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PNW EPC Drug Effectiveness Review Project Summary Report – Atopic Dermatitis
New Drug Evaluation: Dupilumab

Date of Review: March 2018
Generic Name: Dupilumab
PDL Class: Dermatologicals

Literature Search: December, 2017
Brand Name (Manufacturer): Dupixent® (Regeneron)
AMCP Dossier Received: Yes

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

Research Questions:
1. For adults and children with atopic dermatitis (AD), do dupilumab, crisaborole, pimecrolimus, and tacrolimus differ in effectiveness versus each other or to topical corticosteroids?
2. For adults and children with AD, do dupilumab, crisaborole, pimecrolimus, or tacrolimus differ in harms versus each other or to topical corticosteroids?
3. Are there subgroups of patients based on demographics and comorbidities for which dupilumab, crisaborole, pimecrolimus, or tacrolimus are more effective or have fewer adverse events?

Conclusions:
Drug Effectiveness Review Project Report
- The Drug Effectiveness Review Project (DERP) report evaluated 4 fair quality head-to-head trials of topical calcineurin inhibitors in management of moderate-to-severe AD and concluded short-term treatment response (6 to 12 weeks) was not consistently different between tacrolimus and pimecrolimus. Short-term improvement in symptoms was modestly better with tacrolimus compared to pimecrolimus, using a symptom scale, reduction in the percentage of body surface area affected, and ratings of pruritus.[1] In a meta-analysis of these trials completed by DERP authors, a lower chance of response with pimecrolimus than with tacrolimus was observed [pooled relative risk (RR) 0.73; p=0.02; low statistical heterogeneity (I2) = 33.1%].[1] However, the DERP authors noted the absolute difference in risk was very small and not statistically significant (-0.09%, p=0.18), with moderate statistical heterogeneity (I2 = 68%).[1]
- One good quality systematic review completed in patients with moderate-to-severe AD symptoms concluded response to treatment and symptom improvement was similar between topical calcineurin inhibitors (TCI) and topical corticosteroids (TCS).[2]
- There is inadequate evidence to assess the relative efficacy and safety of crisaborole compared with TCI and TCS treatments.
- There is insufficient evidence regarding the long term safety of crisaborole.
- The DERP meta-analysis of the comparative calcineurin inhibitor trials did not show a difference between pimecrolimus and tacrolimus in withdrawal of therapy due to adverse events (pooled RR 1.16; 95% CI 0.43 to 3.14; I2 = 0%).[1]

- Moderate quality evidence shows that patients using calcineurin inhibitors experienced more adverse events compared to TCS. Specifically, skin burning (30% vs. 9%; RR 3.27; 95% CI 2.48-4.31; p< 0.00001) and pruritus (12% vs. 8%; RR 1.49; 95% CI 1.24-1.79; p<0.00001) occurred more frequently with TCI compared to TCS.[2]
- Patients with atopic dermatitis may have slightly increased risk of lymphoma, but evidence does not find that TCIs increase this risk.[1]
- Information on potential differences in effects of tacrolimus and pimecrolimus in population subgroups based on baseline disease severity, percentage of affected body surface area and ethnicity were identified. Because these observations were noted in small sample sizes or as part of a subgroup analysis, they have limited value to insufficient evidence.

New Drug Evaluation: Dupilumab

- Two good quality, short-term (16 week) randomized controlled trials (RCTs) demonstrated efficacy of dupilumab compared to placebo in managing symptoms of moderate-to-severe AD refractory to other topical therapies.[3] The primary outcome in the SOLO 1 and SOLO 2 trials was the proportion of patients who had both an Investigator Global Assessment (IGA) score of 0/1 and a reduction of 2 points or more in the 5-point IGA score from baseline at week 16. In SOLO 1, the primary outcome occurred in 85 patients (38%; Absolute Risk Reduction (ARR) 28%; Number Needed to Treat (NNT) = 4) who received dupilumab every other week and in 83 patients (37%; ARR 27%; NNT = 4) who received dupilumab weekly, as compared with 23 patients (10%) who received placebo (P<0.001 for both comparisons with placebo).[3] The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 patients (36%) who received dupilumab weekly, as compared with 20 patients (8%) who received placebo (P<0.001; ARR 28%; NNT = 4 for both comparisons with placebo).[3]
- A third phase 3 trial assessed the efficacy and safety of the 2 dose regimens of dupilumab with concomitant therapy of TCS with or without TCI, in comparison to placebo and TCS with or without TCI, over 16 weeks.[4] The co-primary endpoints were the proportion of subjects with IGA 0/1 (on a 5-point scale) and a reduction in IGA from baseline of 2 points or more at week 16. More patients who received dupilumab plus topical TCS (39%) achieved the co-primary endpoints compared to patients who received placebo plus TCS (12%; ARR = 27%; NNT = 4; p<0.0001) at week 16.[4]
- The overall incidence of adverse events was similar in the dupilumab groups and the placebo groups in the two SOLO trials. Serious adverse events and adverse events leading to treatment discontinuation were uncommon.
- There is insufficient evidence to compare dupilumab with TCI monotherapy, systemic cyclosporine or phototherapy. There is insufficient evidence on the expected duration of response to dupilumab, both once a course of therapy has been administered, and with repeated or ongoing therapy.[5]

