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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 is the first systemic agent FDA-approved for the treatment of nasal polyps. 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.

Atopic dermatitis (AD) (a.k.a., atopic eczema) is a chronic, relapsing, pruritic inflammatory skin disease mediated by type 2 helper T (Th2) cells. The disease occurs most frequently in children, but also affects adults. About 70% of AD patients have a family history of atopic diseases (e.g., eczema, asthma, allergic rhinitis). In the US, 10.7% of children are affected by AD, with an onset of disease usually occurring before 5 years of age. Some children will continue to have persistent AD into adulthood, and it is

estimated that 3 and 7% of adults in the US are affected by AD. Dry skin and severe pruritus are the hallmark signs of AD; however, clinical presentation is highly variable depending upon age and disease activity. In adults, AD is more localized and lichenified, and the areas most often involved are the skin flexures. Treatment goals are to reduce symptoms (pruritus, dermatitis), prevent exacerbations, and improve patient quality of life (QoL). Most patients with AD have mild-to-moderate disease that can often be successfully managed with topical treatments. In patients with moderate-to-severe AD, skin lesions can encompass a large body-surface area (BSA) and are frequently accompanied by intense, persistent pruritus, leading to sleep deprivation, symptoms of anxiety or depression, and poor QoL. Severe AD is often refractory to topical treatments. Several disease severity scales [e.g., Investigator's Global Assessment (IGA) score, the SCORing Atopic Dermatitis (SCORAD) index, the Eczema Area and Severity Index (EASI), and the patient-oriented eczema measure (POEM)]] and patient QoL measurement scales have been tested and validated for use in clinical trials, but they are not commonly used in clinical practice.

The American Academy of Dermatology (AAD) 2014 Guidelines of Care for the Management of Atopic Dermatitis make various recommendations. The application of moisturizers should be an integral part of the treatment as there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention. Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. Twice-daily application of corticosteroids is generally recommended for the treatment of AD; however, evidence suggests that once-daily application of some corticosteroids may be sufficient. Proactive, intermittent use of topical corticosteroids as maintenance therapy (1 to 2 times/week) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone. Topical calcineurin inhibitors (TCI) are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with AD, and are particularly useful in selected clinical situations [i.e., recalcitrance to steroids, use on sensitive areas (e.g., face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use]. Proactive, intermittent use of TCI as maintenance therapy (2 to 3 times/week) on areas that commonly flare is recommended to help prevent relapses while reducing the need for topical corticosteroids, and is more effective than the use of emollients alone. Phototherapy is a second-line treatment, after failure of first-line treatment (emollients, topical steroids, and topical calcineurin inhibitors). Phototherapy can be used as maintenance therapy in patients with chronic disease. Systemic immunomodulatory agents are indicated for the subset of adult and pediatric patients in whom optimized topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease. Systemic immunomodulatory agents are indicated when the patient's skin disease has significant negative physical, emotional, or social impact. All immunomodulatory agents should be adjusted to the minimal effective dose once response is attained and sustained. Cyclosporine is effective and recommended as a treatment option for patients with AD refractory to conventional topical treatment. Azathioprine is recommended as a systemic agent for the treatment of refractory AD. Methotrexate is recommended as a systemic agent for the treatment of refractory AD. Folate supplementation is recommended during treatment with methotrexate. Mycophenolate mofetil may be considered as an alternative, variably effective therapy for refractory AD. Dupilumab is not addressed in the guidelines due to its approval after the guidelines.

