuals in whom optimized topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease. Cyclosporine, azathioprine, methotrexate, and mycophenolate are recommended as systemic therapy for individuals with refractory atopic dermatitis. Interferon gamma may be considered in refractory AD individuals who have not responded to or have contraindications to the use of other systemic therapies or phototherapy. Systemic steroids should be avoided if possible and reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapy.

Environmental control, especially avoidance of identified triggers, as well as appropriate skin care habits such as proper bathing techniques and copious use of moisturizers, is key to management.

Drug Pharmacology

Dupilumab is a fully human monoclonal antibody that binds specifically to the share alpha chain subunit of the IL-4 and IL-13 receptors. Binding to these alpha chain subunits results in the inhibition of signaling of IL-4 and IL-13, which are type 2 inflammatory cytokines that may be important drivers of atopic or allergic diseases such as AD or asthma. Dupilumab is injected subcutaneously (SC).

Routine side effects that occurred during the short-term clinical trials for both potential indications are discussed below and are limited to those events reported more often with dupilumab than placebo. See Issue 3 above for a discussion of major safety issues and serious adverse events.

Common adverse events reported in the placebo-controlled studies include injection-site reactions, nasopharyngitis, headache, and upper respiratory infection. These adverse events of mild to moderate intensity were reported more often with dupilumab treatment compared to placebo.

Table 1. Comparison of Representative Topical Corticosteroid Preparations (classified according to the US system)

Potency group	Corticosteroid	Vehicle type/form	Trade names (United States)	Available strength(s), % (except as noted)
Super-high potency (group 1)	Betamethasone dipropionate, augmented	Gel, lotion, ointment (optimized)	Diprolene	0.05
	Clobetasol propionate	Cream, gel, ointment, solution (scalp)	Temovate	0.05
		Cream, emollient base	Temovate E	0.05
		Lotion, shampoo, spray aerosol	Clobex	0.05
		Foam aerosol	Olux-E, Tovet	0.05
		Solution (scalp)	Cormax	0.05
		Spray aerosol	Clobex	0.05

Potency group	Corticosteroid	Vehicle type/form	Trade names (United States)	Available strength(s), % (except as noted)
	Fluocinonide	Cream	Vanos	0.1
	Flurandrenolide	Tape (roll)	Cordran	4 mcg/cm^2
	Halobetasol propionate	Cream, lotion, ointment	Ultravate	0.05
High potency (group 2)	Amcinonide	Ointment	Cyclocort, Amcort	0.1
	Betamethasone dipropionate	Ointment	Diprosone	0.05
		Cream, augmented formulation (AF)	Diprolene AF	0.05
	Clobetasol propionate	Cream	Impoyz	0.025
	Desoximetasone	Cream, ointment, spray	Topicort	0.25
		Gel	Topicort	0.05
	Diflorasone diacetate	Ointment	ApexiCon, Florone	0.05
		Cream, emollient	ApexiCon E	0.05
	Fluocinonide	Cream, gel, ointment, solution	Lidex	0.05
	Halcinonide	Cream, ointment, solution	Halog	0.1
	Halobetasol propionate	Lotion	Bryhali	0.01
High potency (group 3)	Amcinonide	Cream	Cyclocort, Amcort	0.1
		Lotion	Amcort	0.1
	Betamethasone dipropionate	Cream, hydrophilic emollient	Diprosone	0.05
	Betamethasone valerate	Ointment	Valisone	0.1
		Foam	Luxiq	0.12
	Diflorasone diacetate	Cream	Florone	0.05
	Fluocinonide	Cream aqueous emollient	Lidex-E	0.05

Potency group	Corticosteroid	Vehicle type/form	Trade names (United States)	Available strength(s), % (except as noted)
	Fluticasone propionate	Ointment	Cutivate	0.005
	Mometasone furoate	Ointment	Elocon	0.1
	Triamcinolone acetonide*	Cream, ointment	Aristocort HP, Kenalog, Triderm	0.5

*Only triamcinolone 0.5% is high potency.

Consideration of Age

The age noted in the policy statement is based on the US Food and Drug Administration (FDA) labeling for this agent.

Table 2. High Dose Regimens of Inhaled Corticosteroids

High Dose Regimens of Inhaled Corticosteroids			
Drug Name	**Low Dose**	**Medium Dose**	**High Dose**
Beclomethasone HFA (Qvar)	80 to 160 mcg	>160 to 320 mcg	>320 mcg
40 mcg per puff	2 to 4 puffs		
80 mcg per puff	1 to 2 puffs	3 to 4 puffs	>4 puffs
Budesonide DPI (Pulmicort Flexhaler)	180 to 360 mcg	>360 to 720 mcg	>720 mcg
90 mcg per inhalation	2 to 4 inhalations		
180 mcg per inhalation	1 to 2 inhalations	3 to 4 inhalations	>4 inhalations
Ciclesonide HFA (Alvesco)	80 to 160 mcg	>160 to 320 mcg	>320 mcg
80 mcg per puff	1 to 2 puffs	3 to 4 puffs	
160 mcg per puff	1 puff	2 puffs	>2 puffs
Fluticasone propionate	88 to 220 mcg	>220 to 440 mcg	>440 mcg

