Introduction

Atopic dermatitis (AD) is a chronic skin condition. (Chronic means the condition lasts a long time or returns again and again.) Symptoms of AD include weeping, oozing plaques, itchy skin, raised red rashes or rashes that appear to have small blisters, dry and flaky skin, and increased allergic reaction (IgE reactivity). A person with AD may also have a personal or family history of hay fever or other skin conditions. The itchy skin can be triggered by a number of situations. These include heat and perspiration, wool, emotional stress, specific foods, and house dust mites. Scratching and rubbing irritate the skin and increase inflammation, which leads to more itching.

Medications called corticosteroids are often successful in treating AD. Asthma is a long-term lung condition affecting the airways of the lung. Asthma causes the airways to become inflamed. Inhaling certain substances such as tobacco smoke, pet dander, and dust mites can set off a chain reaction. The immune system produces substances called cytokines that contribute to 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. Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a condition where the sinuses and nasal passages become inflamed and contain non-cancerous growths (polyps). Symptoms of CRSwNP include mucus drainage from the nose or down the back of the throat, facial pain, pressure and/or a sensation of fullness, nasal blockage, and a reduced sense of smell. Dupixent® is a drug that is prescribed as an add-on treatment for CRSwNP that isn’t controlled by using an intranasal corticosteroid. This policy describes when Dupixent® may be considered medically necessary to treat AD, asthma or CRSwNP.
**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.

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**Policy Coverage Criteria**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Atopic dermatitis   | Dupixent® (dupilumab) may be considered medically necessary for the treatment of patients 12 years of age and older with moderate to severe atopic dermatitis when:  
  • The patient has a diagnosis of atopic dermatitis involving ≥10% of his or her body surface area (BSA)  
    o **Exception:** this may be granted for extensive recalcitrant facial involvement, pustular involvement of the hands or feet, and genital involvement which interferes with normal sexual function.  
  AND  
  • Patient has had an inadequate response or intolerance to one topical calcineurin inhibitor medication, such as pimecrolimus or tacrolimus.  
  AND  
  • 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.  
    o **Exception:** this may be granted for face or genital involvement  
  AND  
  • For adults the maintenance dose prescribed is 300 mg given every other week  
  OR  
  • For adolescents the maintenance dose prescribed is:  

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-to-severe asthma</td>
<td>Dupixent® (dupilumab) may be considered medically necessary for the treatment of patients 12 years of age and older with moderate-to-severe asthma when:</td>
</tr>
<tr>
<td></td>
<td>• The patient has a diagnosis of moderate-to-severe asthma</td>
</tr>
<tr>
<td></td>
<td>• Patient is 12 years of age or older</td>
</tr>
<tr>
<td></td>
<td>• Patient is using maximum doses of an inhaled corticosteroid</td>
</tr>
<tr>
<td></td>
<td>• Patient is using an inhaled long-acting beta-agonist (LABA)</td>
</tr>
<tr>
<td></td>
<td>• Patient has oral corticosteroid dependent asthma defined as:</td>
</tr>
<tr>
<td></td>
<td>• Two or more asthma exacerbations in the previous 12 months requiring use of oral corticosteroids</td>
</tr>
<tr>
<td></td>
<td>• Has a dependence on oral corticosteroids of at least 5 mg per day of prednisone or equivalent</td>
</tr>
<tr>
<td></td>
<td>• Patient has asthma with an eosinophilic phenotype determined by AT LEAST ONE of the following two criteria:</td>
</tr>
<tr>
<td></td>
<td>• Blood eosinophil** count greater than 150 cells/mcL at the time of treatment</td>
</tr>
<tr>
<td></td>
<td>• Sputum eosinophil** count greater than or equal to 3%</td>
</tr>
<tr>
<td></td>
<td>• For adults and adolescents the maximum maintenance dose prescribed is 300 mg given every other week</td>
</tr>
</tbody>
</table>

**Note:** Eosinophil 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.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Chronic rhinosinusitis with nasal polyposis | Dupixent® (dupilumab) may be considered medically necessary as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP) when:  
  • Patient is 18 years of age or older  
  AND  
  • Diagnosed with chronic rhinosinusitis as supported by at least two of the following four signs/symptoms that are present for 12 weeks or longer:  
    o Anterior and/or posterior nasal mucopurulent drainage  
    o Facial pain, pressure, and/or fullness  
    o Nasal congestion/obstruction  
    o Reduction or loss of sense of smell  
  AND  
  • Nasal polyposis as documented by the presence of bilateral nasal polyps or chart notes documenting previous surgical removal of the bilateral nasal polyps  
  AND  
  • Currently using an intranasal corticosteroid  
  AND  
  • Maintenance dose prescribed is 300 mg given every other week |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
</table>
| Dupixent® (dupilumab)         | Use of Dupixent® (dupilumab) in patients < 12 years of age is considered investigational.  

