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Atopic Dermatitis Class Update and Dupilumab Drug Update

Date of Review: July 2019

Date of Last Review: March 2018
End Date of Literature Search: 4/17/19

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update: Review new evidence for drugs used to manage atopic dermatitis (AD). Evaluate evidence for expanded indications for dupilumab: treatment of moderate-to-severe AD in adolescents and add on therapy to manage moderate-to-severe asthma.

Research Questions:
1. Is there new high quality evidence demonstrating differences in efficacy or effectiveness between the different classes of drugs used to manage AD (topical corticosteroids, topical calcineurin inhibitors, crisaborole, and immunomodulators)?
2. Is there evidence demonstrating differences in harms data between the different AD therapies?
3. Are there subgroups of patients, based on demographics (e.g., age, race, sex), in which one AD medication would be more effective or associated with less harm?

Conclusions:
Atopic Dermatitis Class Update
- A good quality systematic review and meta-analysis published in 2018 sought to evaluate the overall safety and efficacy of dupilumab treatment in moderate-to-severe AD.[1] The pooled of 6 trials with a low risk of bias revealed significant improvements in Eczema Area and Severity Index (EASI) score (standard mean difference [SMD] = −0.89, 95% Confidence Interval [CI] −1.0 to −0.78), percentage of body surface area (SMD = −0.83, 95% CI −0.90 to −0.75), with dupilumab compared to placebo.[1] Dupilumab treatment was also associated with a significant increase in the proportion of patients achieving Investigator's Global Assessment (IGA) response (Relative Risk [RR] = 3.82; 95% CI 3.23 to 4.51) and a similar incidence of adverse events (RR = 1.0; 95% CI 0.96 to 1.04, p = 0.83) versus placebo.[1]
- In August 2018 the National Institute for Health and Care Excellence (NICE) published guidance for dupilumab in treating moderate-to-severe AD.[2] Dupilumab is recommended as an option for treating moderate to severe atopic dermatitis in adults, only if the disease has not responded to at least 1 other systemic therapy, such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil, or if these are contraindicated or not tolerated.[2]

New Indications for Dupilumab
- The use of dupilumab in adolescents for AD was approved by the Food and Drug Administration (FDA) March 2019.[3] The efficacy and safety of dupilumab in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 251 adolescent subjects 12 to 17 years of age, with

moderate-to-severe AD. The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement on the 5 point scale from baseline to Week 16.[3] At week 16, 24% of the dupilumab subjects had an IGA of 0 or 1 versus 2% of the placebo-treated subjects (p<0.001).[3]

- In October 2018, dupilumab received an expanded FDA-approved indication as add-on maintenance therapy in adults and adolescents aged 12 years and older with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.[3] The efficacy and safety of dupilumab for treatment of asthma were evaluated in 2 randomized, double-blind, placebo-controlled, phase 3 trials.[4,5]
- In the smaller trial, 210 patients 12 years of age and older with glucocorticoid- treated severe asthma were randomized to receive add-on treatment with dupilumab 300 mg (following a loading dose of 600 mg) or placebo every 2 weeks for 24 weeks.[4] Moderate quality evidence from this small randomized clinical trial (RCT) showed the mean percentage reduction in the oral corticosteroid dose from baseline to week 24, was 70.1% with dupilumab versus 41.9% with placebo (mean difference (MD) -28.2%; 95% CI -40.7 to -15.8; p<0.001).[4]
- In a trial of 1902 subjects, dupilumab efficacy and safety were assessed in patients aged 12 years of age and older with moderate-to-severe uncontrolled asthma despite treatment with an inhaled glucocorticoid and long acting beta agonist or leukotriene receptor antagonist.[5] Moderate quality evidence from this large placebo-controlled trial showed the annualized rate of severe asthma exacerbations was reduced with dupilumab over 52 weeks. Annualized rate of asthma exacerbations was 0.46 among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 among those assigned to a matched placebo, (RR 0.52; 95% CI 0.41 to 0.66; P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks.[5]
- Moderate quality evidence showed the most frequent adverse event, occurring in 5% or more of the patients and at higher rates among asthmatic patients who received dupilumab than among those who received placebo, was injection-site reaction (in 15.2% of patients who received lower-dose dupilumab vs. 5.4% of those who received matched placebo, and in 18.4% of patients who received higher-dose dupilumab vs. 10.3% of those who received matched placebo).[5]

Recommendations:

- To support administration of PA criteria, remove dupilumab from atopic dermatitis and topical antipsoriatic prior authorization (PA) criteria and create a new PA document for dupilumab utilization in moderate-to-severe asthma and moderate-to-severe AD. Update PA criteria for dupilumab based on FDA approved ages for AD and add renewal criteria.
- Reorder questions in the dupilumab PA criteria to assess the prescribing practitioner at the beginning of the PA review.
- After review costs in executive session, no PDL changes are recommended.

Summary of Prior Reviews and Current Policy

In 2017, the Health Evidence Review Commission (HERC) modified conditions funded on line 424 (moderate/severe inflammatory skin disease) to include psoriasis, and AD.[6] Guideline Note 21 defines severe inflammatory skin disease as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: 1) at least 10% of body surface area involved; and/or 2) hand, foot or mucous membrane involvement.[7] Due to the prioritized list revisions, moderate to severe AD became a funded condition effective January 1, 2018. Mild AD is classified on line 544 and continues to be an unfunded condition. Oregon's legislature approved funding for lines 1-469 of the prioritized list as of January 1, 2019.[7] At the May 2018 meeting, the Pharmacy and Therapeutics (P and T) committee approved revising the PA criteria for topical antipsoriatic drugs to include agents used to manage atopic dermatitis. The recommendation to make dupilumab a non-preferred medication on the Practitioner-Managed Prescription Drug Plan (PMPDP) with PA criteria was also approved at this meeting. After reviewing comparative costs in executive session, tacrolimus 0.03%

ointment, tacrolimus 0.1% ointment, and pimecrolimus 1% cream were designated as preferred agents and crisaborole was maintained as a non-preferred agent. The PDL status for medications used to manage AD is presented in **Appendix 1**.