The safety and efficacy of dupilumab leading to FDA approval for the treatment of atopic dermatitis in adults was established in 2,119 subjects 18 years of age and older with chronic (present for at least 3 years), moderate-to-severe AD not adequately controlled by topical medication during three randomized, double-blind, placebo-controlled studies [SOLO-1 (NCT02277743), SOLO-2 (NCT02277769), and LIBERTY AD CHRONOS (NCT02277769)]. Disease severity was defined by an IGA score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an EASI score ≥16 on a scale of 0 to 72,

and a minimum BSA involvement of ≥10%. At baseline, 59% of subjects were male, 67% were white, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged peak pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0 to 10. In all three trials, subjects in the dupilumab group received subcutaneous injections of 600 mg at Week 0, followed by 300 mg every other week. In the monotherapy trials (SOLO-1 and -2) subjects received dupilumab or placebo for 16 weeks. In the concomitant therapy trial (LIBERTY AD CHRONOS) subjects received dupilumab or placebo with concomitant topical corticosteroids and as needed topical calcineurin inhibitors for problem areas only, such as the face, neck, intertriginous and genital areas for 52 weeks. All three trials assessed the primary endpoint of the change from baseline to Week 16 in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement. Other endpoints include the proportion of subjects with EASI-75 (improvement of at least 75% in EASI score from baseline), and reduction in itch as defined by at least a 4-point improvement in the peak pruritus NRS from baseline to Week 16. The proportion of patients with an IGA score of 0 or 1 and at least a 2-point improvement at week 16 ranged from 36% to 39% for dupilumab-treated patients compared with 9% to 12% for placebo-treated patients. The detailed results are provided in the table below. The most common adverse reactions reported in clinical trials with dupilumab were injection site reactions, conjunctivitis, keratitis, and oral herpes.

Table 1: Efficacy Results at Week 16 in Adults with AD

Outcome	SOLO-1		SOLO-2		LIBERTY AD CHRONOS	
	Dupilumab 300 mg Q2W (n=224)	Placebo (n=224)	Dupilumab 300 mg Q2W (n=233)	Placebo (n=236)	Dupilumab 300 mg Q2W + TCS (n=106)	Placebo + TCS (n=315)
IGA 0 or 1	38%	10%	36%	9%	39%	12%
EASI-75	51%	15%	44%	12%	69%	23%
EASI-90	36%	8%	30%	7%	40%	11%
Peak Pruritus NRS (≥4-point improvement)	41%	12%	36%	10%	59%	20%

The safety and efficacy of dupilumab leading to FDA approval for the treatment of atopic dermatitis in adolescents was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (NCT03054428) in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥10%. Eligible subjects had previous inadequate response to topical medication in the past 6 months. 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 mean age was 14.5 years and the median weight was 59.4 kg. 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. 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 are presented in Table 2 below.

Table 2: Efficacy Results at Week 16 in Adolescents with AD

Outcome	Dupilumab (n=224)	Placebo (n=85)
IGA 0 or 1	24%	2%
EASI-75	42%	8%
EASI-90	23%	2%
Peak Pruritus NRS (≥4-point improvement)	37%	5%

