


## PHARMACY POLICY – 5.01.575

## Dupixent® (dupilumab)

Effective Date:	Jan. 1, 2019	RELATED MEDICAL POLICIES:
Last Revised:	Dec. 19, 2018	5.01.513 Xolair® (omalizumab)
Replaces:	N/A	5.01.559 IL-5 Inhibitors

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## Introduction

Atopic dermatitis (AD) is a chronic skin condition. (Chronic means the condition lasts as 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 the 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. This policy describes when Dupixent may be considered medically necessary to treat AD or asthma.

**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
<p><b>Atopic dermatitis</b></p>	<p><b>Dupixent® (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:</b></p> <ul style="list-style-type: none"> <li>• The patient has a diagnosis of atopic dermatitis involving ≥10% of his or her body surface area (BSA)               <ul style="list-style-type: none"> <li>○ <b>Exception:</b> 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.</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Patient has had an inadequate response or intolerance to one topical calcineurin inhibitor medication, such as tacrolimus or Elidel® (pimecrolimus).</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Patient has had an inadequate response or intolerance to two topical corticosteroid medications of high potency, such as: betamethasone dipropionate, mometasone furoate, fluocinonide, or clobetasol propionate.</li> </ul> <p><b>Re-authorization criteria:</b></p> <ul style="list-style-type: none"> <li>• Initial approval for dupilumab will be authorized for 6 months.</li> <li>• Subsequent re-authorization would require documentation showing improvement in the disease, measured by:               <ul style="list-style-type: none"> <li>○ Decrease in the BSA involvement</li> <li>○ Amelioration of the associated symptoms (ie, pruritus, inflammation, redness, etc.)</li> </ul> </li> </ul>
<p><b>Moderate-to-severe asthma</b></p>	<p><b>Dupixent® (dupilumab) may be considered medically necessary for the treatment of patients 12 years of age and older with moderate-to-severe asthma when:</b></p> <ul style="list-style-type: none"> <li>• The patient has a diagnosis of moderate-to-severe asthma</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Patient is 12 years of age or older</li> </ul>



Indication	Medical Necessity
	<p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Patient is using maximum doses of an inhaled corticosteroid</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Patient is using an inhaled long-acting beta-agonist (LABA)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Patient has oral corticosteroid dependent asthma defined as: <ul style="list-style-type: none"> <li>○ Two or more asthma exacerbations in the previous 12 months requiring use of oral corticosteroids</li> </ul> </li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>○ Has a dependence on oral corticosteroids of at least 5 mg per day of prednisone or equivalent</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Patient has asthma with an eosinophilic phenotype determined by AT LEAST ONE of the following two criteria: <ul style="list-style-type: none"> <li>○ Blood eosinophil** count greater than 150 cells/mcL at the time of treatment</li> </ul> </li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>○ Sputum eosinophil** count greater than or equal to 3%</li> </ul> <p><b>**Note:</b> 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 patient is unresponsive to their regular maintenance (inhaled or oral) corticosteroid treatment, in which case dupilumab can be considered medically necessary.</p> <p><b>Re-authorization criteria:</b></p> <ul style="list-style-type: none"> <li>• Initial approval for dupilumab will be authorized for 6 months.</li> <li>• Subsequent re-authorization would require documentation showing improvement as measured by: <ul style="list-style-type: none"> <li>○ Decrease in requirements for oral steroids, exacerbation frequency, ER and urgent care visits, hospitalizations</li> </ul> </li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>○ Decrease in frequency and severity of asthma symptoms</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>○ Increase in quality of life measures and ability to perform activities of daily living</li> </ul>



Drug	Investigational
Dupixent® (dupilumab)	<p>Use of dupilumab in patients &lt; 12 years of age is considered investigational.</p> <p>All other uses of dupilumab for conditions not outlined in the <b>Medical Necessity</b> section above are considered investigational.</p>

Dosage and Quantity Limits	
Condition	Dosage and Quantity Limit
Moderate-to-severe atopic dermatitis	<ul style="list-style-type: none"> <li>Initial dose of 600mg SC (two 300mg injections in different injection sites), followed by 300mg given every other week</li> </ul>
Moderate-to-severe asthma	<ul style="list-style-type: none"> <li>Initial dose of 400mg SC (two 200mg injections in different injection sites), followed by 200mg given every other week</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Initial dose of 600mg SC (two 300mg injections in different injection sites), followed by 300mg given every other week</li> </ul>

## Coding

N/A

## 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.<sup>10</sup> Disease onset is typically in early childhood, with approximately 45% of patients 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 U.S. 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 inpatient 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 patients 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 patients with AD, however, are unknown.<sup>9</sup> 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 increase susceptibility to infection and superinfections seen in these patients.