The comparative safety and efficacy for omalizumab, benralizumab, reslizumab, and mepolizumab for the treatment of severe asthma were reviewed at the July 2018 P and T Committee meeting. All 4 medications are non-preferred drugs on the PMPDP subject to prior authorization (PA) criteria. Omalizuamb is also indicated for management of chronic urticaria; however, this diagnosis is not funded according to the Health Evidence Review Commission (HERC) prioritized list.[7]

Background:

Atopic Dermatitis

Atopic dermatitis (AD) is chronic skin disorder characterized by pruritus and recurrent eczematous lesions accompanied by inflammation.[8] Other clinical features may include xerosis, erythema, erosions, oozing, and lichenification of the skin. The cause is unknown, but may be due to genetics or immunologic dysfunction.[9] Although it may affect all age groups, AD is most common in children. The disease affects 15-20% of children in developed countries and approximately 11% of U.S children.[10,11] Estimated prevalence of AD in U.S. adults is 3%.[10] Onset of AD is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years.[12] AD can persist into adulthood in about one third of affected individuals.[10]

The mainstays of therapy for AD are skin care with frequent application of an emollient to maintain the skin's epidermal barrier, avoidance of triggers, and anti-inflammatory therapy with topical corticosteroid (TCS) or a topical calcineurin inhibitor (TCI) if needed.[9] The use of TCS and TCI therapies in AD is supported by The American College of Dermatology's 2014 guideline[13] and 2004 guidance from the National Institute for Health and Care Excellence.[14] Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. However, prolonged use of TCS can result in telangiectasia, increased hair, skin tears, easy bruising, poor wound healing, acne and rosacea, and thinning/atrophic skin changes, which can be permanent.[15] TCIs are considered a second-line option in both adults and children with AD who have not responded to TCS or when those treatments are not advisable.[16,17] The main rationale for TCI use is that they do not cause skin atrophy and are therefore of particular value in delicate skin areas such as the face, neck, and skin folds.[13] All topical preparations can sting, but there is evidence that this may be more problematic with TCI preparations.[13]

Patients with AD that cannot be controlled with TCS or TCI therapy can be treated with short-term phototherapy with narrow band ultraviolet B (UVB) light or systemic immunomodulators such as cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, or oral corticosteroids.[13] The use of systemic immunomodulators in AD is considered off label and only oral prednisone is FDA approved to treat AD. Treatment with cyclosporine carries important risks of acute and chronic nephrotoxicity, can have hemodynamic effects that result in hypertension, and can increase the risk of infections and cancer.[13] Cyclosporine nephrotoxicity can be irreversible, and this risk increases with longer durations of treatment.[13] As a result, treatment with cyclosporine for AD is typically limited to one year. 2004 National Institute for Health and Care Excellence (NICE) Guidance recommends systemic corticosteroids, phototherapy, and systemic immunosuppressants as "treatments of last resort" in AD patients.[14] The 2014 American Academy of Dermatology guidelines reinforce the NICE recommendations for systemic immunomodulators as treatments for patients with refractory AD who fail all other therapies.[13] Two additional agents with novel mechanisms of action have recently been added to AD treatment algorithms. Crisaborole is a topical phosphodiesterase 4 (PDE4) inhibitor approved for mild-to-moderate AD in adults and children. PDE4 is a regulator of inflammation, and intracellular inflammatory cell PDE4 activity is increased in AD.[13] Crisaborole is available as an ointment that is applied twice daily. Dupilumab is an injectable monoclonal antibody that has been evaluated as a systemic therapy for moderate-to-severe AD refractory to topical treatments in adults. Clinical trials are currently underway with other biologics including ustekinumab, secukinumab, and apremilast to assess their efficacy in treating patients with AD.[8]

Clinical studies have utilized several scales for defining the severity of AD, including the Eczema Area and Severity Index (EASI) and IGA. The EASI assesses the severity of, and body surface area affected by, AD symptoms including erythema, induration/papulation/edema, excoriations, and lichenification.[12] Each symptom is graded systematically for specific anatomical regions and summarized in a composite score. EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of AD.[12] An EASI score of 7.1 to 21 is classified as mild AD, an EASI score of 21.1 to 50 is considered moderate AD, and severe AD ranges from an EASI score of 50.1 to 72.[12] EASI outcomes are measured as a percentage improvement in EASI score from baseline as EASI 50, 75, or 90. IGA is a clinician-reported outcome measure that has been used to evaluate severity of AD at a given point in time.[12] This measure was used to evaluate clinical response to treatment in studies evaluating new AD therapies.[12] In these trials, a 5-point scale ranging from 0 (clear) to 4 (severe) was used to assess changes in the severity of skin lesions. In most trials, scores less than or equal to 1 were generally classified as "treatment success," whereas scores greater than 1 were considered "treatment failure."[12] The IGA does not assess disease extent as body regions are not included in the IGA scoring. One systematic review concluded that although the IGA is easy to perform, the lack of standardization precludes any meaningful comparisons between studies which impedes data synthesis to inform clinical decision making.[12] These scales are primarily used in clinical trials and rarely in clinical practice, as they were generally not designed for this purpose.[12]

Severe Asthma

Asthma is a heterogeneous disease, characterized by chronic airway inflammation.[18] According to the 2007 National Asthma Education and Prevention Program (NAEPP) guidelines, asthma severity is classified according to symptoms and level of treatment required to control exacerbations.[19] Mild asthma (step 1 or 2) is well controlled with low dose inhaled corticosteroid (ICS) therapy.[19] Moderate (Step 3), and severe (Steps 4 and 5) asthma may require more potent ICS and addition of other controller-drug treatments.[19] The 2018 Global Initiative for Asthma (GINA) guidelines recommend a biologic agent for patients with severe asthma unresponsive to controller-drug treatments.[18] Severe asthma is reported to account for about 5 to 10 percent of the total asthma population, but exact prevalence is unknown due to heterogeneity in presentation of severe asthma.[20] Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with managing exacerbations.[21]