High Dose Regimens of Inhaled Corticosteroids			
Drug Name	**Low Dose**	**Medium Dose**	**High Dose**
HFA (Flovent HFA)			
44 mcg per puff	2 to 5 puffs		
110 mcg per puff	1 to 2 puffs	3 to 4 puffs	
220 mcg per puff		2 puffs	>2 puffs
Fluticasone propionate DPI	100 to 250 mcg	>250 to 500 mcg	>500 mcg
(Flovent Diskus)			
50 mcg per inhalation	2 to 5 inhalations		
100 mcg per inhalation	1 to 2 inhalations	3 to 5 inhalations	
250 mcg per inhalation	1 inhalation	2 inhalations	2 inhalations
500 mcg per inhalation (strength not available in the U.S.)		1 inhalation	>1 inhalation
Fluticasone furoate DPI	50 mcg	100 mcg	200 mcg
(Arnuity Ellipta)*			
50 mcg per inhalation	1 inhalation		
100 mcg per inhalation		1 inhalation	2 inhalations
200 mcg per actuation			1 inhalation
Mometasone DPI	110 to 220 mcg	>220 to 440 mcg	>440 mcg
(Asmanex DPI)			
110 mcg per inhalation	1 to 2 inhalations		
220 mcg per inhalation	1 inhalation	2 inhalations	>2 inhalations
Mometasone HFA	100 to 200 mcg	>200 to 400 mcg	>400 mcg
(Asmanex HFA)			
100 mcg per actuation	1 to 2 inhalations		
200 mcg per actuation	1 inhalation	2 inhalations	>2 inhalations

***Note:** Inhaled fluticasone furoate has a greater anti-inflammatory potency per microgram than fluticasone propionate inhalers. Thus, fluticasone furoate is administered at a lower daily dose and used only once daily.

Evidence Review

Evidence of Efficacy from Clinical Trials

Atopic Dermatitis - Adults

Published data from two 16-week, placebo-controlled, pivotal trials, SOLO 1 and SOLO 2, in respectively 671 and 708 subjects with moderate-to-severe AD demonstrated the superiority of SC injected dupilumab 300 mg every other week and dupilumab 300 mg weekly in improving Investigator's Global Assessment (IGA) scores compared to placebo at week 16.[1] In SOLO 1, 38% of the dupilumab every other week group, 37% of the dupilumab weekly group, and 10% of the placebo group achieved an IGA score of 0 or 1 (clear or almost clear) ($p<0.001$ for both comparisons with placebo). SOLO 2 demonstrated similar results with 36% of the dupilumab every other week group, 36% of the dupilumab weekly group, and 8% of the placebo group achieving an IGA score of 0 or 1 ($p<0.001$ for both comparisons with placebo). IGA scores are utilized in the real-world clinical setting by providers; however, the clinical meaningfulness of this as a clinical trial endpoint has not been well tested and validated. Results of this trial are valid due to well-stratified baseline characteristics, consistency of results, and study design. Limitations of the results lie within the short time horizon of the studies and the use of rescue treatment in at least 15% of individuals in the dupilumab treatment groups, making it difficult to extrapolate the long-term effectiveness of dupilumab as a monotherapy option for maintenance treatment for AD.

Key secondary endpoints in SOLO 1 showed that 51% of dupilumab every other week individuals, 52% of dupilumab weekly individuals, and 15% of placebo individuals achieved improvement on the Eczema Area and Severity Index (EASI) score of at least 75% ($p<0.0001$ for all comparisons). The least squares mean percent reductions in EASI score from baseline to week 16 were 72.3±2.6, 72.0±2.6, and 37.6±3.3 for the every other week group, the weekly group, and the placebo group respectively. Significantly more individuals receiving dupilumab achieved an improvement of at least 4 points at weeks 2, 4, and 16 or at least 3 points at week 16 on the weekly average of peak scores for numerical rating scale (NRS) pruritus compared to placebo ($p<0.001$ for all comparisons).

Key secondary endpoint results in SOLO 2 were similar to those in SOLO 1. 75% EASI score improvements were achieved in 44% of individuals in the dupilumab every other week group and 48% of weekly group and 12% in the placebo group. The least squares mean percent reductions in EASI score from baseline to week 16 were 69.1±2.5, 67.1±2.5, and 30.9±3.0 for the every other week group, the weekly group, and the placebo group respectively. A total of at least 3 individuals must be treated with dupilumab every other week or every week for 12 weeks in order to see an improvement in EASI score. Significantly more individuals receiving dupilumab

improved at least 4 points at weeks 2, 4, and 16 or at least 3 points at week 16 on the weekly average of peak scores for NRS pruritus compared to placebo ($p<0.001$ for all comparisons).

The long-term efficacy of dupilumab in adults with moderate to severe AD and inadequate response to topical corticosteroids was tested in LIBERTY AD CHRONOS[16], a randomized, double-blind, placebo-controlled, phase 3 trial that allowed background therapy of low/medium potency topical corticosteroid with/without topical calcineurin inhibitors. The one-year trial enrolled 740 individuals and randomized them to 3 groups: dupilumab qw plus potency topical corticosteroids (n = 319), dupilumab q2w plus topical corticosteroids (n = 106), and placebo plus topical corticosteroids (n = 315). The topical corticosteroids used were limited to low/medium potency options. Efficacy was evaluated at week 16 and week 52. Only 623 (270, 89, and 264 respectively) participants were evaluable at week 52. Results from week 16 and week 52 were similar. At week 16, each of the dupilumab groups saw 39% of individuals achieving IGA score 0/1 and reduction of greater than or equal to 2 points from baseline (vs 12% of placebo group); at week 52, 36% of the every other week group and 40% of the weekly group reached that coprimary endpoint (vs 13% of placebo group). At week 16, 69% of the biweekly group and 64% of the weekly group attained an EASI-75 response (vs. 23% of placebo group); at week 52, 65% of the biweekly group and 64% of the weekly group reached that coprimary endpoint (vs. 22% of placebo group). Both the biweekly group and the placebo group saw roughly half of their 16-week responders became non-responders at week 52. On the other hand, 23% of the 16-week non-responders in the biweekly group (vs. 7%) became responders at week 52. However, no information was available regarding the weekly group.