The efficacy and safety of dupilumab leading to FDA approval for the treatment of asthma was assessed in three randomized, placebo-controlled, multicenter trials [Trial 1 – a phase 2b dose-ranging trial, Trial 2 - Liberty Asthma QUEST, and Trial 3 – Liberty Asthma VENTURE) for six months to one year (24 to 52 weeks). Subjects enrolled in Trials 1 and 2 were required to have (1) uncontrolled, moderate to severe asthma while taking a medium or high-dose inhaled corticosteroid plus an additional controller(s), and (2) a history of one 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 Trial 3 were required to have (1) uncontrolled, severe asthma while taking a high-dose inhaled corticosteroid plus an additional controller(s), and (2) dependence on daily oral corticosteroids (≥5 mg prednisone or equivalent). All trials enrolled patients irrespective of minimum baseline eosinophil levels. In Trial 2 (the largest trial, n=1,902), the average age was 49 years, average number of exacerbations in previous year was 2.2, average % predicted FEV1 at baseline was 61%, use of high-dose inhaled corticosteroid was 50%, and average baseline blood eosinophil count was 350 cells/mcL. As compared to placebo, dupilumab reduced the rate of severe asthma exacerbations by 46 to 48% and improved lung function in the overall population. Of note, the benefits in exacerbations were seen in patients with eosinophil counts ≥150 cells/microliter (66 to 67% reduction), which represented 70% of the patients enrolled. In subjects with baseline blood eosinophil count <150 cells/mcL, similar severe exacerbation rates were observed between dupilumab and placebo. Efficacy improved in patients with higher eosinophil counts (i.e., 150 to <300 vs. 300 to <500 vs. 500 or more). In Trial 3 (n=210), the average age was 51 years, the average number of exacerbations in previous year was 2.1, the average % predicted FEV1 at baseline was 52%, use of high-dose inhaled corticosteroid was 89%, and average baseline blood eosinophil count was 350 cells/mcL. Dupilumab reduced average daily oral corticosteroid dose by 70% vs. 42% with placebo at Week 24. More than half of patients treated with dupilumab (52%) completely eliminated use of oral corticosteroids vs. 29% with placebo. Also, at Week 24 asthma exacerbations were 59% lower in subjects receiving dupilumab vs. placebo {annualized rate of 0.65 vs. 1.60). Effects on lung function and on oral steroid and exacerbation reduction were similar for dupilumab irrespective of baseline blood eosinophil levels. Evidence-based practice guidelines or position statements from the American Academy of Allergy, Asthma and Immunology (AAAAI), European Respiratory Society/American Thoracic Society (ERS/ATS), Global Initiative for Chronic Obstructive Lung Disease (GOLD), and National Heart, Lung and Blood Institute (NHLBI) have not been updated to include recommendations surrounding the use of dupilumab. The Global Initiative for Asthma (GINA), Global Strategy for Asthma Management and Prevention 2019 Update do include the following regarding dupilumab - Dupilumab (anti-IL4 receptor α) is now recommended as an additional treatment option for patients ≥12 years with severe Type 2 asthma or OCS-depended asthma.

The efficacy and safety of dupilumab leading to FDA approval for the treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) was assessed in two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies [CSNP Trial 1 (SINUS-24, NCT02912468) and CSNP Trial 2 (SINUS-52, NCT02898454] in 724 subjects aged 18 years and older on background intranasal corticosteroids. 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. An endoscopic bilateral nasal polyps score (NPS) of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) was required. Subject also had to have ongoing symptoms (for at least 8 weeks) of nasal congestion/blockage/obstruction with moderate or severe symptom severity (score 2 or 3) and another symptom such as loss of smell, rhinorrhea (anterior/posterior). In CSNP Trial 1, subjects were randomized to receive either dupilumab 300 mg or placebo every other week for 24 weeks. In CSNP Trial 2, subjects were randomized to receive either dupilumab 300 mg every other week for 52 weeks, dupilumab 300 mg every other week until week 24 followed by every 4 weeks until week 52, or placebo. 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. A total of 63% of subjects reported previous sinus surgery, with a mean number of 2 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. The co-primary efficacy endpoints were change from baseline to Week 24 in bilateral endoscopic NPS (0 to 8 scale) and change from baseline to Week 24 in nasal congestion/obstruction score averaged over 28 days (NC; 0 to 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). The primary endpoint results at Week 24 are summarized in Table 3.

Table 3: Primary Endpoints in CRSwNP Trials at Week 24

	Placebo		**Dupixent 300 mg Q2W**		**LS mean difference (95% CI)**
Scores	Baseline mean	LS mean change	Baseline mean	LS mean change	
CSNP Trial 1	n=133		n=143		
NPS	5.86	0.17	5.64	-1.89	-2.06 (-2.43, -1.69)
NC	2.45	-0.45	2.26	-1.34	-0.89 (-1.07, -0.71)
CSNP Trial 2	n=153		n=295		
NPS	5.96	0.10	6.18	-1.71	-1.80 (-2.10, -1.51)
NC	2.38	-0.38	2.46	-1.25	-0.87 (-1.03, -0.71

The American College of Allergy, Asthma & Immunology's 2014 publication "Diagnosis and management of rhinosinusitis: a practice parameter update" do not address the use of dupilumab. The guidelines do include a treatment algorithm for CRRwNP that addresses appropriate evaluation, imaging, and first-line use of nasal corticosteroids. Recommendations for surgery are also included.