Recognition that asthma is not a single disease, but multiple, overlapping, phenotypes of disease has changed the way asthma is categorized and treated.[22,23] Phenotyping severe asthma based on demographic or clinical characteristics may help target treatments more effectively. Some asthma phenotypes include eosinophil predominant, neutrophil predominant, and allergic asthma.[23] Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody that has been available for over a decade to manage severe allergic asthma and chronic urticaria. Three additional monoclonal antibodies; mepolizumab, reslizumab, and benralizumab, mediate the effects of interleukin (IL)-5 and are effective in management of eosinophilic asthma as add on therapy. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion. The monoclonal antibodies that mediate IL-5 activity are FDA-approved to treat severe asthma in patients with an eosinophilic phenotype of asthma. Safety and efficacy of these agents have not been assessed in head-to-head trials. Several monoclonal antibodies targeting different cytokines (IL-4 and IL-13) are currently being investigated for their safety and efficacy in treating severe asthma. Dupilumab, an IL-4 receptor antagonist, recently received an expanded indication as add on maintenance therapy for moderate to severe asthma.[3]

Although the biologic agents used to manage severe asthma are well-tolerated, serious adverse reactions have been reported. Anaphylaxis has been reported in 0.3% of patients receiving reslizumab, so the drug carries an FDA boxed warning recommending observation after infusion.[24] Hypersensitivity reactions have been observed with mepolizumab and benralizumab; however neither drug has a boxed warning regarding anaphylaxis.[25,26] There is insufficient evidence on the long-term safety and effectiveness of monoclonal antibodies used to manage severe asthma as the length of follow-up in some of the randomized trials with the biologic agents was only 24 weeks, and no trial was longer than 15 months.

There are notable differences between each biologic agent approved to treat asthma primarily related to the age of administration, route of administration, dosing regimen, and FDA-approved indication. Currently, 4 of the monoclonal antibodies used to manage asthma (benralizumab, reslizumab, mepolizumab, and omalizumab) must be administered by a health care provider. Dupilumab is the only monoclonal antibody approved for self-administration.[3] **Table 1** summarizes significant prescribing information for the 5 biologic agents with FDA approval to treat severe asthma.

Table 1. Monoclonal Antibodies Approved to Manage Severe Asthma [3,24-27]

Generic Name	Brand Name	FDA Approval Year	Target	FDA Approved Indication	Maintenance Dose and Administration Route	FDA Approved Administration Age	FDA Boxed Warning	Blood Eosinophil Levels in Clinical Trials in Primary Analysis Population
Dupilumab	Dupixent®	2018	IL-4 Receptor	-Moderate to severe atopic dermatitis -Add on maintenance treatment for moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	Atopic Dermatitis: 1. Adults: 300 mg SC every 2 weeks 2. Adolescents: < 60 kg: 200 mg SC every 2 weeks ≥60 kg: 300 mg SC every 2 weeks -Asthma: Adults and Adolescents: 200 to 300mg SC every 2 weeks	Atopic Dermatitis: ≥ 12 yo Moderate to Severe Asthma: ≥ 12 yo	No	Subjects enrolled in clinical trials without requiring a minimum baseline blood eosinophil count
Benralizumab	Fasenra™	2017	IL-5 Receptor	Severe asthma with an eosinophilic phenotype	30 mg SC every 8 weeks	≥ 12 yo	No	≥300 cells/µL
Reslizumab	Cinqair®	2016	IL-5	Severe asthma with an eosinophilic phenotype	3 mg/kg IV infusion every 4 weeks	≥ 18 yo	Yes: for possible anaphylaxis	≥ 400 cells/µL
Mepolizumab	Nucala®	2015	IL-5	-Severe asthma with an eosinophilic phenotype -EGPA in adults	-Asthma: 100 mg SC every 4 weeks -EGPA: 300 mg SC every 4 weeks	-Asthma: ≥ 12 yo -EGPA: ≥ 18 yo	No	≥ 150 cells/µL at screening or ≥ 300 cells/µL in the previous year
Omalizumab	Xolair®	2003	IgE	-Moderate to severe persistent asthma -Antihistamine refractory CSU	-Asthma: 75 to 375 mg SC every 2 to 4 weeks. (Dosing is determined by weight and serum IgE levels for asthma) -CSU: 150 to 300 mg SC every 4 weeks	-Asthma: ≥ 6 yo -CSU: ≥ 12 yo	Yes: for possible anaphylaxis	Not Applicable

Abbreviations: CSU = Chronic Spontaneous Urticaria; EGPA = Eosinophilic Granulomatosis with Polyangiitis; FDA = Food and Drug Administration; IgE = immunoglobulin E; IL-5 = interleukin-5; IV = intravenous; SC = subcutaneous; YO = years old

Clinically relevant outcomes to assess treatments of severe asthma include reduction in asthma exacerbations that result in: 1) decreased Emergency Department (ED) visits or hospitalizations; 2) decreased chronic use of oral corticosteroids; 3) improved quality of life; and 4) improved symptom management. Three instruments are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma. These tests are self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users. The Asthma Control Questionnaire (ACQ) is a 5-item

questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[28] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units the minimally clinical important difference.[29] An ACQ score consistently greater than 1.5 indicates poor symptom control.[29] Change from baseline in forced expiratory volume in 1 second (FEV1) is a common surrogate endpoint used in asthma treatment trials since it is highly reproducible. Minimally important values from research in COPD patients suggest minimally important FEV1 changes range from 100-140 ml.[30]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Safety and efficacy of Dupilumab
A good quality systematic review and meta-analysis published in 2018 evaluated the overall safety and efficacy of dupilumab treatment in moderate-to-severe atopic dermatitis.[1] Six trials with a low risk of bias involving 2447 patients met inclusion criteria.[1] However, all the included trials were funded by the manufacturer (Sanofi and Regeneron Pharmaceuticals).[1] Duration of treatment ranged from 4 to 52 weeks and dupilumab was administered via the subcutaneous route in doses ranging from 300 mg once weekly to 300 mg biweekly.[1] In 4 trials dupilumab was analyzed as monotherapy, while in the other 2 trials dupilumab was administered in combination with topical corticosteriods.[1]