Recommendations:

- Revise PA criteria for topical antipsoriatic drugs to include agents used to manage atopic dermatitis. Categorize these 2 classes of drugs as “Atopic Dermatitis Drugs” and “Antipsoriatics, Topical” on the OHP Preferred Drug List (PDL).
- Designate dupilumab as a non-preferred medication on the Practitioner-Managed Prescription Drug Plan (PMPDP). Apply clinical prior authorization (PA) criteria to dupilumab. Limit use to:
    - Moderate-to-Severe atopic dermatitis
    - Age of 18 years or greater
    - Prescribed by a dermatologist or allergist
    - History of documented contraindication or failed trial of the following treatments: moderate to high potency topical corticosteroid, topical calcineurin inhibitor, and oral immunomodulatory therapy.
- After reviewing comparative costs in executive session, designate tacrolimus 0.03% ointment, tacrolimus 0.1% ointment, and pimecrolimus 1% cream as preferred agents.

Background:

Atopic dermatitis (AD) is chronic skin disorder characterized by pruritus and recurrent eczematous lesions accompanied by inflammation.[6] Other clinical features may include xerosis, erythema, erosions, oozing, and lichenification of the skin. The most commonly affected areas include the face, elbows, knees, hands, and feet. The cause is unknown, but may be due to genetics or immunologic dysfunction.[7] 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.[8,9] Estimated prevalence of AD in U.S. adults is 3%.[8] 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.[10] AD can persist into adulthood in about one third of affected individuals.[8] Itching, sleep deprivation, and social embarrassment due to visible lesions can have substantial effects on the quality of life.[11] Sleep disturbance is a common association of AD and is thought to be largely attributable to pruritus.[10] Sleep disruption can lead to daytime drowsiness and irritability, resulting in impaired performance at school or work. The prevalence of depression, anxiety, conduct disorder is higher than the general population, particularly in severely affected children with AD.[7] Adults with AD are more likely to have depression than healthy individuals.[7] The skin of patients with AD is prone to secondary infections.[7] Progression to infection is often associated with a worsening of the disease. One report found that that the density of *Staphylococcus aureus* was associated with severity of AD.[12] Eczema herpeticum is a widespread skin infection with herpes simplex virus that occurs in up to 3% of patients, particularly in severely affected patients.[7]

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 TCS or a calcineurin inhibitor (e.g., pimecrolimus or tacrolimus) as needed.[7] Calcineurin inhibitors exert their anti-inflammatory properties by inhibiting calcineurin-dependent T-cell activation, thereby impeding production of proinflammatory cytokines and mediators.[13] The use of TCS and TCI therapies in AD is supported by The American College of Dermatology's 2014 guideline[14] and 2004 guidance from the National Institute for Health and Care Excellence.[5] 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] Tacrolimus 0.03% ointment and pimecrolimus cream are indicated for use in individuals age 2 years and older, whereas tacrolimus 0.1% ointment is only approved in those older than 15 years.[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 is even more of a problem with TCI preparations.[18] Furthermore, the Food and Drug Administration (FDA) labeling for tacrolimus and pimecrolimus include boxed warnings regarding a theoretical risk for skin cancers and lymphoma associated with TCI administration.[16,17] 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.[19] 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,[20] and can increase the risk of infections and cancer.[21] Cyclosporine nephrotoxicity can be irreversible, and this risk increases with longer durations of treatment.[20] 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.[5] 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.[22]

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.[23] 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. More information about dupilumab is presented later in this report. Clinical trials are currently underway with other biologics including ustekinumab, secukinumab, and apremilast to assess their efficacy in treating patients with AD.[6]