In addition to the three phase 3 trials above, there were two peer-reviewed publications covering several earlier phase 2 trials that assessed the efficacy of dupilumab in individuals with moderate-to-severe AD. Beck, et al., included a 12-week, randomized, double-blind, placebo-controlled trial that demonstrates the superiority of weekly dupilumab 300 mg in improving the percentage change in the EASI score of 109 subjects.[2] The percentage reduction in the EASI score was consistently greater with dupilumab than with placebo at week 12 (change in EASI score $\pm$ SD: placebo group, -23.3 $\pm$ 6.7; dupilumab group, -74.0 $\pm$ 3.6; $p<0.001$). Key secondary endpoints show that the proportion of individuals with reductions of 50% (EASI-50) in the EASI score and IGA score of 0 or 1 were greater in the dupilumab group compared to placebo ($p<0.001$ for both endpoints at week 12). Approximately 3 individuals would need to be treated with dupilumab in order to have at least one individual achieve an IGA score of 0 or 1. Reductions in pruritus NRS score and the number of individuals with reductions of 75% (EASI-75) in the EASI score were greater in the dupilumab group compared to the placebo group, but were not statistically significant. It should be noted that these studies did not utilize a loading dose when initiating therapy as seen in the phase 3 trials and the duration of therapy for this study was not long enough to extrapolate the long-term efficacy of dupilumab.

Thaçi, et al. enrolled individuals with moderate-to-severe AD in a randomized, placebo-controlled, double-blind dupilumab dosing trial.[3] Subjects were given dupilumab 300 mg weekly, every 2 weeks, or every 4 weeks, dupilumab 200 mg every 2 weeks or every 4 weeks, dupilumab 100 mg every 4 weeks, or placebo weekly. The percent change in EASI Score from baseline to week 16 was superior in all dupilumab groups when compared to placebo ($p<0.0001$). The greatest least square (LS) mean percentage change from baseline to week 16 in EASI scores were seen in the dupilumab 300 mg once a week group and dupilumab every 2 weeks group (LS mean % change from baseline (SE): 300 mg every week, -73.7% (5.2); 300 mg every 2 weeks, -68.2% (5.1)). These results reflect the appropriate dupilumab dosage strengths utilized in the Phase 3 trials. Key secondary endpoints: proportion of individuals that achieved an IGA of 0 or 1, EASI-50, EASI-75, and 90% reduction in EASI scores (EASI-90) were significantly greater in the dupilumab 300 mg weekly, dupilumab 300 mg every 2 weeks, and dupilumab 200 mg every 2 weeks when compared to placebo ($p<0.0001$ for all comparisons). Improvement in percentage change in weekly pruritus NRS scores of 33-47% were seen in all dupilumab groups ($p<0.0001$ for all comparisons, except $p=0.0007$ for dupilumab 100 mg every 4 weeks) when compared to placebo. Although dupilumab 300 mg weekly or every 2 weeks seems like an effective dose for the treatment of AD, the study was not adequately powered for statistical comparisons among the different dupilumab dosing levels. This study has limited applicability as dupilumab monotherapy may not be reflective of real-world practice and there is limited evidence regarding the efficacy and appropriate dosing of dupilumab in combination with topical medications.

Beck et al. conducted a 4-week, randomized, placebo-controlled trial that assessed the efficacy of weekly dupilumab 300 mg or placebo in combination with topical glucocorticoids in adults with moderate-to-severe AD.[2] Percent changes in the EASI score, proportion of individuals with an IGA score of 0 or 1, proportion of individual with EASI-50, and score on the pruritus NRS were pre-specified exploratory endpoints. Improvements in all exploratory endpoints were greater in the dupilumab combined with topical glucocorticoids group compared to placebo combined with topical glucocorticoids. Change in the pruritus NRS scores and EASI-50 were the only endpoints that demonstrated statistical significance. Although this is the only published trial that demonstrates the efficacy of dupilumab in combination with topical glucocorticoids, the study is limited due to efficacy being an exploratory endpoint, short duration, and its small sample size.

A 52-week trial of the use of monotherapy dupilumab for the treatment of individuals with moderate-to-severe asthma should be assessed when available to understand the long-term efficacy of the drug.

Atopic Dermatitis - Adolescents

One multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of dupilumab monotherapy in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD defined by an Investigator's Global Assessment (IGA) score greater than or equal to 3 (scale of 0 to 4), an Eczema Area and Severity Index (EASI) score greater than or equal to 16 (scale of 0 to 72), and a minimum BSA involvement of greater than or equal to 10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Subjects in the dupilumab 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 greater than or equal to 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 mean age was 14.5 years, the median weight was 59.4 kg, 41% of subjects were female, 63% were White, 15% were Asian, and 12% were Black. At baseline 46% of subjects had an IGA score of 3 (moderate AD), 54% had an IGA score of 4 (severe AD), the mean BSA involvement was 57%, and 42% had received prior systemic immunosuppressants. Also, at baseline the mean EASI score was 36, and the weekly average Peak Pruritus Numeric Rating Scale (NRS) was 8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 66% had allergic rhinitis, 54% had asthma, and 61% had food allergies.

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 (greater than or equal to 4-point improvement). At week 16 24% of dupilumab users had an IGA 0 or 1 vs. 2% for placebo, 42% of duplimumab users had an EASI-75 score vs. 8% for placebo, 23% of dupilumab users had an EASI-90 score vs. 2% for placebo, and 37% of dupilumab users had a Peak Pruritis NRS (greater than or equal to 4-point improvement) vs. 5% for placebo.