The meta-analysis revealed significant improvements in EASI score with moderate heterogeneity (SMD = −0.89, 95% CI −1.0 to −0.78; P<0.001; I^2=45%) and percentage of body surface area with minimal heterogeneity (SMD = −0.83, 95% CI −0.90 to −0.75; P<0.001; I^2=9%) with both doses of dupilumab compared to placebo.[1] A standardized mean difference greater than 0.8 represents a clinically significant improvement in AD symptoms. Subgroup analysis showed that the 300 mg once weekly dosage seemed more effective than the every 2 week dosage in reduction of EASI (-0.93 vs −0.86), however, there was significant heterogeneity in 300 mg once weekly group (I^2 = 55%, p=0.05).[1] There was a high level of heterogeneity with the pooled analysis of puritis NRS scores and quality of life (DLQI) scores.[1] Dupilumab treatment was also associated with a significant increase in the proportion of patients achieving IGA response with minimal heterogeneity (RR = 3.82; 95% CI 3.23 to 4.51; p<0.001; I^2=16%) and a similar incidence of adverse events with minimal heterogeneity (RR = 1.0; 95% CI 0.96 to 1.04, p=0.83; I^2=11%) versus placebo.[1] The most frequently reported adverse events included nasopharyngitis, exacerbation of AD, headache and upper respiratory infection.[1] This analysis provides evidence that dupilumab results in clinically relevant improvements in signs and symptoms of AD.[1] However, more trials are needed to further investigate the long-term efficacy and safety of dupilumab in moderate-to-severe AD. Both dose regimens of dupilumab seemed to have similar benefits in ameliorating signs and symptoms of AD.[1] The FDA-approved dose of dupilumab for AD in adults is 300 mg subcutaneously given every other week after an initial 600 mg dose.[3]

After review, 2 systematic review was excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[31,32]

New Guidelines:

High Quality Guidelines:

National Institute for Health and Care Excellence

In August 2018 the National Institute for Health and Care Excellence (NICE) published guidance for dupilumab in treating moderate-to-severe AD.[2] Recommendations include:

1. Dupilumab is recommended as an option for treating moderate to severe atopic dermatitis in adults, only if:
    - the disease has not responded to at least 1 other systemic therapy, such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated.[2]
2. Stop dupilumab at 16 weeks if the atopic dermatitis has not responded adequately. An adequate response was defined as:
    - at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started and
    - at least a 4‑point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started.

After review, 2 guidelines were excluded due to poor quality.[33,34]

New Indications

Dupilumab approved for use in adolescents with atopic dermatitis

The use of dupilumab in adolescents for AD was approved by the FDA March 2019.[3] When originally approved for adults, dupilumab was only available as a 300 mg/2 ml prefilled syringe. With the expanded indication for use in patients 12 years and older, dupilumab is presently available in a 200 mg/1.4 ml pre-filled syringe. The efficacy and safety of dupilumab in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 251 subjects 12 to 17 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum body surface area (BSA) involvement of ≥10%.[3] Eligible subjects enrolled into this trial had previous inadequate response to topical medication.[3] Patients were randomized into one of three treatment groups for the controlled period of 16 weeks: the first group was treated with dupilumab subcutaneous injection 200 mg or 300 mg every two weeks, based on weight (with an initial dose of 400 mg or 600 mg respectively). The second group was treated with 300 mg dupilumab every four weeks (with an initial dose of 600 mg), and the third group was treated with placebo every two weeks. 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.[3] At week 16, 24% of the dupilumab subjects had an IGA of 0 or 1 versus 2% of the placebo-treated subjects ($p<0.001$).[3] The safety profile of dupilumab in these subjects through week 16 was similar to the safety profile from studies in adults with atopic dermatitis.[3]

Dupilumab approved as add on therapy for asthma

In October 2018, dupilumab received an expanded FDA-approved indication as add-on maintenance therapy in adults and adolescents aged 12 years and older with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.[3] The efficacy and safety of dupilumab were evaluated in 2 randomized, double-blind, placebo-controlled, phase 3 trials.[4,5] In the smaller trial, 210 patients 12 years of age and older with glucocorticoid-treated severe asthma were randomized to receive add-on treatment with dupilumab 300 mg (following a loading dose of 600 mg) or placebo every 2 weeks for 24 weeks.[4] Subjects were also receiving inhaled corticosteroids and 2 additional asthma controller medications. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Oral corticosteroid doses were reduced every 4 weeks from week 4 to week 20 as long as asthma control was

maintained.[4] Moderate quality evidence shows the mean percentage reduction in the oral corticosteroid dose from baseline to week 24, was 70.1% with dupilumab versus 41.9% with placebo (mean difference (MD) -28.2%; 95% CI -40.7 to -15.8; p<0.001).[4] At week 24, 52% of patients in the active treatment group had completely discontinued oral corticosteroids, compared to 29% of those in the placebo group (OR 2.74; p=0.002).[4] Use of dupilumab also decreased severe asthma exacerbations (annualized rate 0.65 for dupilumab vs. 1.60 for placebo; RR 0.41; 95% CI 0.26 to 0.63) and improved lung function (FEV1) was 0.22 liters higher; 95% CI 0.09 to 0.34) compared to placebo.[4] The benefits were greatest in patients with higher baseline blood eosinophil counts.[4] Injection-site reactions were more common with dupilumab than with placebo (9% vs. 4%).[4] Transient blood eosinophilia was observed in more patients in the dupilumab group than in the placebo group (14% vs. 1%).[4] In patients with glucocorticoid-dependent severe asthma, dupilumab treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV1.[4]