Clinical studies have utilized several scales for defining the severity of AD, including the Severity Scoring of Atopic Dermatitis (SCORAD) index, the Eczema Area and Severity Index (EASI) and IGA. The SCORAD tool incorporates clinician estimates of disease extent and severity and subjective patient assessment of itching and sleep loss.[24] The extent of AD is graded by the clinician for specific areas of the body (head/neck, upper limbs, lower limbs, trunk and back) and is given a percentage score. AD severity includes a clinician assessment of the intensity of redness, swelling, oozing, dryness, scratch marks, and lichenification, which are graded on a 4-point scale rated as 0 (none), 1 (mild), 2 (moderate) or 3 (severe). Subjective symptoms such as itching and sleeplessness are scored by the patient using a visual analog scale (VAS) from 0 (no symptoms) to 10 (worst imaginable) for a total score of 20. When all 3 areas are added together, the total SCORAD score can range from 1 to 100. A SCORAD score greater than or equal to 50 indicates severe AD while a score less than 25 corresponds to mild AD.[24] The EASI assesses the severity of, and body surface area affected by, AD symptoms including erythema, induration/papulation/edema, excoriations, and lichenification.[25] 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.[25] 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.[26] This measure was used to evaluate clinical response to treatment in studies evaluating new AD therapies.[4,27] 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."[1] 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.[26] The Investigator's Static Global Assessment (ISGA) does not assess changes in severity of skin lesions with treatment and may use a 6-point scale ranging from 0 (clear) to 5 (very severe). **Table 1** summarizes the 3 different measures used in clinical trials evaluating the efficacy of AD treatments. These scales are primarily used in clinical trials and rarely in clinical practice, as they were generally not designed for this purpose.[10]

Table 1. Assessment of Atopic Dermatitis in Clinical Trials[24,25,28]

	SCORAD	**EASI**	**IGA/ISGA**
Scoring	Range: 0 to 100 Score ≤ 25: Mild AD Score ≥ 50 : Severe AD	Range: 0 to 72 Mild AD: 7.1 – 21.0 Moderate AD: 21.1 – 50 Severe AD: 50.1 - 72	Range: 0 to 4 *or* 0 to 5 Score of 0 or 1 indicates disease clearing
Scale	4 point scale assessing intensity of erythema, edema/papulation, oozing/crusts, excoriations, and lichenification: 0 - absent 1 - mild 2 - moderate 3 - severe	4 point scale assessing erythema, induration, infiltration/papulation, edema, excoriation, and lichenification: 0 - none 1 - mild 2 - moderate	5 or 6 point scale based on assessment of erythema and infiltration/papulation: 0 - clear 1 - almost clear 2 - mild disease 3 - moderate disease 4 - severe disease 5- very severe disease

		3 - severe	
Body Regions	Distribution rated on a 0 to 4 scale for each body region (Head/Neck, Trunk Upper limbs, and Lower limbs): 0= no affected site 1 = 1 affected site 2 = 2 affected sites 3 = 3 affected sites 4= more than 4 affected sites	Proportionate values assigned to 4 separate body regions: Upper limbs (20%) Lower limbs (40%) Trunk (30%) Head/Neck (10%)	Not Used
Additional Assessments	Patient assessment of itching and sleep loss on a 0 to 10 VAS	None	None

Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ISGA = Investigator's Static Global Assessment; SCORAD = Severity Scoring of Atopic Dermatitis; VAS = Visual Analog Scale

The Health Evidence Review Commission (HERC) recently modified conditions funded on line 424 (moderate/severe inflammatory skin disease) to include psoriasis, AD, lichen planus, Darier disease, pityriasis rubra pilaris and discoid lupus.[29] 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. In addition, the HERC guidance stipulates first-line agents for treatment of severe AD/eczema include TCS, narrowband UVB, cyclosporine, methotrexate, and azathioprine. Second-line agents include topical pimecrolimus and topical tacrolimus and should be limited to those who fail or have contraindications to first-line agents.[29] When crisaborole was presented to the P and T committee at the May 2017 meeting, AD was an unfunded condition. Due to these recent changes to the prioritized list, moderate to severe AD will now be funded by HERC effective January 1, 2018. Mild AD is classified on line 544 and will therefore remain unfunded.