The efficacy and safety of Dupixent use concomitantly with topical corticosteroids (TCS) in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 367 subjects 6 to 11 years of age, with AD defined by an IGA score of 4 (scale of 0 to 4), an EASI score greater than or equal to 21 (scale of 0 to 72), and a minimum BSA involvement of greater than or equal to 15%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (<30 kg; greater than or equal to 30 kg).

The mean age was 8.5 years, and the median weight was 29.8 kg. At baseline, the mean BSA involvement was 58%, and 17% had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 37.9, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 64% had food allergies, 63% had other allergies, 60% had allergic rhinitis, and 47% had asthma.

A greater proportion of subjects randomized to Dupixent + TCS achieved an improvement in the Peak Pruritus NRS compared to placebo + TCS (defined as greater than or equal to 4-point improvement at Week 16).

Atopic Dermatitis – Children 6 to 11 Years Old

The efficacy and safety of Dupixent use concomitantly with topical corticosteroid (TCS) in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1652; NCT03345914) in 367 subjects 6 to 11 years of age, with AD defined by an Investigator's Global Assessment (IGA) score of 4 (scale of 0 to 4), an Eczema Area and Severity Index (EASI) score greater than or equal to 21 (scale of 0 to 72), and a minimum body surface area (BSA) involvement of greater than or equal to 15%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (<30 kg; greater than or equal to 30 kg).

Subjects in the Dupixent Q4W + TCS group received an initial dose of 600 mg on Day 1, followed by 300 mg Q4W from Week 4 to Week 12, regardless of weight. Subjects in the Dupixent Q2W + TCS group with baseline weight of <30 kg received an initial dose of 200 mg on Day 1, followed by 100 mg Q2W from Week 2 to Week 14, and subjects with baseline weight of greater than or equal to 30 kg received an initial dose of 400 mg on Day 1, followed by 200 mg Q2W from Week 2 to Week 14. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In AD-1652, the mean age was 8.5 years, the median weight was 29.8 kg, 50% of subjects were female, 69% were White, 17% were Black, and 8% were Asian. At baseline, the mean BSA involvement was 58%, and 17% had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 37.9, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 64% had food allergies, 63% had other allergies, 60% had allergic rhinitis, and 47% had asthma.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at Week 16. 30% of subjects in the Dupixent Q4W + TCS group had an IGA 0 or 1 vs. 13% in the placebo + TCS group. 39% of subjects in the Dupixent Q2W + TCS group had an IGA 0 or 1 vs. 10% in the placebo + TCS group.

Atopic Dermatitis – Children 6 Months to 5 Years Old

The efficacy and safety of Dupixent use concomitantly with topical corticosteroid (TCS) in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1539; NCT03346434) in 162 subjects 6 months to 5 years of age, with moderate-to-severe AD defined by an Investigator's Global Assessment (IGA) score greater than or equal to 3 (scale of 0 to 4), an Eczema Area and Severity Index (EASI) score greater than or equal to 16 (scale of 0 to 72), and a minimum body surface area (BSA) involvement of greater than or equal to 10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (greater than or equal to 5 to <15 kg and greater than or equal to 15 to <30 kg).

Subjects in the Dupixent Q4W + TCS group with baseline weight of greater than or equal to 5 to <15 kg received an initial dose of 200 mg on Day 1, followed by 200 mg Q4W from Week 4 to Week 12, and subjects with baseline weight of greater than or equal to 15 to <30 kg received an initial dose of 300 mg on Day 1, followed by 300 mg Q4W from Week 4 to Week 12. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In AD-1539, the mean age was 3.8 years, the median weight was 16.5 kg, 39% of subjects were female, 69% were White, 19% were Black, and 6% were Asian. At baseline, the mean BSA involvement was 58%, and 29% of subjects had received prior systemic immunosuppressants. Also, at baseline the mean EASI score was 34.1, and the weekly average of daily worst scratch/itch score was 7.6 on a scale of 0-10. Overall, 81.4% of subjects had at least one comorbid allergic condition; 68.3% had food allergies, 52.8% had other allergies, 44.1% had allergic rhinitis, and 25.5% had asthma.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at Week 16. 28% of subjects in the Dupixent Q4W + TCS group had an IGA 0 or 1 vs. 4% in the placebo + TCS group.

Asthma

The clinical evidence for dupilumab in asthma presented here encompasses the two Phase 3 trials (QUEST and VENTURE). In the Phase 3 trials described below, dupilumab was investigated as an add-on therapy and was administered by subcutaneous injection every two weeks.

QUEST was a 52-week double-blind, randomized, placebo-controlled trial that enrolled 1,902 subjects at least 12 years of age with moderate-to-severe asthma who had experienced at least one asthma exacerbation in the preceding year. Of note, mean baseline eosinophil counts were in excess of 350 cells/ µL, indicating a majority of subjects had an eosinophilic phenotype. The primary outcome results show that overall, dupilumab 200mg and dupilumab 300mg were both superior to placebo in reducing the rate of asthma exacerbations ($p<0.001$). However, pre-specified subgroup analyses reveal that this benefit was only observed in subjects with a baseline eosinophil count of more than 150 cells/µL. Also, there was no dose-dependent effect observed. Change in respiratory function, as measured by FEV_1, was a co-primary endpoint in the QUEST study. Subjects in the dupilumab 200mg group had an improvement in FEV_1 of 0.32 liters vs. 0.18 liters with placebo. This 0.14 liter treatment effect was statistically significant, $p<0.001$. Subjects in the dupilumab 300mg group had an improvement in FEV1 of 0.34 liters vs. 0.21 liters with placebo. This 0.13 liter treatment effect was statistically significant, $p<0.001$.