In a trial of 1902 subjects, dupilumab efficacy and safety were assessed in patients aged 12 years of age and older with moderate-to-severe uncontrolled asthma despite treatment with an inhaled glucocorticoid and long acting beta agonist or leukotriene receptor antagonist.[5] Patients were randomized in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks.[5] The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the FEV1 before bronchodilator use in the trial population.[5] Change from baseline in forced expiratory volume in 1 second (FEV1) is a common surrogate endpoint used in asthma treatment trials. Research in COPD patients suggest minimal clinically important FEV1 changes range from 100-140 ml.[30] Moderate quality evidence from this trial showed the annualized rate of severe asthma exacerbations was reduced with dupilumab compared to placebo over 52 weeks. Annualized rate of asthma exacerbations was 0.46 among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 among those assigned to a matched placebo, (RR 0.52; 95% CI 0.41 to 0.66; P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks (0.52 with dupilumab vs. 0.97 with placebo; RR 0.54; 95% CI 0.43 to 0.68; P<0.001).[5] At week 12, the FEV_1 had increased by 0.32 liters in patients assigned to the lower dose of dupilumab (difference vs. matched placebo, 0.14 liters; P<0.001); similar results were seen with the higher dose.[5] The most frequent adverse event, occurring in 5% or more of the patients and at higher rates among patients who received dupilumab than among those who received placebo, was injection-site reaction (in 15.2% of patients who received lower-dose dupilumab vs. 5.4% of those who received matched placebo, and in 18.4% of patients who received higher-dose dupilumab vs. 10.3% of those who received matched placebo).[5] More details about the 2 trials are outlined in **Table 2.**

How dupilumab compares to the other monoclonal antibodies that are approved for treatment of eosinophilic asthma (i.e.; benralizumab, mepolizumab, and reslizumab) remains to be determined, and there is insufficient data to evaluate long-term safety of dupilumab.

New FDA Safety Alerts: No new safety alerts have been issued.

Table 2. Comparative Evidence Table: Dupilumab in Severe Asthma

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Rabe, et al.[4] VENTURE DB, PC,MC, RCT N = 210	1. Dupilumab 600 mg SC loading dose x 1 dose followed by 300 mg SC every 2 weeks for 24 weeks. 2. Placebo SC every 2 weeks for 24 weeks	Demographics: 1. Mean age: 51 yo 2. Female Gender: 60% 3. Former Smoker: 20% 4. Number of severe asthma exacerbations in the year prior: 2 5. Mean blood eosinophil count: 350 cells/µL 6. ACQ-5 score: 2.5 7. Blood eosinophils ≥ 300 cell/µL: 47% (dupilumab); 38% (placebo) 8. Mean oral glucocorticoid dose: prednisone 11 mg Key Inclusion Criteria: 1. Patients 12 yo or older with asthma for ≥ 1 year receiving systemic glucocorticoids in the previous 6 months. 2. During the 4 weeks before screening treatment had to include high dose inhaled glucocorticoid and 2 controllers (LABA or LRA for at least 3 months. 3.FEV1 ≤ 80% Key Exclusion Criteria: 1. Weight less than 30 kg 2. COPD or other lung disease that impairs lung function 3. Current smoker 4. Previous smoker with smoking history > 10 pack years	ITT: 1. 103 2. 107 PP: 1. 101 2. 102 Attrition: 1. 2 (2%) 2. 5 (5%)	Primary Endpoint: Percentage reduction in oral glucocorticoid dose from baseline to week 24. 1. -70.1 ± 4.9% 2. -41.9 ± 4.6% MD -28.2 (95% CI -40.7 to -15.8) P<0.001 Secondary Endpoint: 1. Proportion of patients with reduction of at least 50% of oral glucocorticoid at week 24 1. 82 (79.6%) 2. 57 (53.3)% OR 3.98 (95% CI 2.06 to 7.67) P<0.001 2. Proportion of patients with a reduction in oral glucocorticoid to < 5 mg per day at week 24 1. 74 (71.8%) 2. 40 (37.4%) OR 4.48 (95% CI 2.39 to 8.39) P<0.001	NA 26.3%/4 34.4%/3	AEs 1. 64 (62%) 2. 69 (64%) SAEs 1. 9 (9%) 2. 6 (6%) AE leading to drug discontinuation 1. 1 (1%) 2. 4 (4%) P value and 95% CI NR for all	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomly assigned in a 1:1 ratio via IVRS. Stratified according to oral glucocorticoid dose (≤10 mg per day vs. > 10 mg per day prednisone or prednisolone). Performance Bias: Low. Dupilumab and placebo provided in identically matched 2 mL prefilled syringes Detection Bias: Both the patient and the Investigator blinded to treatment assignment. Attrition Bias: Low. Low rate of attrition. Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Protocol developed by Sanofi and Regeneron. Several authors report receiving grants from Regeneron and Sanofi. **Applicability**: Patient: Patients with glucocorticoid dependent severe asthma were the primary subjects. Blood eosinophils counts were not part of the inclusion criteria. Intervention: Dupilumab doses studied in Phase 2 trial. Comparator: Placebo: head to head trial with another biologic agent would be more meaningful. Outcomes: Duration of trial was 24 weeks: relatively short time to assess safety. Primary outcome was reduction in oral steroid use, which was also substantial in the placebo arm. Reduction in severe asthma exacerbations was a secondary endpoint, but would have been a preferred primary outcome. Setting: Percentage of subjects enrolled in each geographic area is unclear. 1.East Europe: Hungary, Poland, Romania, Russia, Ukraine 2.Latin America: Argentina, Brazil, Chile, Colombia, Mexico 3.Western Countries: Belgium, Canada, Israel, Italy, Netherlands, Spain, US