All other uses of Dupixent® (dupilumab) for conditions not outlined in the Medical Necessity section above are considered investigational. |

<table>
<thead>
<tr>
<th>Length of Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td></td>
</tr>
<tr>
<td>Initial authorization</td>
<td>Dupixent® (dupilumab) may be approved up to 6 months.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of Dupixent® (dupilumab) may be approved up to 12 months as long as the drug-specific</td>
</tr>
</tbody>
</table>
## Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coverage criteria are met and chart notes demonstrate that the patient continues to show a positive clinical response to therapy as documented by the following for each diagnosis:</td>
</tr>
</tbody>
</table>

**Atopic dermatitis**
- Decrease in the BSA involvement
  
  AND
  
  - Amelioration of the associated symptoms (ie, pruritus, inflammation, redness, etc.)

**Moderate-to-severe asthma**
- Decrease in requirements for oral steroids, exacerbation frequency, ER and urgent care visits, hospitalizations
  
  OR
  
  - Decrease in frequency and severity of asthma symptoms
  
  OR
  
  - Increase in quality of life measures and ability to perform activities of daily living

**Chronic rhinosinusitis with nasal polyposis**
- Decrease from baseline of nasal polyp size unless previous surgical removal of nasal polyps
  
  AND
  
  - Decrease from baseline of nasal congestion/obstruction
  
  AND
  
  - Improvement from baseline of sense of smell

## Documentation Requirements

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:
- Office visit notes that contain the diagnosis, relevant history, physical evaluation, lab results and medication history
**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
</tr>
</tbody>
</table>

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

**Related Information**

**Disease Background (Pathophysiology and Treatment Alternatives)**

**Atopic Dermatitis**

In 1998, the prevalence of AD in the US was found to be 6%, of which 30% reported mild disease, 53% moderate disease, and 18% severe disease in a population-based survey. 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
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 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)*

<table>
<thead>
<tr>
<th>Potency group*</th>
<th>Corticosteroid</th>
<th>Vehicle type/form</th>
<th>Trade names (United States)</th>
<th>Available strength(s), % (except as noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Super-high potency (group 1)</strong></td>
<td>Betamethasone dipropionate, augmented</td>
<td>Ointment, optimized</td>
<td>Diprolene</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Lotion</td>
<td>Diprolene</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gel</td>
<td>Diprolene</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clobetasol propionate</td>
<td>Ointment</td>
<td>Temovate</td>
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</tr>
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<td></td>
<td>Cream</td>
<td>Temovate</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cream, emollient base</td>
<td>Temovate E</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gel</td>
<td>Temovate</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lotion</td>
<td>Clobex</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foam aerosol</td>
<td>Olux-E</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foam aerosol (scalp)</td>
<td>Olux</td>
<td>0.05</td>
<td></td>
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<tr>
<td></td>
<td>Shampoo</td>
<td>Clobex</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solution (scalp)</td>
<td>Temovate, Cormax</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Spray aerosol</td>
<td>Clobex</td>
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</tr>
<tr>
<td></td>
<td>Diflucortolone valerate (not available in United States)</td>
<td>Ointment, oily cream</td>
<td>Nirisone Forte (United Kingdom, others)</td>
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<tr>
<td></td>
<td>Fluocinonide</td>
<td>Cream</td>
<td>Vanos</td>
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<td></td>
<td>Flurandrenolide</td>
<td>Tape (roll)</td>
<td>Cordran</td>
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<td>Halobetasol propionate</td>
<td>Ointment</td>
<td>Ultravate</td>
<td>0.05</td>
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<tr>
<td></td>
<td></td>
<td>Cream</td>
<td>Ultravate</td>
<td>0.05</td>
</tr>
<tr>
<td>Potency group*</td>
<td>Corticosteroid</td>
<td>Vehicle type/form</td>
<td>Trade names (United States)</td>
<td>Available strength(s), % (except as noted)</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>----------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>High potency (group 2)</strong></td>
<td>Amcinonide</td>
<td>Ointment</td>
<td>Cyclocort(^f), Amcort(^f)</td>
<td>0.1</td>
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<tr>
<td></td>
<td></td>
<td>Ointment</td>
<td>Diprosone</td>
<td>0.05</td>
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<tr>
<td></td>
<td></td>
<td>Cream, augmented formulation (AF)</td>
<td>Diprolene AF</td>
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<tr>
<td></td>
<td>Desoximetasone</td>
<td>Ointment</td>
<td>Topicort</td>
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<tr>
<td></td>
<td></td>
<td>Cream</td>
<td>Topicort</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gel</td>
<td>Topicort</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Diflorsone diacetate</td>
<td>Ointment</td>
<td>ApexiCon(^f), Florone(^f)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cream, emollient</td>
<td>ApexiCon E</td>
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</tr>
<tr>
<td></td>
<td>Fluocinonide</td>
<td>Ointment</td>
<td>Lidex(^f)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gel</td>
<td>Lidex(^f)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cream anhydrous</td>
<td>Lidex(^f)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution</td>
<td>Lidex(^f)</td>
<td>0.05</td>
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<tr>
<td></td>
<td>Halcinonide</td>
<td>Ointment</td>
<td>Halog</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cream</td>
<td>Halog</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>High potency (group 3)</strong></td>
<td>Amcinonide</td>
<td>Cream</td>
<td>Cyclocort(^f), Amcort(^f)</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lotion</td>
<td>Amcort(^f)</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Betamethasone dipropionate</td>
<td>Cream, hydrophilic emollient</td>
<td>Diprosone</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Betamethasone valerate</td>
<td>Ointment</td>
<td>Valisone(^f)</td>
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<tr>
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<td></td>
<td>Foam</td>
<td>Luxiq</td>
<td>0.12</td>
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<td>Diflorsone diacetate</td>
<td>Cream</td>
<td>Florone(^f)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Diflucortolone valerate (not available in United States)</td>
<td>Cream, oily cream, ointment</td>
<td>Nerisone (Canada, United Kingdom, others)</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Fluocinonide</td>
<td>Cream aqueous emollient</td>
<td>Lidex-E(^f)</td>
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</tr>
</tbody>
</table>
### Potency group*