Successful management of AD includes not only clearance of skin lesions, control of itch, minimizing or eliminating triggers, minimizing or prevent adverse events from medications, and providing adequate social and psychological support for the patient, 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 patients and there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention.<sup>12</sup> 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 patients who have failed to respond to good skin care and regular use of emollients alone.<sup>9</sup> The choice of corticosteroid depends on a variety of factors, such as patient age, areas of body to which the medication will be applied, and other patient factors such as degree of xerosis, patient 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 has been shown to be clinically helpful in patients with AD, however, it is not routinely recommended. In patients 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 patients, phototherapy may worsen the AD and is not recommended in patients whose disease flares up when exposed to sunlight.

Systemic immunomodulatory agents are indicated for patients 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 patients with refractory atopic dermatitis. Interferon gamma may be considered in refractory AD patients 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 shared 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.

## 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)
<b>Super-high potency (group 1)</b>	Betamethasone dipropionate, augmented	Ointment, optimized	Diprolene	0.05
		Lotion	Diprolene	0.05
		Gel	Diprolene	0.05
	Clobetasol propionate	Ointment	Temovate	0.05
		Cream	Temovate	0.05
		Cream, emollient base	Temovate E	0.05



Potency group*	Corticosteroid	Vehicle type/form	Trade names (United States)	Available strength(s), % (except as noted)
		Gel	Temovate	0.05
		Lotion	Clobex	0.05
		Foam aerosol	Olux-E	0.05
		Foam aerosol (scalp)	Olux	0.05
		Shampoo	Clobex	0.05
		Solution (scalp)	Temovate, Cormax	0.05
		Spray aerosol	Clobex	0.05
	Diflucortolone valerate (not available in United States)	Ointment, oily cream	Nerisone Forte (United Kingdom, others)	0.3
	Fluocinonide	Cream	Vanos	0.1
	Flurandrenolide	Tape (roll)	Cordran	4 mcg/cm <sup>2</sup>
	Halobetasol propionate	Ointment	Ultravate	0.05
Cream		Ultravate	0.05	
Lotion		Ultravate	0.05	
<b>High potency (group 2)</b>	Amcinonide	Ointment	Cyclocort <sup>†</sup> , Amcort <sup>†</sup>	0.1
		Ointment	Diprosone	0.05
		Cream, augmented formulation (AF)	Diprolene AF	0.05
	Desoximetasone	Ointment	Topicort	0.25
		Cream	Topicort	0.25
		Gel	Topicort	0.05
	Diflorasone diacetate	Ointment	ApexiCon <sup>†</sup> , Florone <sup>†</sup>	0.05
		Cream, emollient	ApexiCon E	0.05
	Fluocinonide	Ointment	Lidex <sup>†</sup>	0.05
		Gel	Lidex <sup>†</sup>	0.05
		Cream anhydrous	Lidex <sup>†</sup>	0.05
		Solution	Lidex <sup>†</sup>	0.05





Potency group*	Corticosteroid	Vehicle type/form	Trade names (United States)	Available strength(s), % (except as noted)
	Halcinonide	Ointment	Halog	0.1
		Cream	Halog	0.1
<b>High potency (group 3)</b>	Amcinonide	Cream	Cyclocort <sup>†</sup> , Amcort <sup>†</sup>	0.1
		Lotion	Amcort <sup>†</sup>	0.1
	Betamethasone dipropionate	Cream, hydrophilic emollient	Diprosone	0.05
		Betamethasone valerate	Ointment	Valisone <sup>†</sup>
	Foam		Luxiq	0.12
	Diflorasone diacetate	Cream	Florone <sup>†</sup>	0.05
	Diflucortolone valerate (not available in United States)	Cream, oily cream, ointment	Nerisone (Canada, United Kingdom, others)	0.1
	Fluocinonide	Cream aqueous emollient	Lidex-E <sup>†</sup>	0.05
	Fluticasone propionate	Ointment	Cutivate	0.005
Triamcinolone acetonide	Ointment	Kenalog <sup>†</sup>	0.15	
	Cream	Triderm, Aristocort HP <sup>†</sup>	0.51	

## Consideration of Age

The age noted in the policy statement is based on the FDA labeling for this agent.