2. Castro, et al.[5] QUEST DB, PC, MC, PG, RCT N=1902	1. Dupilumab 600 mg x 1 dose followed by 300 mg SC every 2 weeks over 52 weeks 2. Dupilumab 400mg x 1 dose followed by 200 mg SC every 2 weeks over 52 weeks 3. Placebo loading dose followed by matched 2ml placebo SQ every 2 weeks over 52 weeks 4. Placebo loading dose followed by matched 1.14 ml placebo SC every 2 weeks over 52 weeks	<u>Demographics</u>: 1. Mean age: 48 yo 2. Female Gender: 63% 3. Former Smoker: 19% 4. Number of severe asthma exacerbations in the previous year: 2 5. Mean blood eosinophil count: 360 cells/µL 6. Mean ACQ-5 score: 2.76 7.Blood eosinophil count ≥ 300 cells/ µL: 47% <u>Key Inclusion Criteria</u>: 1. Patients ≥12 yo with uncontrolled moderate-to-severe asthma 2. Use of inhaled glucocorticoids plus up to two additional controllers (e.g. LABA, LRA) 3. FEV1 < 80% of predicted normal 4. ACQ-5 score ≥1.5 5.Experienced either: a. treatment with systemic steroid in the past year b. hospitalization or ED medical care for asthma <u>Key Exclusion Criteria</u>: 1. Weight less than 30 kg 2. COPD or other lung disease that impairs lung function 3. Current smoker 4. Previous smoker with smoking history > 10 pack years.	<u>ITT</u>: 1. 633 2. 631 3. 321 4. 317 <u>PP</u>: 1. 469 2. 487 3. 248 4 .230 <u>Attrition</u>: 1. 164 (26%) 2. 144 (23%) 3. 73 (23%) 4. 87 (27%)	<u>Primary Endpoint</u>: .Annualized rate of severe asthma exacerbations over 52 weeks 1. 0.52 2. 0.46 3. 0.97 4. 0.87 1 vs. 3 RR 0.54 (95% CI 0.43 to 0.68) P<0.001 2 vs. 4 RR 0.52 (95% CI 0.41 to 0.66) P<0.001 2.Absolute increase from baseline in pre-bronchodilator FEV_1 at week 12 1. 0.34 L 2. 0.32 L 3. 0.21 L 4. 0.18 L 1 vs. 3 MD 0.13 (95% CI 0.08 to 0.18) P<0.001 2 vs. 4 MD 0.14 (95% CI 0.08 to 0.19 P<0.001 <u>Secondary Endpoints</u>: 1.Percent increase from baseline in pre-bronchodilator FEV_1 at week 12 1. 23.1% 2. 21.3% 3. 13.7% 4. 12.1% 1 vs. 3 MD 9.4% (95% CI 5.74 to 13.07) P<0.001 2 vs. 4 MD 9.2% (95% CI 5.54 to 12.92) NS	NA NA NA NA NA NA	<u>AEs</u> 1. 515 (82%) 2. 508 (81%) 3. 270 (8.4%) 4. 257 (82%) <u>SAEs</u> 1. 55 (8.7%) 2. 49 (7.8%) 3. 27 (8.4%) 4.26 (8.3%) <u>AE leading to drug discontinuation</u> 1. 44 (7.0%) 2. 19 (3.0%) 3. 10 (3.1%) 4. 19 (6.1%) <u>Death</u> 1. 4 (0.6%) 2. 1 (0.2%) 3. 0 (0%) 4. 3(1%) P value and 95% CI NR for all	NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: Low. Randomized 2:2:1:1 via IVRS at a centralized treatment allocation system. Stratified by age (< 18 yo, 18-64 yo, ≥65 yo) and eosinophil count (≤150 cells/µL, 150-299 cells/µL, ≥ 300 cells/µL) at screening. Baseline demographics were similar across treatment arms. <u>Performance Bias</u>: Low. Placebo matched in similar volume to 200 or 300 mg dupilumab dose in identically matched glass pre-filled syringes. <u>Detection Bias</u>: Unclear. Patients and investigators blinded to assigned drug or placebo, but not the dose level of placebo/dupilumab. Injection site reactions with the active drug may have resulted in unblinding of treatment assignment. <u>Attrition Bias</u>: High. Attrition rates were greater than 20% in all arms. More patients in the 300mg dupilumab arm dropped out due to adverse effects compared to the 200mg arm (7% vs. 3%). <u>Reporting Bias</u>: Low. Protocol available on-line. <u>Other Bias:</u> Unclear. Protocol developed by Sanofi and Regeneron. Data collected by investigators and analyzed by sponsors. Several authors report receiving grants from Regeneron and Sanofi. **Applicability**: <u>Patient</u>: Results apply to patients with uncontrolled moderate-to-severe asthma on multiple therapies. Blood eosinophils counts were not part of the inclusion criteria <u>Intervention</u>: Dupilumab doses studied in Phase 2 trial. <u>Comparator</u>: Placebo: head to head trial with another biologic agent would be more meaningful. <u>Outcomes</u>: Reduction in rate of asthma exacerbations is a relevant primary endpoint. <u>Setting</u>: International study. Percentage of subjects enrolled in each geographic area is unclear.

