**Introduction**

Atopic Dermatitis (AD) is a chronic, pruritic inflammatory skin disease that predominantly affects the pediatric population with a low prevalence in adults. The clinical manifestations of AD include erythematous papules and plaques with oozing, scale, crust, excoriations, and lichenification. This skin disease is commonly associated with other atopic disorders, such as allergic rhinitis and asthma.

There is no objective diagnostic test that confirms the presence of AD; however, some signs, symptoms and other factors are commonly used in its diagnosis. Common signs, symptoms, and factors include pruritus, early age of onset, eczematous skin lesions that vary with age, chronic and relapsing courses, dry and flaky skin, immunoglobulin E (IgE) reactivity, family or personal history of asthma or hay fever, or other atopic diseases. Allergy skin testing may be an option in identifying factors that trigger flares of AD; however, positive test results may not always be related to disease activity or could be a false positive.

An essential feature of AD is pruritus, and a diagnosis cannot be made if there is no history of itching. Pruritus can be trigged by a variety of factors, such as heat and perspiration, wool, emotional stress, certain foods, alcohol, upper respiratory infections, and house dust mites. Scratching and rubbing may further irritate the skin, increasing inflammation, and exacerbate itchiness.

Patients with AD are prone to skin infections due to atopic skin being drier and the stratum corneum having weakened protective abilities. These skin features combined with abnormal skin barrier function and immune defense leave patients at an increase risk of secondary bacterial
skin infections with staphylococci or streptococci and viral infections such as herpes simplex or even fungal infections. Relieving pruritus through constant scratching may cause excoriations, further compromising the integrity of the skin barrier.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
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<tbody>
<tr>
<td>Dupilumab (Dupixent®) SC</td>
<td>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:</td>
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<tr>
<td></td>
<td>• The patient has a diagnosis of atopic dermatitis involving ≥10% of his or her body surface area (BSA)</td>
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<td>o <strong>Exception</strong>: 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.</td>
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<td><strong>AND</strong></td>
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<td></td>
<td>• Patient has had an inadequate response or intolerance to one topical calcineurin inhibitor medication, such as tacrolimus or Elidel.</td>
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<td><strong>AND</strong></td>
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<td></td>
<td>• 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.</td>
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</table>

**Re-authorization criteria:**

• Initial approval for dupilumab will be authorized for 6 months. Subsequent re-authorization would require documentation showing improvement in the disease, measured by:
  o Decrease in the BSA involvement
**Drug**

<table>
<thead>
<tr>
<th>Medical Necessity</th>
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<tbody>
<tr>
<td>○ Amelioration of the associated symptoms (i.e. pruritus, inflammation, redness, etc.)</td>
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</table>

**Drug**

<table>
<thead>
<tr>
<th>Investigational</th>
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<tbody>
<tr>
<td>Dupilumab (Dupixent®) SC</td>
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**Dosage and Quantity Limits**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage and Quantity Limit</th>
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<tbody>
<tr>
<td>Moderate to severe atopic dermatitis</td>
<td>• Initial dose of 600mg SC (two 300mg injections in different injection sites), followed by 300mg given every other week.</td>
</tr>
</tbody>
</table>

**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.¹⁰ 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. 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. 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. 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 adequate 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 share alpha chain subunit of the IL-4 and IL-13 receptors. Binding to these alpha chain subunits results in the inhibition of signaling of IL-4 and IL-13, which are type 2 inflammatory cytokines that may be important drivers of atopic or allergic diseases such as AD or asthma. Dupilumab is injected subcutaneously (SC).

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

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

**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 671 subjects with moderate-to-severe AD demonstrate 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. 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 achieved 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. A limitation of the results lies within the short time horizon of the studies and at least 15% of patients in the dupilumab treatment groups receiving rescue treatment, 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 (LS percent change: 72.3 ± 2.6), 52% of dupilumab weekly patients (Least squares (LS) percent change: 72.0 ± 2.6), and 15% of placebo patients (LS percent change: 37.6 ± 3.3) achieved improvement on the EASI score of at least 75% (p<0.0001 for all comparisons) and 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. EASI score improvements were achieved in 36% of patients in the dupilumab every other week group (LS percent change: 69.1 ± 2.5) and weekly group (LS percent change: 67.1 ± 2.5) and 8% in the placebo group (LS percent change: 30.9 ± 3.0). 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).

In addition to the two trials above, there were two 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. The percentage reduction in the EASI score was consistently greater with dupilumab than with placebo at week 12 (change in EASI score ± SD: placebo group, -23.3 ± 6.7; dupilumab group, -74.0 ± 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. 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. is the only publication that included 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. 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.

**Evidence of Safety**

**Atopic Dermatitis**

Two Phase 3, placebo-controlled studies for the treatment of AD have identified the most common adverse events with dupilumab to be injection-site reactions and nasopharyngitis.\(^1\) The incidence of nasopharyngitis was generally balanced across dupilumab and placebo groups, however, dupilumab-treated patients had a higher incidence of injection-site reactions. Rates of conjunctivitis with an unspecified cause and allergic conjunctivitis were higher in dupilumab groups than in the placebo groups. The only serious adverse event reported in these studies 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. The safety profile of dupilumab was consistent across studies conducted for the treatment of AD.

There is one completed trial that assesses the long-term safety of dupilumab in patients with moderate-to-severe AD, however, data has not been published at this time.

Two published Phase 2 studies for the treatment of asthma yielded safety results consistent to the two 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.

**References**


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>05/01/17</td>
<td>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.</td>
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</tbody>
</table>
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Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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