An important secondary endpoint in the QUEST trial was ACQ-5, a measure of asthma control. Although there was a statistically significant difference favoring dupilumab vs. placebo in this outcome, the treatment effect failed to meet the minimally important difference (MID) of 0.5 points.

VENTURE was a 24-week, double-blind, placebo-controlled, randomized trial involving 210 asthmatics of at least 12 years of age who were routinely taking 5 mg to 35 mg per day of oral prednisone and high dose inhaled corticosteroid (ICS). Many of these subjects had an eosinophilic phenotype. Dupilumab 300mg was superior to placebo in reducing the daily dose of oral prednisone by 28.2%, but subgroup analyses show no statistically significant benefit in subjects with baseline eosinophil counts under 150 cells/µL. Analyses of secondary endpoints shown in section B demonstrate dupilumab 300mg superior to placebo in reducing oral prednisone doses by 50% and to less than 5mg daily.

The efficacy and safety of Dupixent in pediatric subjects was evaluated in a 52-week multicenter, randomized, double-blind, placebo-controlled study (AS Trial 4) in 408 subjects 6 to 11 years of age, with moderate-to-severe asthma on a medium or high-dose ICS and a second controller medication or high-dose ICS alone. Subjects were required to have a history of 1 or more asthma exacerbation(s) 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 were randomized to Dupixent (N=273) or matching placebo (N=135) every other week based on body weight <30 kg (100 mg Q2W) or greater than or equal to 30 kg (200 mg Q2W). The effectiveness of Dupixent 300 mg Q4W was extrapolated from efficacy of 100 mg Q2W in AS Trial 4 with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W.

The primary endpoint was the annualized rate of severe asthma exacerbation events during the 52-week placebo-controlled period. Severe asthma exacerbations were 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. The key secondary endpoint was the change from baseline in pre-bronchodilator FEV1 percent predicted at Week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACQ-7-IA (Asthma Control Questionnaire-7-Interviewer Administered) and PAQLQ(S)-IA (Pediatric Asthma Quality of Life Questionnaire with Standardized Activities Interviewer Administered) scores. Dupixent significantly reduced the annualized rate of severe asthma exacerbation events during the 52-week treatment period compared to placebo in populations with an eosinophilic phenotype as indicated by elevated blood eosinophils and/or the population with elevated FeNO.

Significant improvements in percent predicted pre-bronchodilator FEV1 were observed at Week 12. Significant improvements in percent predicted FEV1 were observed as early as Week 2 and were maintained through Week 52 in AS Trial 4. Improvements were also observed for ACQ-7-IA and PAQLQ(S)-IA at Week 24 and were sustained at Week 52. Greater responder rates were observed for ACQ-7-IA and PAQLQ(S)-IA compared to placebo at Week 24. The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-7-IA and 1-7 for PAQLQ(S)-IA). In the subgroup of subjects with baseline blood eosinophil count greater than or equal to 300 cells/mcL, Dupixent led to a higher proportion of subjects with a response in ACQ-7-IA (80.6% versus 64.3% for placebo) with an OR of 2.79 (95% CI: 1.43, 5.44), and in PAQLQ(S)-IA (72.8% versus 63.0% for placebo) with an OR of 1.84 (95% CI: 0.92, 3.65) at Week 24.

Chronic Obstructive Pulmonary Disease (COPD)

The safety and efficacy of Dupixent in COPD were evaluated in two replicate Phase 3, 52-week, randomized, double-blind, placebo-controlled trials: BOREAS (NCT03930732) and NOTUS (NCT04456673). The trials enrolled a total of 1874 adults with COPD with moderate to severe airflow limitation, evidence of type 2 inflammation (BEC greater than or equal to 300 cells/μL), and a high exacerbation risk (greater than or equal to 2 moderate or greater than or equal to 1

severe exacerbation in the past year) despite current maintenance treatment with inhaled LABA + LAMA + ICS triple therapy. The primary endpoints were met in both the BOREAS and NOTUS trials, with Dupixent demonstrating a 29% and 34% reduction, respectively, in the annualized rate of moderate or severe COPD exacerbations compared to placebo when added to background maintenance therapy. Dupixent decreased the risk of a moderate to severe COPD exacerbation, as measured by time to first exacerbation when compared with placebo in BOREAS (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.66, 0.98) and NOTUS (HR 0.71; 95% CI, 0.57, 0.89).

Chronic Rhinosinusitis with Nasal Polyposis

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) in 724 subjects aged 18 years and older on background intranasal corticosteroids (INCS). These studies included subjects with CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Individuals 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 dupilumab (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 dupilumab (N=150) every other week for 52 weeks, 300 mg dupilumab (N=145) every other week until week 24 followed by 300 mg dupilumab 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. For NPS, polyps on each side of the nose were graded on a categorical scale (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower

border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity). The total score was the sum of the right and left scores. Nasal congestion was rated daily by the subjects on a 0 to 3 categorical severity scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms). Statistically significant efficacy was observed in CSNP Trial 1 and 2 with regard to improvement in bilateral endoscopic NPS scores at week 24 and at week 52 in the CNSP Trial 2. At Week 52, the LS mean difference for nasal congestion in the dupilumab group versus placebo was -0.98 (95% CI -1.17, -0.79). In both studies, significant improvements in nasal congestion were observed as early as the first assessment at Week 4. The LS mean difference for nasal congestion at Week 4 in the dupilumab group versus placebo was -0.41 (95% CI: -0.52, -0.30) in CSNP Trial 1 and -0.37 (95% CI: -0.46, -0.27) in CSNP Trial 2.