Methods:

The final December 2017 drug class report on AD by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1]

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

The objective of the DERP report focused on drugs to treat to AD is to review evidence for the comparative effectiveness and comparative harms of dupilumab, crisaborole, pimecrolimus, and tacrolimus when compared to each other and when compared to TCS or placebo.[1] In addition, the report reviewed evidence to determine if there are any subgroups of patients for which dupilumab, crisaborole, pimecrolimus, or tacrolimus are more effective or associated with fewer

adverse events.[1] The DERP reviewers completed a systematic review based on a literature search from November 2007 through September 2017. Evidence from 46 publications are included in the DERP report: 37 articles reporting on 43 original trials, 2 companion publications to the included trials, 5 observational studies and 2 systematic reviews.[1] Pairwise meta-analyses were conducted by the DERP authors for dupilumab and crisaborole versus placebo studies, and for studies comparing TCI products. DERP authors also conducted a network meta-analyses of data from trials of topical calcineurin inhibitors and topical crisaborole compared with topical steroids or placebo. Since the network meta-analysis is comprised of indirect comparisons, this summary of the DERP report will focus on direct comparisons of the AD agents with an emphasis on treatment of moderate to severe AD, which is funded by HERC. The results are organized according to the severity of patient symptoms (e.g., mild-to-moderate, moderate-to-severe, or resistant to topical treatment) as described in the corresponding trials. **Table 2** summarizes the mechanism, dosage form and FDA approved populations for the 4 drugs included in the AD DERP report.

Table 2. Drug Information for the AD Drugs summarized in the DERP report[1]

Generic Name	Trade Name	Mechanism	Dosage Form	FDA Approved Population
Dupilumab	Dupixent®	Monoclonal antibody	Subcutaneous Injection	Moderate to severe AD
Crisaborole	Eucrisa™	PDE4 inhibitor	Ointment	Mild to moderate AD
Pimecrolimus	Elidel®	Calcineurin inhibitor	1% Cream	Mild to moderate AD
Tacrolimus	Protopic®	Calcineurin inhibitor	0.03% and 0.1% Ointment	Moderate to severe AD
Abbreviations: AD = Atopic Dermatitis; DERP = Drug Effectiveness Review Project; FDA = Food and Drug Administration; PDE4 = Phosphodiesterase 4				

Efficacy and Safety

Head-to-Head Trials of Topical Calcineurin Inhibitors in Moderate to Severe AD

The DERP reviewers identified 4 fair quality head-to-head trials of tacrolimus ointment (0.03% or 0.1%) versus pimecrolimus 1% cream in patients with moderate to severe AD.[30-33] Two of the studies enrolled only children,[30,31] 1 study enrolled only adults,[32] and 1 study enrolled children and adults.[33] All but 1 study were 6 weeks in duration and the other study was 12 weeks in duration. The smallest trial (n=20) was open-label,[33] while the other 3 were investigator-blinded. All 4 trials reported response to treatment, with 3 trials using an IGA score of 0 or 1 to indicate disease clearing, while the open label trial did not describe the method of determining treatment success. The differences in improvement as measured by the EASI scale were statistically significantly greater with tacrolimus by 11% to 16% compared to pimecrolimus in 2 of 3 investigator-blinded trials.[1] Improvements in the percent of body surface area affected by AD varied widely across the studies, from a 64.6% reduction with tacrolimus in 1 study down to a 7% improvement with tacrolimus in another study.[1] Pruritus was improved more with tacrolimus than pimecrolimus in 1 of 3 studies reporting this outcome.[1] When the DERP authors pooled the results of these 4 studies, a lower chance of response with pimecrolimus than with tacrolimus was observed [pooled RR 0.73; p=0.02; I2 = 33.1%].[1] However, the DERP authors noted the absolute difference in risk was very small and not statistically significant (-0.09%, p=0.18), with moderate statistical heterogeneity (I2 = 68%).[1] This difference in response rate results indicates less certainty in the benefit of tacrolimus over pimecrolimus.[1]

Three of the TCI comparative trials evaluated adverse effects.[30-32] Application site reactions were evaluated in 3 trials, with 1 trial reporting adverse effects as the primary outcome.[31] The types of reactions reported were burning or stinging, itching, and erythema or irritation. One trial in children with moderate AD reported similar proportions of patients with any application site reaction at 4 days (28% vs. 24%), and also reported that the incidence decreased over time.[31] Across the 3 trials, significant differences were not consistently found in specific application site reactions, or other adverse events, such as skin infections.[30-32] The DERP meta-analysis of these 3 trials did not show a difference between pimecrolimus and tacrolimus in withdrawal of therapy due to adverse events (pooled RR 1.16, 95% CI 0.43 to 3.14, I2 = 0%).[1]