<table>
<thead>
<tr>
<th>Corticosteroid type/form</th>
<th>Trade names (United States)</th>
<th>Available strength(s), % (except as noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone propionate</td>
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</tr>
<tr>
<td>Triamcinolone acetonide</td>
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</tr>
<tr>
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<td>Cream</td>
<td>0.51</td>
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</tbody>
</table>

### 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 - Adults**

Published data from two 16-week, placebo-controlled, pivotal trials, SOLO 1 and SOLO 2, in respectively 671 and 708 subjects with moderate-to-severe AD demonstrated the superiority of SC injected dupilumab 300 mg every other week and dupilumab 300 mg weekly in improving IGA scores compared to placebo at week 16.¹ In SOLO 1, 38% of the dupilumab every other week group, 37% of the dupilumab weekly group, and 10% of the placebo group achieved an IGA score of 0 or 1 (clear or almost clear) (p<0.001 for both comparisons with placebo). SOLO 2 demonstrated similar results with 36% of the dupilumab every other week group, 36% of the dupilumab weekly group, and 8% of the placebo group achieving an IGA score of 0 or 1 (p<0.001 for both comparisons with placebo). IGA scores are utilized in the real-world clinical setting by providers; however, the clinical meaningfulness of this as a clinical trial endpoint has not been well tested and validated. Results of this trial are valid due to well-stratified baseline characteristics, consistency of results, and study design. Limitations of the results lie within the short time horizon of the studies and the use of rescue treatment in at least 15% of 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±2.6, 72.0±2.6, and 37.6±3.3 for the every other week group, the weekly group, and the placebo group respectively. Significantly more 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±2.5, 67.1±2.5, and 30.9±3.0 for the every other week group, the weekly group, and the placebo group respectively. A total of at least 3 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, 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 ≥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. 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. 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. 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.

**Atopic Dermatitis - Adolescents**

One multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of dupilumab monotherapy in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD defined by an Investigator’s Global Assessment (IGA) score ≥3 (scale of 0 to 4), an Eczema Area and Severity Index (EASI) score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Subjects in the dupilumab group with baseline weight of <60 kg received an initial dose of 400 mg at Week 0, followed by 200 mg Q2W for 16 weeks. Subjects with baseline weight of ≥60 kg received an initial dose of 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

The mean age was 14.5 years, the median weight was 59.4 kg, 41% of subjects were female, 63% were White, 15% were Asian, and 12% were Black. At baseline 46% of subjects had an IGA score of 3 (moderate AD), 54% had an IGA score of 4 (severe AD), the mean BSA involvement was 57%, and 42% had received prior systemic immunosuppressants. Also, at baseline the mean EASI score was 36, and the weekly averaged Peak Pruritus Numeric Rating Scale (NRS) was 8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 66% had allergic rhinitis, 54% had asthma, and 61% had food allergies.
The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement). At week 16 24% of dupilumab users had an IGA 0 or 1 vs. 2% for placebo, 42% of dupilumab users had an EASI-75 score vs. 8% for placebo, 23% of dupilumab users had an EASI-90 score vs. 2% for placebo, and 37% of dupilumab users had a Peak Pruritus NRS (≥ 4-point improvement) vs. 5% for placebo.