Eosinophilic Esophagitis

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.

Demographics and baseline characteristics were similar in Parts A and B. A total of 81 subjects (61 adults and 20 pediatric subjects) were enrolled in Part A and 159 subjects (107 adults and 52 pediatric subjects) were enrolled in Part B. The mean age in years was 32 years (range 13 to 62 years) in Part A and 28 years (range 12 to 66 years) in Part B. The majority of subjects were male (60% in Part A and 68% in Part B) and White (96% in Part A and 90% in Part B). The mean baseline DSQ score (SD) was 33.6 (12.4) in Part A and 37.2 (10.7) in Part B.

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 ≤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 ≤6 eos/hpf) compared to placebo. Treatment with Dupixent also resulted in a significant improvement in LS mean

change in DSQ score compared to placebo at Week 24. 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

Dupixent for the treatment of prurigo nodularis (PN) 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.

In these trials, the mean age was 49.5 years, the median weight was 71 kg, 65% of subjects were female, 57% were White, 6% were Black, and 34% were Asian. 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). Eleven percent (11%) of subjects were taking stable doses of antidepressants at baseline and were instructed to continue taking these medications during the trial. Forty-three percent (43%) had a history of atopy (defined as having a medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma, or food allergy).

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.

In PRIME and PRIME2, 60% and 58% of individuals receiving Dupixent, respectively, experienced a greater than or equal to 4-point reduction in WI-NRS from baseline at 24 weeks, compared with 18% and 20% of individuals receiving placebo. In addition, 48% and 45% of individuals receiving Dupixent in the PRIME and PRIME2 trials, respectively, achieved clear or almost clear

skin at 24 weeks on the Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA PN-S) scale, compared with 18% and 16% of individuals receiving placebo.

Evidence of Safety

Atopic Dermatitis

The three phase 3 trials have identified the most common adverse events with dupilumab to be injection-site reactions, conjunctivitis, and nasopharyngitis.[1] The incidence of nasopharyngitis was generally balanced across dupilumab and placebo groups. Dupilumab-treated individuals had a higher incidence of injection-site reactions, and the rates may be related to the dosing frequency. RSOLO-1 and SOLO-2 observed that rates of conjunctivitis with an unspecified cause and allergic conjunctivitis were higher in dupilumab groups than in the placebo groups. LIBERTY AD CHRONOS showed that the dupilumab plus topical corticosteroid groups had higher risk of eye disorders in general. The only serious adverse event reported in SOLO-1 and SOLO-2 was serious exacerbation of AD, which occurred in 2 individuals receiving weekly dupilumab 300mg and 3 receiving placebo in SOLO 1, and 1 individual receiving weekly dupilumab 300 mg and 5 individuals receiving placebo in SOLO 2. LIBERTY AD CHRONOS had reports of severe allergic conjunctivitis (one individual each in the dupilumab qw plus topical corticosteroids and placebo plus topical corticosteroids groups) and severe bacterial conjunctivitis (one individual in the dupilumab qw plus topical corticosteroids group. The safety profile of dupilumab was consistent across studies conducted for the treatment of AD.

Two published phase 2 studies for the treatment of asthma yielded safety results consistent to the phase 3 studies for the treatment of AD. Common adverse events such as injection-site reactions, nasopharyngitis, nausea, and headache occurred more frequently with dupilumab than with placebo. No clinically important safety signals were observed in these studies.

In the dupilumab with concomitant TCS trial through week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in dupilumab 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued dupilumab because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject). The safety profile of dupilumab + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

The safety of dupilumab was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis and the safety profile in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis. The long-term

safety of dupilumab was also assessed in an open-label extension study in subjects 12 to 17 years of age and the safety profile of dupilumab in subjects followed through Week 52 was similar to the safety profile observed at Week 16 and was consistent with that seen in adults with atopic dermatitis.

Asthma

No serious safety concerns were highlighted in the pivotal trials of dupilumab in asthma. However, data past one year of use are not available to further define the safety profile.

There are only a few serious adverse events (SAEs) reported in the pivotal trials of dupilumab in asthma, so individual-level details of those are discussed here. There were five deaths with dupilumab in the QUEST trial, all but one was in the high dose dupilumab group. Three deaths were reported in the placebo group. None were deemed related to treatment. No deaths were reported in the VENTURE trial. In QUEST, pneumonia occurred in four individuals on dupilumab vs. two individuals on placebo. SAEs occurred more frequently with dupilumab vs. placebo (9% vs. 6 %) in VENTURE, but no details were provided.

Injection site reaction (ISR) was the only common adverse event seen more frequently with dupilumab than placebo in the QUEST trial (15.2% to 18.4% vs. 5.4% to 10.3%). ISRs were also more common with dupilumab vs. placebo in the VENTURE trial (9% vs. 4%). Other common adverse events reported more frequently with dupilumab compared to placebo in VENTURE were: bronchitis (7% vs. 6%), sinusitis (7% vs. 4%), and eosinophilia (14% vs. 1%). Antibody formation was detected but did not appear to result in clinically significant effects.