## Evidence Review



## Evidence of Efficacy from Clinical Trials

### *Atopic Dermatitis*

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 IGA scores compared to placebo at week 16.<sup>1</sup> 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 patients 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 patients, 52% of dupilumab weekly patients, and 15% of placebo patients achieved improvement on the 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  $72.3 \pm 2.6$ ,  $72.0 \pm 2.6$ , and  $37.6 \pm 3.3$  for the every other week group, the weekly group, and the placebo group respectively. Significantly more patients 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 patients 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  $69.1 \pm 2.5$ ,  $67.1 \pm 2.5$ , and  $30.9 \pm 3.0$  for the every other week group, the weekly group, and the placebo group respectively. A total of at least 3 patients 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 patients 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<sup>16</sup>, 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 patients 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 patients achieving IGA score 0/1 and reduction of  $\geq 2$  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 patients 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.<sup>2</sup> 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 patients 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 patients would need to be treated with dupilumab in order to have at least one patient achieve an IGA score of 0 or 1. Reductions in pruritus NRS score and the number of patients 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 patients with moderate-to-severe AD in a randomized, placebo-controlled, double-blind dupilumab dosing trial.<sup>3</sup> 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 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 patients 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.<sup>2</sup> Percent changes in the EASI score, proportion of patients with an IGA score of 0 or 1, proportion of patient 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 patients with moderate-to-severe asthma should be assessed when available to understand the long-term efficacy of the drug.



## *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/  $\mu\text{L}$ , 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/ $\mu\text{L}$ . Also, there was no dose-dependent effect observed. Change in respiratory function, as measured by  $\text{FEV}_1$ , was a co-primary endpoint in the QUEST study. Subjects in the dupilumab 200mg group had an improvement in  $\text{FEV}_1$  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  $\text{FEV}_1$  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/ $\mu\text{L}$ . 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.



## 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.<sup>1</sup> The incidence of nasopharyngitis was generally balanced across dupilumab and placebo groups. Dupilumab-treated patients 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 patients receiving weekly dupilumab 300mg and 3 receiving placebo in SOLO 1, and 1 patient receiving weekly dupilumab 300 mg and 5 patients receiving placebo in SOLO 2. LIBERTY AD CHRONOS had reports of severe allergic conjunctivitis (one patient each in the dupilumab qw plus topical corticosteroids and placebo plus topical corticosteroids groups) and severe bacterial conjunctivitis (one patient 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.

Two studies assessing the safety profile of long-term dupilumab treatment in adults with moderate-to-severe asthma are currently ongoing.

### *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 patient-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 patients on dupilumab vs.



two patients 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.

## 2018 Update

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

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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.
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





Date	Comments
	of Atopic Dermatitis" to "Dupixent® (dupilumab)". Added medical necessity criteria for the treatment of moderate-to-severe asthma.

**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 and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

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Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357  
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200 Independence Avenue SW, Room 509F, HHH Building  
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)  
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**አማርኛ (Amharic):**

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀዳሾች ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለመጠበቅና በአስፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መሰታወቅ አለዎት። በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

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សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កិច្ចការផ្ទៃក្នុងដូចជា ឆន្ទៈនិងការគ្រប់គ្រងធនធានរបស់អ្នក ឬប្រាក់ជំនួយចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

**ਪੰਜਾਬੀ (Punjabi):**

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਨਵ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

**فارسی (Farsi):**

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

**Polskie (Polish):**

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

**Português (Portuguese):**

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

**Română (Romanian):**

Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

**Русский (Russian):**

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

**Fa'asamoa (Samoan):**

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

**Español (Spanish):**

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

**Tagalog (Tagalog):**

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

**ไทย (Thai):**

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

**Український (Ukrainian):**

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

**Tiếng Việt (Vietnamese):**

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).