Abbreviations [alphabetical order]: ACQ-5: 5-item Asthma Control Questionnaire; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; FEV_1 = forced expiratory volume in 1 second; ITT = intention to treat; IVRS = interactive voice response system; mITT = modified intention to treat; LABA = long acting beta2 agonist; L = liters; LRA = leukotriene receptor antagonist; MC = multi-center; ml = milliliter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = odds ratio; PC = placebo controlled; PG = parallel group; PP = per protocol; RCT = randomized clinical trial; SC = subcutaneous

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Appendix 1: Current Preferred Drug List for Atopic Dermatitis and Miscellaneous Asthma Drugs

Generic	Brand	Form	PDL
tacrolimus	PROTOPIC	OINT. (G)	Y
tacrolimus	TACROLIMUS	OINT. (G)	Y
pimecrolimus	ELIDEL	CREAM (G)	Y
pimecrolimus	PIMECROLIMUS	CREAM (G)	Y
crisaborole	EUCRISA	OINT. (G)	N
dupilumab	DUPIXENT	SYRINGE	N

Generic	Brand	Form	PDL
montelukast	SINGULAIR	TAB CHEW	Y
montelukast	MONTELUKAST	TAB CHEW	Y
montelukast	MONTELUKAST	TABLET	Y
montelukast	SINGULAIR	TABLET	Y
benralizumab	FASENRA	SYRINGE	N
mepolizumab	NUCALA	VIAL	N
montelukast	MONTELUKAST	GRAN PACK	N
montelukast	SINGULAIR	GRAN PACK	N
omalizumab	XOLAIR	SYRINGE	N
omalizumab	XOLAIR	VIAL	N
reslizumab	CINQAIR	VIAL	N
roflumilast	DALIRESP	TABLET	N
zafirlukast	ACCOLATE	TABLET	N
zafirlukast	ZAFIRLUKAST	TABLET	N
zileuton	ZYFLO	TABLET	N
zileuton	ZILEUTON ER	TBMP 12HR	N
zileuton	ZYFLO CR	TBMP 12HR	N

Appendix 2: New Comparative Clinical Trials

A total of 15 citations were manually reviewed from the initial literature search. After further review, 14 citations were excluded because of wrong study design (eg, observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Blauvelt A, et al.[35] Phase 2, DB, MC, PC, PG, RCT	Dupilumab 300 mg once a week for 16 weeks Vs. Placebo And Single dose of Tdap and quadrivalent meningococcal polysaccharide vaccine at week 12	Patients aged 18-64 yo with moderate-to-severe AD for ≥ 3 yrs, with inadequate response to topical therapy, EASI ≥ 16, IGA ≥ 3, and BSA ≥ 10% N=178	Proportion of patients achieving satisfactory IgG response to tetanus toxoid at week 16	Similar positive immune responses (≥4-fold increase in antibody titer, or an antibody titer of ≥8) were achieved in the dupilumab and placebo groups to tetanus (83.3% and 83.7%, respectively; 90% CI difference -9.41 to 8.69) and meningococcal polysaccharide (86.7% and 87.0%, respectively; 90% CI difference -4.29 to 6.27). Vaccination after 12-week dupilumab therapy was not associated with adverse clinical effects
Abbreviations: AD = atopic dermatitis; BSA = Body Surface Area; CI = confidence interval; DB = double blind, EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; MC= multi-center; PC = placebo control; PG = parallel group; RCT = randomized clinical trial; Tdap – Tetanus, Diphtheria, Pertussis vaccine; YO = years old; YRS = years				

Appendix 3: Abstracts of Comparative Clinical Trials

Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis.

Blauvelt A1, Simpson EL2, Tyring SK3, Purcell LA4, Shumel B4, Petro CD4, Akinlade B4, Gadkari A4, Eckert L5, Graham NMH4, Pirozzi G6, Evans R4.

BACKGROUND: The impact of dupilumab, an anti-interleukin (IL) 4 receptor α antibody that inhibits IL-4 and IL-13 signaling, on vaccine responses of patients with atopic dermatitis (AD) is unknown.

OBJECTIVES: To assess T-cell-dependent and T-cell-independent humoral immune responses to tetanus and meningococcal vaccines, IgE seroconversion to tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination, and dupilumab efficacy and safety.

METHODS: In a randomized, double-blinded, placebo-controlled study (NCT02210780), adults with moderate-to-severe AD received dupilumab (300 mg) or placebo weekly for 16 weeks, and single doses of Tdap and quadrivalent meningococcal polysaccharide vaccines at week 12. Primary endpoint was proportion of patients achieving satisfactory IgG response to tetanus toxoid at week 16.

RESULTS: In total, 178 patients completed the study. Similar positive immune responses (≥4-fold increase in antibody titer, or an antibody titer of ≥8) were achieved in the dupilumab and placebo groups to tetanus (83.3% and 83.7%, respectively) and meningococcal polysaccharide (86.7% and 87.0%, respectively). Dupilumab significantly decreased total serum IgE; most dupilumab-treated patients were Tdap-IgE seronegative at week 32 (62.2% dupilumab and 34.8% placebo). Dupilumab improved key AD efficacy endpoints ($P < .001$). Injection-site reactions and conjunctivitis were more common with dupilumab; AD exacerbations more frequent with placebo.

LIMITATION: Patients' prior vaccination status was not available before enrollment.

CONCLUSION: Dupilumab did not affect responses to the vaccines studied, significantly decreased IgE, and improved measures of AD severity versus placebo, with an acceptable safety profile.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April Week 2 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to April 17, 2019

1. Dermatitis, Atopic/	12649
2. Eczema/	3458
3. Calcineurin Inhibitors/	3506
4. Pimecrolimus.mp.	862
5. Tacrolimus/	12888
6. Crisaborole.mp.	53
7. Dupilumab.mp.	250
8. 1 or 2	15591
9. 3 or 4 or 5 or 6 or 7	15533
10. 8 and 9	898
11. limit 10 to (english language and humans and yr="2018 -Current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	15

Atopic Dermatitis and Topical Antipsoriatics

Goal(s):

Restrict dermatological drugs only for funded OHP diagnoses. Moderate/severe psoriasis and moderate/severe atopic dermatitis treatments are funded on the OHP. Treatments for mild psoriasis, seborrheic dermatitis, keratoderma and other hypertrophic and atrophic conditions of skin are not funded.