Chronic Obstructive Pulmonary Disease (COPD)

In pooled BOREAS and NOTUS safety data, the most common adverse events (AEs) (greater than or equal to 2%) more frequently observed in individuals treated with Dupixent compared to placebo were viral infection, headache, nasopharyngitis, back pain, diarrhea, arthralgia, urinary tract infection, local administration reaction, rhinitis, eosinophilia, toothache, and gastritis. Among individuals with COPD, the frequency of conjunctivitis and keratitis was 1.4% and 0.1% in the Dupixent group and 1% and 0% in the placebo group, respectively. Cholecystitis was reported in 0.6% of individuals on Dupixent versus 0.1% of individuals on placebo.

Chronic Rhinosinusitis with Nasal Polyposis

A total of 722 adult subjects with chronic rhinosinusitis with nasal polyposis (CRSwNP) were evaluated in 2 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (CSNP Trials 1 and 2). The safety pool consisted of data from the first 24 weeks of treatment from both studies. In the safety pool, the proportion of subjects who discontinued treatment due to adverse events was 5% of the placebo group and 2% of the dupilumab 300 mg Q2W group. Adverse reactions that occurred at a rate of at least 1% in subjects treated with dupilumab and at a higher rate than in their respective comparator group in CSNP Trials 1 and 2 were injection site reactions, conjunctivitis, arthralgia, gastritis, insomnia, eosinophilia and toothache.

Eosinophilic Esophagitis

A total of 239 adult and pediatric subjects 12 to 17 years of age, weighing at least 40 kg, with EoE were evaluated in a randomized, double-blind, parallel-group, multicenter, placebo-controlled trial, including two 24-week treatment periods (Parts A and B) and received either Dupixent 300 mg QW or placebo. The proportion of subjects who discontinued treatment due to adverse events was 2% of the placebo group and 2% of the Dupixent 300 mg QW group. Adverse reactions occurring in greater than or equal to 2% of individuals with EoE treated with Dupixent in a placebo- controlled trial (Parts A and B; 24-Week Safety Pool) were injections site reactions (38% Dupixent vs. 33% placebo), upper respiratory tract infections (18% Dupixent vs. 10% placebo), arthralgia (2% Dupixent vs. 1% placebo), and herpes viral infection (2% Dupixent vs. 1% placebo).

Prurigo Nodularis

A total of 309 adult subjects with prurigo nodularis were evaluated in two 24-week randomized, double-blind, placebo-controlled, multicenter trials (PRIME and PRIME2). The safety pool included data from the 24-week treatment and 12-week follow-up periods from both trials.

The proportion of subjects who discontinued treatment due to adverse events was 3% of the placebo group and 0% of the Dupixent 300 mg Q2W group. Adverse reactions that occurred at a rate of at least 2% in subjects treated with Dupixent and at a higher rate than placebo in Prime and Prime 2 were nasopharyngitis, conjunctivitis, herpes infection, dizziness, myalgia, and diarrhea.

2018 Update

Added medical necessity criteria for moderate-to-severe asthma along with phase 3 trials for asthma (QUEST and VENTURE).

2019 Update

Updated atopic dermatitis indication for the treatment of individuals aged 12 years and older and added clinical trial data for treatment of atopic dermatitis in adolescents.

2020 Update

Reviewed Dupixent prescribing information and conducted a literature search from March 1, 2019, through February 28, 2020. No new evidence was identified that would change the criteria in this policy.

2021 Update

Reviewed Dupixent prescribing information and conducted a literature search from March 1, 2020, through March 31, 2021. GINA (Global Initiative for Asthma) Guidelines document that individuals with biomarkers for inflammation (blood eosinophils, sputum eosinophils, and FeNO) are often suppressed by oral corticosteroids (OCS) and if possible, these tests should be performed before starting OCS. For individuals with OCS dependent asthma not able to discontinue use of OCS the asthma criteria were updated for blood eosinophil or sputum eosinophil tests to take this into consideration. Updated the comparison of representative topical corticosteroid preparations table.

2022 Update

Reviewed Dupixent prescribing information and added a new indication for the treatment of adult and pediatric individuals aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis (EoE). Dupixent is the first FDA approved therapy for EoE which is a

chronic, progressive, inflammatory disease characterized by esophageal dysfunction and eosinophilic infiltration. Updated atopic dermatitis coverage to include pediatric individuals 6 months of age and older based. For AD updated the topical calcineurin inhibitor requirement and high potency topical corticosteroid requirement to apply to individuals 2 years of age or older. For individuals 6 months to 2 years of age added requirement of inadequate response or intolerance to one topical prescription corticosteroid medication of any potency.

2023 Update

Reviewed Dupixent prescribing information and conducted a literature search from October 31, 2022, through November 1, 2023. No new evidence was identified that would change the criteria in this policy.

2024 Update

Reviewed Dupixent prescribing information. Updated Dupixent (dupilumab) age requirement to 1 year and older for eosinophilic esophagitis. Updated criteria clarifying that combination use with Tezspire (tezepelumab-ekko) is not allowed for the treatment of asthma. Updated criteria clarifying that combination use with Nucala (mepolizumab) or Xolair (omalizumab) is not allowed for the treatment of CRSwNP. Updated asthma criteria to include a prescriber requirement. The following updates are effective January 3, 2025. Updated asthma criteria eosinophil count from 150 cells/mcL within the last 12 months to 300 cells/mcL within the last 12 months. Updated asthma criteria to include the following alternative definitions of moderate-to-severe asthma: One or more asthma exacerbations requiring a hospitalization, an emergency department visit or an urgent care visit in the previous 12 months and FEV1 <80% predicted.