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 **BOTH** of the following criteria are met ("1" and "2"):

1. Dupilumab is administered for an indication listed in Table 3, and **ALL** of the indication-specific criteria are met
2. The dosage of dupilumab does not exceed the following:
    a. Atopic dermatitis
        i. 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
        ii. Pediatric members (6 to 17 years of age)
            1. Weight of 15 kg to less than 30 kg
                - 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
            2. 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
            3. 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
    b. Chronic rhinosinusitis with nasal polyposis - 300 mg every two weeks (no loading dose)
    c. 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
    d. Eosinophilic esophagitis (18 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

Table 4

Indications and Specific Criteria

Indication	**Specific Criteria**
Moderate-to-severe atopic dermatitis (AD)	When **ALL** of the following are met ("1" to "7"): 1. The member is 6 years of age or older 2. Dupilumab is prescribed by a dermatologist **OR** allergist/immunologist 3. The member has a documented diagnosis of moderate-to-severe atopic dermatitis (AD) as supported by **EITHER** of the following ("a" or "b") [supportive medical record documentation must be submitted]: a. 10% or more of the member's body surface area (BSA) has AD involvement b. AD involvement is less than 10% of the member's BSA but the symptoms are causing severe impairment of the member's activities of daily living (ADL) and/or causing very poor health-related quality of life (QoL) – the specific symptoms and the specific impact on ADLs and/or QoL must be provided 4. Alternative causes of pruritic inflammatory skin disease (e.g., contact dermatitis, psoriasis, scabies, cutaneous drug reactions, ichthyoses, seborrheic dermatitis, etc.) have been ruled out or are being actively managed 5. The member is adherent with conservative, non-pharmacologic measures [i.e., daily use of a skin moisturizer/emollient and limitation of exacerbating factors such as harsh soaps/detergents/cleansers, low humidity, and stress] 6. **EITHER** of the following ("a" or "b'), **OR** treatment or continued treatment is not advisable due to FDA-labeled contraindication(s) or intolerable adverse effect(s) to **ALL** treatment options below (i.e., topical corticosteroid, topical calcineurin inhibitor, phototherapy, and systemic immunosuppressant) [the specific adverse effect(s) or contraindication(s) must be provided]: a. The member has had an inadequate response to a sufficient trial of **BOTH** of the following topical treatments ("i" and "ii") [the specific duration of treatment must be provided]. At least one of the topical treatments must have been used in the past 12 months. i. A topical corticosteroid – **EITHER** of the following: • One or more AD disease flares that did not adequately respond to at least 3 weeks of daily treatment with a high-potency topical corticosteroid (group II or greater potency – see Table 2 in "Other" section), unless the member's AD involvement is limited to the face and intertriginous areas in which a lower-potency corticosteroid may be used • Inadequate response to maintenance therapy that includes intermittent use (at least 2 days per week) for at least 3 months of a moderate-to-high-potency topical corticosteroid (group IV or greater potency – see Table 2 in "Other" section), unless the member's AD involvement is limited to the face and intertriginous areas in which a lower-potency corticosteroid may be used