**Asthma**

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

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

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

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

**Chronic Rhinosinusitis with Nasal Polyposis**

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) in 724 subjects aged 18 years and older on background intranasal corticosteroids (INCS). These studies included subjects with CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Patients with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator’s discretion. In CSNP Trial 1, a total of 276 subjects were randomized to receive either 300 mg dupilumab (N=143) or placebo (N=133) every other week for 24 weeks. In CSNP Trial 2, 448 subjects were randomized to receive either 300 mg dupilumab (N=150) every other week for 52 weeks, 300 mg dupilumab (N=145) every other week until week 24 followed by 300 mg dupilumab every 4 weeks until week 52, or placebo (N=153). All subjects had evidence of sinus opacification on the Lund Mackay (LMK) sinus CT scan and 73% to 90% of subjects had opacification of all sinuses. Subjects were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). A total of 63% of subjects reported previous sinus surgery, with a mean number of 2.0 prior surgeries, 74% used systemic corticosteroids in the previous 2 years with a mean number of 1.6 systemic corticosteroid courses in the previous 2 years, 59% had co-morbid asthma, and 28% had NSAID-ERD.

The co-primary efficacy endpoints were change from baseline to Week 24 in bilateral endoscopic nasal polyps score (NPS; 0-8 scale) as graded by central blinded readers, and change from baseline to Week 24 in nasal congestion/obstruction score averaged over 28 days (NC; 0-3 scale), as determined by subjects using a daily diary. For NPS, polyps on each side of the nose were graded on a categorical scale (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity). The total score was the sum of the right and left scores. Nasal congestion was rated daily by the subjects on a 0 to 3 categorical severity scale (0=no
symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms). Statistically
significant efficacy was observed in CSNP Trial 1 and 2 with regard to improvement in bilateral
endoscopic NPS scores at week 24 and at week 52 in the CNSP Trial 2. At Week 52, the LS mean
difference for nasal congestion in the dupilumab group versus placebo was -0.98 (95% CI -1.17,
-0.79). In both studies, significant improvements in nasal congestion were observed as early as
the first assessment at Week 4. The LS mean difference for nasal congestion at Week 4 in the
dupilumab group versus placebo was -0.41 (95% CI: -0.52, -0.30) in CSNP Trial 1 and -0.37 (95%
CI: -0.46, -0.27) in CSNP Trial 2.

**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. 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. RSOL-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.

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

The safety of dupilumab was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis and the safety profile in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis. The long-term safety of dupilumab was also assessed in an open-label extension study in subjects 12 to 17 years of age and the safety profile of dupilumab in subjects followed through Week 52 was similar to the safety profile observed at Week 16 and was consistent with that seen in adults with atopic dermatitis.

**Asthma**

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

There are only a few serious adverse events (SAEs) reported in the pivotal trials of dupilumab in asthma, so 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.

**Chronic Rhinosinusitis with Nasal Polyposis**

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

2018 Update

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

2019 Update

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

References


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>01/01/18</td>
<td>Interim Review, approved December 6, 2017. Added topical high potency corticosteroids table.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<tr>
<td>09/21/18</td>
<td>Minor update. Added Consideration of Age statement.</td>
</tr>
<tr>
<td>01/01/19</td>
<td>Interim Review, approved December 19, 2018. Title changed from “Pharmacotherapy of Atopic Dermatitis” to “Dupixent® (dupilumab)”. Added medical necessity criteria for the treatment of moderate-to-severe asthma.</td>
</tr>
<tr>
<td>05/01/19</td>
<td>Annual Review, approved April 2, 2019. Updated atopic dermatitis indication for the treatment of patients aged 12 years and older. Added HCPCS code J3490.</td>
</tr>
<tr>
<td>09/01/19</td>
<td>Interim Review, approved August 13, 2019. Added criteria for chronic rhinosinusitis with nasal polyposis.</td>
</tr>
</tbody>
</table>

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