Head-to-Head Trials of Topical Calcineurin Inhibitors in Mild to Moderate AD

There are 2 fair quality trials of patients with mild to very moderate AD disease that compared tacrolimus ointment (0.03% or 0.1%) with pimecrolimus 1% cream which were summarized in one publication.[30] The pediatric study included only children with mild AD (n=426), while the adult study (n=413) included patients with mild (32%), moderate (45%), and severe disease (23%). The previously summarized DERP meta-analysis of TCI included a sub-group analysis from the 1 study that included adults with moderate AD disease. The studies were 6 weeks in duration and the investigators were blinded to treatment when conducting assessments. At the end of treatment, the percentage of improvement from baseline, by reduction in EASI score, was greater for tacrolimus ointment than for pimecrolimus cream in adults with any level of disease (54.1% vs. 34.9%, respectively; p<0.0001).[30] In the pediatric patients with mild AD, there was a statistically significant difference favoring tacrolimus over pimecrolimus at week 1 (39.2% vs. 31.2%, respectively; p = 0.04) and a trend for a continued advantage of tacrolimus compared with pimecrolimus at the end of treatment (52.1% vs. 42.7%, respectively; p = 0.07).[30] In both studies, regardless of treatment, the most common adverse events were local application site reactions, including stinging or burning. In the pediatric study, there were no significant differences noted between tacrolimus-treated and pimecrolimus-treated patients in the incidence rate of adverse events, although there was numerically greater incidence of burning with pimecrolimus (9.2%) than with tacrolimus (5.3%).[30] However, in the adult study, although there were no differences in withdrawals due to adverse events, application site burning occurred more frequently in the tacrolimus-treated patients than the pimecrolimus-treated patients (p=0.02).[30]

Topical Calcineurin Inhibitors Compared to Topical Corticosteroids in Moderate to Severe AD

When TCI were compared to TCS in patients with moderate to severe AD, the DERP investigators identified 1 good-quality systematic review[2] and 1 fair-quality trial.[34] The systematic review included 12 RCTs of moderate quality comparing calcineurin inhibitors (n=3492) to corticosteroids (n=3462) in children and adults.[2] Eleven of the 12 trials were conducted among patients with moderate-severe AD. The systematic review did not specify the potency of the corticosteroids used in the studies. The methods or scores used to determine treatment success across studies were not disclosed. The included trials were published between 2001 and 2015. Mean follow-up was 101 weeks (range 2-260 weeks). All participants applied calcineurin inhibitors or corticosteroids twice daily and all but 1 trial was funded by a pharmaceutical company. Treatment success was similar in the systematic review for calcineurin inhibitors and corticosteroids (72% vs. 68%; RR 1.15; 95% CI 1.00-1.31; p=0.04).[2] In addition, calcineurin inhibitors and corticosteroids had a similar percentage of patients with improvement of dermatitis (81% vs. 71%; RR 1.18; 95% CI 1.04-1.34; p=0.02).[2] There was high heterogeneity across studies (I2=93%).[1]

The systematic review noted there were no differences in adverse events requiring discontinuation between the corticosteroid and calcineurin treatment groups (1.8% vs. 1.9%; RR 0.95; 95% CI 0.66-1.38; p=0.79), severe adverse events (8.2% vs. 7.2%; RR 1.15; 95% CI 0.98-1.34; p=0.08), atrophy (0.8% vs. 0%; RR 5.66; 95% CI 1.00-31.91; p=0.05), or skin infection (12% vs. 11%; RR 1.08; 95% CI 0.94-1.24; p=0.29).[2] However, the number of adverse events (74% vs. 64%; RR 1.28; 95% CI 1.05-1.58; p=0.02) and adverse events related to treatment (11% vs. 8%; RR 1.45; 95% CI 1.15-1.83; p=0.002) were higher in the calcineurin inhibitor group compared with the corticosteroid group, with a higher rate of skin burning (30% vs. 9%; RR 3.27; 95% CI 2.48-4.31; P< 0.00001) and pruritus (12% vs. 8%; RR 1.49; 95% CI 1.24-1.79; p<0.00001).[2]

Crisaborole in Mild to Moderate AD

No studies were found comparing crisaborole with a TCI, dupilumab, or TCS formulations. To date, there are only 3 trials of crisaborole, all compared to placebo in patients with mild to moderate AD.[35,36] A good quality systematic review compiled by the Institute for Clinical and Economic Review (ICER) that evaluated these studies was also identified by the DERP reviewers.[23] Two 4-week studies similar in design enrolled children (n = 1522) with mild to moderate AD (39%

mild), with 18% body surface area affected.[35] The other trial enrolled adults (n = 25) for 6 weeks to compare crisaborole to placebo.[36] Modest improvement was seen by investigators in more pediatric patients using crisaborole than placebo in erythema (59% vs. 40%; p<0.001), exudation (40% vs. 30%; p<0.001), excoriation (60% vs. 48%; p<0.001), induration/papulation (55% vs. 48%; p=0.008) and lichenification (52% vs. 41%; p<0.001).[35] Patient assessment of pruritus improvement at day 29 was also greater with crisaborole (63% vs. 53%; p=0.002).[1] In these trials there were no serious adverse events reported, and very few patients withdrew due to adverse events. Application site pain was the most common adverse event reported (4.6% vs. 1.7%).[1] The other adverse events reported in the trials were not different between groups.