	ii. A topical calcineurin inhibitor [i.e., pimecrolimus (Elidel) or tacrolimus (Protopic)] - **EITHER** of the following: • One or more AD disease flares that did not adequately respond to at least 6 weeks of daily treatment • Inadequate response to maintenance therapy that includes intermittent use (at least 2 days per week) for at least 3 months b. The member has had an inadequate response to a 3-month or longer trial of **EITHER** of following treatments in the past 12 months ("i" or "ii") [the specific duration of treatment must be provided]: i. Phototherapy (e.g., PUVA, UVB) ii. Systemic immunosuppressant therapy (e.g., cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, or interferon gamma) 7. Dupilumab will **NOT** be used in combination with another biologic agent for the treatment of atopic dermatitis [e.g., omalizumab (Xolair), mepolizumab (Nucala), reslizumab (Cinqair), rituximab (Rituxan), etanercept (Enbrel), infliximab products]
Moderate-to-severe asthma	When **ALL** of the following are met ("1" to "5"): 1. The member is 12 years of age or older 2. Dupilumab is prescribed by an allergist, immunologist, or pulmonologist 3. Member's symptoms remain uncontrolled or inadequately controlled despite treatment with at least ONE of the following ("a", "b", "c", or "d") a. 12 months of moderate- to high-dose inhaled corticosteroids (see Table 3) used in combination with a long-acting beta agonist (e.g., formoterol fumarate (Foradil), salmeterol xinafoate (Serevent)) for a minimum of 3 months b. 12 months of moderate- to high-dose inhaled corticosteroids (see Table 3) used in combination with a leukotriene modifier (e.g., montelukast, zafirlukast) for a minimum of 3 months c. 12 months of moderate- to high-dose inhaled corticosteroids (see Table 3) used in combination with theophylline for a minimum of 3 months d. 6 months of moderate- to high-dose inhaled corticosteroids (see Table 3) with daily oral corticosteroids used in combination with at least one additional controller medication (i.e., long-acting beta agonist, leukotriene modifier, theophylline) for a minimum of 3 months 4. At least **ONE** of the following ("a" or "b"): a. Member is dependent on continuous oral corticosteroid treatment for at least 6 months at dosage of 5 mg or more per day of prednisolone or prednisone (or equivalent dose of another steroid) – validated by claims history when possible b. **BOTH** of the following ("i" and "ii"): i. In the past year, the member has a history of **ONE** or more exacerbations requiring systemic glucocorticoids, an emergency

	department visit, or hospitalization ii. Member's eosinophil count is at least 150 cells/microliter during the previous six weeks – laboratory documentation must be provided 5. Dupilumab will **NOT** be used in combination with another biologic agent for the treatment of asthma [e.g., omalizumab (Xolair), mepolizumab (Nucala), reslizumab (Cinqair), benralizumab (Fasenra)]
Chronic rhinosinusitis with nasal polyposis (CRSwNP)	When **ALL** of the following are met ("1" to "7"): 1. The member is 18 years of age or older 2. Dupilumab is prescribed by an allergist/immunologist, **OR** otolaryngologists [ear, nose and throat (ENT) specialist] 3. The member has **BOTH** moderate to severe symptoms of nasal obstruction **AND** either rhinorrhea or decreased sense of smell for 12 weeks or more 4. Bilateral sinonasal polyposis reaching below the lower border of the middle turbinate or beyond in each nostril has been confirmed by nasal endoscopy or sinus CT scan – documentation of the imagining study findings must be provided 5. **ANY** of the following ("a", "b", or "c"): a. The member has had prior sinus surgery to remove polyps b. The member has had an inadequate response to at least 8 weeks of continuous treatment with an intranasal corticosteroid in the past 2 years c. **BOTH** of the following: • The member has had intolerable adverse effects, or has an FDA-labeled contraindication to treatment with an intranasal corticosteroid – the specific contraindication or adverse effect(s) must be provided • Member is not a candidate for sinus surgery to remove polyps – reason(s) for non-candidacy must be provided 6. The member will be using a daily intranasal corticosteroid during treatment with dupilumab, unless they have an FDA-labeled contraindicated or prior intolerable adverse effects - the specific contraindication or adverse effect(s) must be provided 7. Dupilumab will NOT be used in combination with another biologic agent for the treatment of CRSwNP [e.g., omalizumab (Xolair), mepolizumab (Nucala), reslizumab (Cinqair), benralizumab (Fasenra)]
Eosinophilic esophagitis [orphan indication]	When **ALL** of the following are met ("1" to "5"): 1. The member is 18 years of age or older 2. Dupilumab is prescribed by a gastroenterologist **OR** allergist/immunologist 3. The members diagnosis has been confirmed by an endoscopic esophageal biopsy showing the presence of eosinophils (e.g., ≥15 eosinophils per high power field) – the biopsy results confirming the