2025 Update

Reviewed Dupixent prescribing information. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Updated age requirement to from 18 years and older to 12 years and older for the treatment of chronic rhinosinusitis with nasal polyps. Updated asthma coverage criteria eosinophil count from 300 cells/mcL within the last 12 months to 150 cells/mcL within the last 12 months. Added coverage criteria for the treatment of certain individuals with

chronic obstructive pulmonary disease (COPD). Updated asthma coverage criteria by removing the requirement to have confirmation of asthma with an eosinophilic phenotype documented in the previous 12 months. Updated the asthma coverage criteria from using maximum doses of an inhaled corticosteroid to using maximum tolerated doses of an inhaled corticosteroid.

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History

Date	Comments
05/01/17	New policy, add to Prescription Drug section. Approved on April 11, 2017. Dupilumab may be considered medically necessary for the treatment of adult patients (18 years of age and older) with moderate to severe atopic dermatitis when criteria are met; for those under 18 and all other uses, considered investigational.
01/01/18	Interim Review, approved December 6, 2017. Added topical high potency corticosteroids table.

Date	Comments
06/01/18	Annual Review, approved May 3, 2018. Added phase 3 trial (LIBERTY AD CHRONOS). Edited high potency topical corticosteroid table based on AAD Guidelines.
09/21/18	Minor update. Added Consideration of Age statement.
01/01/19	Interim Review, approved December 19, 2018. Title changed from "Pharmacotherapy of Atopic Dermatitis" to "Dupixent (dupilumab)". Added medical necessity criteria for the treatment of moderate-to-severe asthma.
05/01/19	Annual Review, approved April 2, 2019. Updated atopic dermatitis indication for the treatment of patients aged 12 years and older. Added HCPCS code J3490.
09/01/19	Interim Review, approved August 13, 2019. Added criteria for chronic rhinosinusitis with nasal polyposis.
04/01/20	Annual Review, approved March 19, 2020. Reviewed prescribing information and conducted literature search from March 1, 2019, to February 28, 2020. No changes to coverage criteria. Removed HCPCS code J3490, added J3590.
08/01/20	Interim Review, approved July 2, 2020. Updated atopic dermatitis indication for the treatment of patients aged 6 years and older and added dosing for pediatric patients less than 30 kg.
10/01/20	Interim Review, approved September 17, 2020. Added criteria that Dupixent (dupilumab), Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab) are not to be used as combination therapy with each other for the treatment of asthma.
02/01/21	Interim Review, approved January 12, 2021. Updated coverage criteria for CRSwNP adding coverage for prior use of oral corticosteroids and intranasal corticosteroids and provider specialty.
05/01/21	Annual Review, approved April 22, 2021. Updated asthma criteria for patients with oral corticosteroid dependent asthma not able to discontinue use of oral corticosteroids for blood eosinophil or sputum eosinophil tests.
12/01/21	Interim Review, approved November 18, 2021. Updated asthma indication to include treatment of patients aged 6 years and older and added dosage limits for patients 6 to 11 years of age.
04/01/22	Interim Review, approved March 8, 2022. Updated atopic dermatitis criteria changing requirement from two to one for treatment with topical corticosteroid medications and added a requirement that medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.
09/01/22	Annual Review, approved August 9, 2022. Updated atopic dermatitis (AD) indication from 6 years of age and older to 6 months of age and older. For AD updated the topical calcineurin inhibitor requirement and high potency topical corticosteroid requirement to apply to patients 2 years of age or older. For patients 6 months to 2 years of age added requirement of inadequate response or intolerance to one topical

Date	Comments
	prescription corticosteroid medication of any potency. Added coverage criteria for the treatment of eosinophilic esophagitis.
12/01/22	Interim Review, approved November 8, 2022. Added coverage criteria for the treatment of prurigo nodularis. Changed the wording from "patient" to "individual" throughout the policy for standardization.
12/01/23	Annual Review, approved November 20, 2023. No changes to policy statements.
05/01/24	Annual Review, approved April 9, 2024. Updated Dupixent (dupilumab) age requirement to 1 year and older for eosinophilic esophagitis.
06/01/24	Interim Review, approved May 13, 2024. Minor correction made to the age requirement for eosinophilic esophagitis.
07/01/24	Interim Review, approved June 24, 2024. Updated criteria clarifying that combination use with Tezspire (tezepelumab-ekko) is not allowed for the treatment of asthma. Updated criteria clarifying that combination use with Nucala (mepolizumab) or Xolair (omalizumab) is not allowed for the treatment of CRSwNP. Updated asthma criteria to include a prescriber requirement.
10/01/24	Interim Review, approved September 10, 2024. The following policy changes are effective January 3, 2025, following a 90-day provider notification. Updated asthma criteria eosinophil count from 150 cells/mcL within the last 12 months to 300 cells/mcL within the last 12 months. Updated asthma criteria to include the following alternative definitions of moderate-to-severe asthma: One or more asthma exacerbations requiring a hospitalization, an emergency department visit or an urgent care visit in the previous 12 months and FEV1 <80% predicted.
02/01/25	Annual Review, approved January 14, 2025. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Updated Dupixent (dupilumab) age requirement to from 18 years and older to 12 years and older for the treatment of chronic rhinosinusitis with nasal polyps. Updated asthma criteria eosinophil count from 300 cells/mcL within the last 12 months to 150 cells/mcL within the last 12 months. Added coverage criteria for the treatment of certain individuals with chronic obstructive pulmonary disease (COPD).
04/01/25	Interim Review, approved March 11, 2025. Updated asthma coverage criteria by removing the requirement to have confirmation of asthma with an eosinophilic phenotype documented in the previous 12 months. Updated the asthma coverage criteria from using maximum doses of an inhaled corticosteroid to using maximum tolerated doses of an inhaled corticosteroid.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review

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