Length of Authorization:

- From 6 to 12 months

Requires PA:

Non-preferred antipsoriatics
All atopic dermatitis drugs
STC = 92 and HIC = L1A, L5F, L9D, T0A
This PA does not apply to biologics for psoriasis, which is subject to separate clinical PA criteria.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for seborrheic dermatitis, keratoderma or other hypertrophic and atrophic conditions of skin?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the diagnosis psoriasis?	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Is the Psoriasis Moderate/Severe? Moderate/Severe psoriasis is defined as:[1] • Having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one of the following: 1. At least 10% body surface area involved or with functional impairment and/or: 2. Hand, foot or mucous membrane involvement	**Yes:** Go to #5	**No:** Pass to RPh; deny, not funded by the OHP.
5. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #6
6. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Approve for length of treatment; maximum 1 year.
7. Is the diagnosis atopic dermatitis?	**Yes:** Go to #8	**No:** Go to #12

Approval Criteria		
8. Is the diagnosis Moderate/Severe Atopic Dermatitis (AD)? Moderate/Severe psoriasis is defined as:[1] • Having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one of the following: 1. At least 10% body surface area involved or with functional impairment and/or: 2. Hand, foot or mucous membrane involvement	**Yes:** Go to #9	**No:** Pass to RPh. Deny; not funded by the OHP.
9. What is the age of the patient?	**Age less than 2 years**: Pass to RPh. Deny; medical appropriateness.	**Ages 2 years and older:** Go to #10
10. Does the patient meet the age requirements per the FDA label? • Tacrolimus 0.1% ointment is FDA approved for patients 16 years of age and older. • Tacrolimus 0.03% ointment, pimecrolimus 1% cream, and crisaborole ointment are FDA approved for patients 2 years of age and older.	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Does the patient have a documented contraindication, intolerance or failed trials of at least 2 first line agents indicated for the treatment of moderate to severe AD (topical corticosteroids)?* *Note pimecrolimus and crisaborole are FDA approved to manage mild to moderate AD, while tacrolimus is FDA approved to manage moderate to severe AD.	**Yes:** Document drug and dates trialed, and intolerances (if applicable): 1._____(dates) 2._____(dates) Approve for length of treatment; maximum 6 months.	**No:** Pass to RPh. Deny; medical appropriateness
12. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.*	**If funded, or clinic provides supporting literature:** Approve for 1 year.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *7/19 (DM); 5/19 (DM) 3/18 (DM); 9/17; 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *8/19/19; 4/16/18; 10/15; 8/15; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06*

**The Health Evidence Review Commission has stipulated via Guideline Note 21 that mild, uncomplicated inflammatory skin conditions including psoriasis, atopic dermatitis, lichen planus, Darier disease, pityriasis rubra pilaris, and discoid lupus are not funded. Uncomplicated is defined as no functional impairment; and/or involving less than 10% of body surface area and no involvement of the hand, foot, or mucous membranes.*

References:

1. Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed May 3, 2019.

Dupilumab

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

- 6 months

Requires PA:

- Dupilumab (Dupixent)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #5

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Go to # 6
6. Is the medication being prescribed by or in consultation with a dermatologist or allergist who specializes in management of severe asthma?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. What is the age of the patient? • Dupilumab injection is FDA approved for patients 12 years of age and older	**Age 11 years or younger**: Pass to RPh. Deny; medical appropriateness.	**Ages 12 years and older:** Go to #8
8. Is the diagnosis Moderate/Severe Atopic Dermatitis (AD)? Moderate/Severe psoriasis is defined as:[1] • Having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one of the following: 1. At least 10% body surface area involved or with functional impairment and/or: 2. Hand, foot or mucous membrane involvement	**Yes:** Go to #9	**No:** Go to #10

Approval Criteria		
9. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide,mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
10. Is the claim for moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, benralizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12
12. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #13 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
13. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew dupilumab for atopic dermatitis?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with dupilumab therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started OR • at least a 2 point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 7/19 (DM)
Implementation: 8/19/19
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Monoclonal Antibodies for Severe Asthma

Goal(s):

Restrict use of monoclonal antibodies to patients with severe asthma requiring chronic systemic corticosteroid use or with history of asthma exacerbations in the past year that required an Emergency Department visit or hospitalization. Restrict use for conditions not funded by the OHP (e.g., chronic urticaria).

Length of Authorization:

- Up to 12 months

Requires PA:

Omalizumab
Mepolizumab
Reslizumab
Benralizumab
This PA does not apply to dupilumab, which is subject to separate clinical PA criteria.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Maximum Adult Doses for Inhaled Corticosteroids.

High Dose Corticosteroids:	**Maximum Dose**
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Aerospan (flunisolide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for omalizumab, mepolizumab, reslizumab, or benralizumab?	**Yes:** Go to #5	**No:** Go to #4
4. Is the request for a newly approved monoclonal antibody for severe asthma and does the indication match the FDA-approved indication?	**Yes:** Go to #9	**No:** Go to #5
5. Is the claim for reslizumab in a patient under 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is the claim for mepolizumab or benralizumab in a patient under 12 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Is the claim for omalizuamb in a patient under 6 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the claim for mepolizumab in an adult patient diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	**Yes:** Approve 300 mg (3 x 100mg syringes) every 4 weeks x 1 year	**No:** Go to #9
9. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is the diagnosis an OHP-funded diagnosis? Note: chronic urticaria is not an OHP-funded condition	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #13 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, benralizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #15
15. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	**Yes:** Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	**No:** Go to #16

Approval Criteria		
16. If the claim is for mepolizumab, benralizumab or reslizumab, can the prescriber provide documentation of severe eosinophilic asthma, confirmed by blood eosinophil count ≥300 cells/μL in the past 12 months?	**Yes:** Approve once every 4 to 8 weeks for up to 12 months. Note: Initial benralizumab dose is 30 mg every 4 weeks x 3 doses followed by 30 mg every 8 weeks Document eosinophil count (date):_____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew mepolizumab for EGPA?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with mepolizumab therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has the number of ED visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.