	diagnosis must be submitted 4. The member has had an inadequate response, intolerable adverse effects, or contraindications to **ALL** the following treatments ("a", "b", and "c") – the specific contraindication(s) or adverse effect(s) must be provided: a. Dietary therapy (i.e., avoidance of food allergen triggers) b. Proton pump inhibitor (e.g., esomeprazole, pantoprazole) for at least 8 weeks c. Topical corticosteroid (e.g., fluticasone propionate, budesonide) 5. Dupilumab will **NOT** be used in combination with another biologic agent for the treatment of eosinophilic esophagitis [e.g., omalizumab (Xolair), mepolizumab (Nucala), reslizumab (Cinqair), anti-TNF therapies]
Approval duration: 6 months	

Continuation of dupilumab (Dupixent) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7"):

1. An authorization or reauthorization for dupilumab has been previously approved by Florida Blue or another health plan in the past 2 years [the use of samples does **NOT** qualify] for the treatment of a condition listed in Table 4, **OR** the member has previously met all indication-specific initiation criteria
2. **EITHER** of the following ("a" or "b") based on the indication for use and duration of treatment:
    a. 18 or more months of treatment (all indications) – member continues to maintain a clinically meaningful benefit as compared to before treatment with dupilumab
    b. Less than 18 months of treatment:
        i. Asthma - member has had a clinically meaningful beneficial response to dupilumab therapy as compared to their baseline status (before dupilumab treatment) as evidenced by at least **ONE** of the following [supportive medical record documentation must be submitted]:
            - Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids)
            - Increase in predicted FEV1 from pretreatment baseline
            - Reduction in reported asthma-related symptoms, such as, asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing
            - Decreased dose or frequency of systemic corticosteroid treatment
        ii. Atopic dermatitis - member has had a clinically meaningful beneficial response to dupilumab therapy as compared to their baseline status (before dupilumab treatment) as evidenced by **TWO or more** of the following [supportive medical record documentation must be submitted]:
            - Reduction in disease severity (e.g., erythema, dryness, edema/papulation, excoriations, lichenification, oozing/crusting)
            - Reduction in the frequency or intensity of pruritus
            - Reduction in the frequency of disease exacerbations/flairs
            - Reduction in the BSA with AD involvement
            - Improvement in overall patient quality of life (e.g., improved sleep, less depression or anxiety, etc.)

iii. CRSwNP - member has had a clinically meaningful beneficial response to dupilumab therapy as compared to their baseline status (before dupilumab treatment) as evidenced by a reduction in disease severity (e.g., reduction in nasal congestion, nasal polyp size, anterior or posterior rhinorrhea, sinonasal inflammation, facial pressure/pain; improved sese of smell; or reduction in corticosteroid use) [supportive medical record documentation must be submitted]

iv. Eosinophilic esophagitis - member has had a clinically meaningful beneficial response to dupilumab therapy as compared to their baseline status (before dupilumab treatment) as evidenced by less frequent or less severe esophagitis symptoms (e.g., dysphasia, heartburn, chest pain, regurgitation, abdominal pain, nausea, and vomiting) [supportive medical record documentation must be submitted]