The DERP meta-analysis of these 3 trials found crisaborole resulted in more patients achieving response when compared to placebo (44% vs. 21%; pooled RR 1.67; 95% CI 1.15 to 2.47) using the Investigator's Static Global Assessment (ISGA) tool in children or the AD Severity Index (ADSI) score in adults, with total or partial clearance of disease constituting response.[1] There was moderate statistical heterogeneity in this analysis, (I2 = 68%), likely due to the larger treatment effect seen in the very small study of adults.[1] The DERP reviewers noted that a meta-analysis of the 2 pediatric trials was conducted by the authors of the ICER report and success rate was moderately higher in the pooled crisaborole arms than in the placebo arms (32.1% vs. 21.7%; p<0.0001).[23]

The main evidence on crisaborole comes from trials that randomized a total of 1016 patients to crisaborole therapy for 28 days compared to placebo.[23] There is inadequate evidence to assess the relative efficacy of crisaborole compared with topical calcineurin inhibitors and TCS.[23] Although crisaborole was well tolerated over this period of time, it is difficult to assess its safety compared with the other topical agents.[23] In the absence of longer trials or head-to-head trials, relative efficacy and safety of crisaborole is uncertain.[23]

Dupilumab in Moderate to Severe AD

Six RCTs compared dupilumab to placebo in adult patients with moderate to severe AD inadequately controlled with topical treatments. Three trials are of fair-quality due to lack of clarity related to randomization, allocation concealment and blinding.[37] The other 3 trials are of good quality.[27,38] The dupilumab trials were from 4 to 16 weeks in duration. There were no important differences in baseline characteristics between treatment and control groups in any of the 6 trials.[23] Trials were conducted at various sites across Europe, Asia and North America. All 6 trials comparing dupilumab to placebo reported response to treatment, using an IGA score of 0 or 1 to indicate disease clearing. All trials showed statistically significantly greater IGA responses in the dupilumab arms compared to placebo. The response rates were 11.8% to 40% for the dupilumab arms, with little difference between weekly and every other week dosing, and were 1.6% to 10.3% in the placebo arms.[1] The DERP meta-analysis of dupilumab included all 6 trials and found an increased chance of achieving an IGA response with dupilumab compared to placebo (pooled RR 4.10, 95% CI 3.10 – 5.42, p<0.0001, I2 = 0%).[1] Severe or serious adverse events with dupilumab were rare during treatment up to 16 weeks. The most common adverse events observed at 16 weeks were injection site reactions, nasopharyngitis, and headache, all having higher rates than placebo. The rates of any adverse event, serious adverse events, and discontinuation due to adverse event were slightly lower with dupilumab than placebo. In the DERP meta-analysis of the 6 trials comparing dupilumab to placebo, no statistically significant difference in withdrawals to adverse events between the two groups was found (pooled RR 0.98; 95% CI 0.50 – 1.92, p=0.96, I2 = 0%).[1]

Additional outcomes assessing symptom improvement, including percent change in EASI score and percent change in pruritus numerical rating scale (NRS) were reported in these trials. Dupilumab substantially increased the likelihood of achieving improvement on the EASI compared to placebo.[27] Results were similar with weekly or every other week dosing and in patients treated or not treated with topical TCS.[4] Dupilumab also improved pruritus. Four trials assessed the reduction of pruritus symptoms using percent change from baseline peak NRS score. Across the 4 trials, the reduction in peak NRS ranged from 40% to 56% in the dupilumab arms versus 5% to 29% in the placebo arms.[4,27,38] Dupilumab improved patient quality of life as measured by the Dermatology Life Quality Index (DLQI). Four trials measured the change in mean DLQI from baseline at 16 weeks and found greater improvement with dupilumab than placebo.[4,27,38] Anxiety

and depression were measured by the Hospital Anxiety and Depression Scale (HADS) in 3 trials, and improvement was noted in patients taking dupilumab in all 3 studies.[4,27]