3. Dupilumab is prescribed by, or in consultation with, one of the following specialists based on the indication for use:
   a. Asthma – a pulmonologist **OR** allergist/immunologist
   b. Atopic dermatitis – a dermatologist **OR** allergist/immunologist
   c. CRSwNP – otolaryngologists [ear, nose and throat (ENT) specialist] **OR** allergist/immunologist
   d. Eosinophilic esophagitis – a gastroenterologist **OR** allergist/immunologist
4. The member meets the following age requirement based on the indication for use:
   a. Atopic dermatitis - 6 years of age or older
   b. Asthma - 12 years of age or older
   c. CRSwNP and eosinophilic esophagitis - 18 years of age or older
5. Dupilumab will **NOT** be used in combination with another biologic agent for the treatment of the member's disease [e.g., omalizumab (Xolair), mepolizumab (Nucala), reslizumab (Cinqair), benralizumab (Fasenra), rituximab (Rituxan), etanercept (Enbrel), infliximab products]
6. For CRSwNP only - the member is using a daily intranasal corticosteroid during treatment with dupilumab, unless they have an FDA-labeled contraindicated or prior intolerable adverse effects – the specific contraindication or adverse effect(s) must be provided
7. The dosage of dupilumab does not exceed the following:
   a. Atopic dermatitis
      - Age 6 to 17 years old and weight less than 30 kg – 300 mg every 4 weeks
      - Age 6 to 17 years old and weight 30 kg to less than 60 kg - 200 mg every 2 weeks
      - Age 18 years or older, or weight 60 kg or more - 300 mg every two weeks
   b. All other indications - 300 mg every two weeks

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 patients aged 6 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 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 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. The recommended dose in pediatric 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. 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. 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 with moderate-to-severe asthma aged 12 years and older with 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. 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 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, **OR**
    - An initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week
    - 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

Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)

- Indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.
- The recommended dose for adult patients is 300 mg given every other week.

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 syringes (200 mg/1.14 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 generalized urticaria, rash, erythema nodosum, and serum sickness or serum sickness-like reactions were reported in less than 1% of subjects who received dupilumab in clinical trials. If a systemic hypersensitivity reaction occurs, discontinue dupilumab immediately and initiate appropriate therapy.
- **Conjunctivitis and Keratitis** - 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. Members should report new onset or worsening eye symptoms to their healthcare provider.
- **Eosinophilic Conditions** – Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with dupilumab in adult patients who participated in the asthma development program. A causal association between dupilumab and these conditions has not been established.
- **Acute Asthma Symptoms or Deteriorating Disease** - Dupilumab should not be used to treat acute asthma symptoms or acute exacerbations. Do not use to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma 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.

- **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.
- **Live Vaccines** - 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
J45.40 – J45.42	Moderate persistent asthma
J45.50 – J45.52	Severe persistent asthma
J82.83	Eosinophilic asthma
K20.0	Eosinophilic esophagitis
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

ICD-10 Diagnosis Codes That Support Medical Necessity

C9399	Unclassified drugs or biologicals (Hospital outpatient use ONLY)
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.

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:

Benralizumab (Fasenra), 09-J2000-92

Mepolizumab (Nucala), 09-J2000-54

Omalizumab (Xolair), 09-J0000-44

Psoralens with Ultraviolet A (PUVA), 02-10000-16

Reslizumab (Cinqair) IV infusion, 09-J2000-63

OTHER:

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 5: 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

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginaasthma.org.

Table 6: Relative Potencies of Topical Corticosteroids

Class	Drug	Dosage form(s)	Strength (%)
I. Very high potency	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. High potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III to IV. Medium potency	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate	Cream	0.1

	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamcinolone acetonide	Cream, ointment	0.1
V. Lower-medium potency	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
VI. Low potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution	0.01
VII. Lowest potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5 to 1

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/14/20.

GUIDELINE UPDATE INFORMATION:

06/15/17	New Medical Coverage Guideline.
01/15/18	Revision to the guideline consisting of updating the position statement in regards 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.