There is 1 fair-quality[37] and 1 good-quality trial[4] comparing dupilumab plus TCA to placebo plus TCA in adult patients with moderate-severe AD inadequately controlled with topical treatments. The 2 trials comparing dupilumab plus TCA to placebo plus TCA reported a response to treatment, with both studies using an IGA score of 0 or 1 to indicate disease clearing.[4,37] Pooling these 2 studies results in increased chance of response with dupilumab and corticosteroid than with corticosteroid alone (pooled RR 3.94, 95% CI 2.93 – 5.31, p<0.0001, I2=0%).[1] In 2 trials comparing dupilumab plus corticosteroid to corticosteroid alone, withdrawal due to adverse events was less likely for patients receiving dupilumab plus corticosteroids compared to corticosteroids alone (pooled RR 0.43, 95% CI 0.15 - 1.4, p = 0.12, I2 = 0%).[1] The DERP reviewers noted a recent systematic review conducted by ICER evaluated the effectiveness and value of dupilumab in AD.[23] The ICER review includes similar trials to those in the DERP report, and draws the same conclusions as the DERP reviewers.[1,23]

Risk of Cancer

The risk of cancers in patients with AD has been studied in 9 cohort and 19 case-control studies.[1] Many of these reports were included in a good-quality systematic review that specifically examined the risk of lymphoma with the use of TCI.[39] The systematic review found that there is a small increased risk of lymphoma among patients with AD compared to the general population, based on 4 cohort studies (odds ratio (OR) 1.43, 95% CI 1.12 to 1.81).[39] However, among patients with AD, the risk of lymphoma was not significantly increased with either tacrolimus (2 studies, OR 3.13, 95% CI 0.67 to 14.57) or pimecrolimus use (2 studies, OR 1.58, 95% CI 0.83 to 3.00).[39] Case control studies found no increased risk of lymphoma among patients with AD versus patients without AD, or with the topical calcineurin inhibitors.[1] In a fair-quality study of children conducted in the U.S. using the Pediatric Eczema Elective Registry (n=7,457), there was not an increased risk of lymphoma with pimecrolimus compared with the general population (OR 2.9, 95% CI 0.7 to 11.7).[40] The study was developed with input from the FDA and had 26,792 person-years of follow-up.[40] Tacrolimus was not studied in this evaluation. A poor-quality case-control study of 2,821 children found no increased risk of skin cancer with previous use of TCI (OR 0.50, 95% CI 0.25 to 0.98).[41] This study relied on survey data, with the potential for recall bias. Three cohort studies reported on the risk of any cancer with use of TCI in patients with AD.[40,42,43] In pediatric patients, there was no increased risk of cancer compared with the general population (OR 1.2, 95% CI 0.5 to 2.8).[40] The other 2 studies found the difference in risk for having used tacrolimus or pimecrolimus versus non-use to not be statistically significant.[42,43] Both studies had relatively short follow-up for studies of cancer development. Based on FDA analysis, reported cancers have occurred 90 to 159 days after treatment initiation.[1]

Effectiveness and Harms in Subgroups of Patients

Information on potential differences in effects of tacrolimus and pimecrolimus in subgroups of the population based on baseline disease severity, percentage of affected body surface area and ethnicity were identified. Because these observations were noted in small sample sizes or as part of a subgroup analysis, they have limited value due to insufficient evidence in these subgroups of AD populations.

New Drug Evaluation: Dupilumab

See **Appendix 2** for Highlights of Prescribing Information from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Dupilumab is an injectable interleukin (IL)-4 receptor antagonist approved for use in adults with moderate to severe AD not controlled with topical therapy. Binding of interleukin-4 receptor by dupilumab results in inhibition of IL-4 and IL-13 signaling which alters type 2 helper T (Th2) cell mediated immune responses and improves epidermal barrier abnormalities in AD.[37] Dupilumab therapy is initiated with a 600 mg subcutaneous (SC) injection loading dose followed by 300 mg SC every other week. Safety and efficacy of dupilumab in pediatric patients has not been established, although trials are currently being conducted in this population. In addition, several trials are currently investigating the efficacy of dupilumab in managing asthma refractory to other therapies.

Clinical Efficacy:

The Food and Drug Administration (FDA) approval of dupilumab is based upon 3 randomized, placebo-controlled, phase 3 trials. Two trials evaluated dupilumab as monotherapy and a third study evaluated dupilumab in combination with TCS. The 2 dupilumab monotherapy trials (SOLO 1 and SOLO 2) were of identical design and enrolled adults with moderate-to-severe atopic dermatitis (IGA score ≥ 3) whose disease was inadequately controlled by topical treatment.[27] The baseline demographics of the enrolled subjects was similar with respect to age (range of means: 35-39 years), duration of AD (range of means: 24-31 years), and baseline AD severity (47%-49% baseline IGA of 4). Many patients had received prior systemic treatments, including systemic corticosteroids (32-33%) and systemic immunosuppressants (25-31%).[27] The majority of patients treated with immunosuppressants received cyclosporine (20 - 23% of all patients).[27] Patients were randomly assigned in a 1:1:1 ratio to receive once weekly SC dupilumab (600 mg at week 0 followed by 300 mg), placebo SC once weekly, or dupilumab (600 mg at week 0 followed by 300 mg and placebo alternating every other week) for 16 weeks. The primary outcome was the proportion of patients who had both an IGA score of 0 or 1 (clear or almost clear) and a reduction of 2 points or more in the 5-point IGA score from baseline at week 16. SOLO 1 recruited 671 patients and SOLO 2 enrolled 708 patients in North America, Europe and Asia. In SOLO 1, the primary outcome occurred in 85 patients (38%; ARR 28%; NNT=4) who received dupilumab every other week and in 83 patients (37%; ARR 27%; NNT = 4) who received dupilumab weekly, as compared with 23 patients (10%) who received placebo (P<0.001 for both comparisons with placebo).[27] The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 patients (36%) who received dupilumab weekly, as compared with 20 patients (8%) who received placebo (P<0.001; ARR 28%; NNT=4 for both comparisons with placebo).[27]

A secondary outcome for SOLO 1 and SOLO 2 was the proportion of patients who had achieved EASI 75 from baseline to week 16. In both trials, EASI 75 response was reported in more patients who received each regimen of dupilumab (44% to 52%) than in patients who received placebo (12-15%; p<0.001; ARR 32% to 37%; NNT = 3 for all comparisons with placebo).[27] Dupilumab was also associated with reduction in pruritus. The baseline pruritus NRS score was based on the average of daily NRS scores for maximum itch intensity (daily score: 0 to 10) during the 7 days immediately preceding randomization for the dupilumab trials.[44] During the 2 trials, patients reported the intensity of their pruritus using the pruritus NRS via an interactive voice response system. At week 16, an improvement of at least 4 points in the peak score on the pruritus NRS occurred in more patients receiving dupilumab (35% to 40%) than in those receiving placebo (10% to 12%; ARR = 25% to 28%; NNT = 4; p<0.001 for all comparisons).[27]

Rescue treatment for AD could be provided at the discretion of the investigator. Subjects who received rescue treatment during the study treatment period were considered treatment failures, but were to continue study treatment if rescue consisted of topical medications. If a subject received rescue treatment with systemic corticosteroids or systemic immunosuppressive drugs, study treatment was immediately discontinued. In the two trials, more patients in the placebo group than in either dupilumab group received rescue treatment. In SOLO 1, the rates of rescue treatment were 21% among those receiving dupilumab every

other week and 23% among those receiving dupilumab every week, as compared with 51% among those receiving placebo; in SOLO 2, the rates were 15%, 21%, and 52%, respectively.[27]

Limitations of the SOLO trials include: 1) insufficient power to test differences between the two doses of dupilumab, 2) duration of the trials was not long enough to assess long-term safety, and 3) the trials only enrolled adults, although AD is more prevalent in children. It is notable that patients studied in the SOLO 1 and SOLO 2 trials had a substantial burden of disease. Although the entry criteria for the SOLO trials required an EASI score of at least 16 and an affected body surface area of at least 10%, the median EASI score at baseline was around 30 and the median affected body surface area was around 50%. Thus, the majority of patients had more severe disease than was required by the entry criteria for the trial. Although the indication for dupilumab in the FDA label is for moderate-to-severe disease that is inadequately controlled with topical treatment or for whom topical treatment is medically inadvisable, it is uncertain whether the patients for whom dupilumab is recommended by their clinicians will have similarly severe disease to those subjects in the randomized trials.[23]

A third trial phase 3 trial (LIBERTY AD CHRONOS) assessed efficacy and safety of the two dose regimens of dupilumab with concomitant therapy of TCS with or without TCI, in comparison to placebo and TCS with or without TCI at week 16 and week 52.[4] Adults with moderate-to-severe AD who had a previously documented inadequate response to topical medication or systemic treatment were enrolled in this trial.[4] The study was a randomized, double blind, multi-center, parallel group study in 740 adult subjects. Subjects were randomized in a 3:1:3 ratio to receive once weekly or every other week SC injections of 300 mg dupilumab, following a loading dose of 600 mg on Day 1, or matching placebo, respectively. All patients received concomitant TCS preparations and TCI formulations could be used in body locations considered inadvisable for TCS. Starting on day 1, all patients used once-daily medium-potency TCS, or low-potency TCS for sensitive skin areas (e.g., face). After AD was controlled (clear or almost clear), patients using medium-potency TCS switched to low-potency TCS for 7 days, then stopped; for sensitive skin locations, low-potency TCS or TCI could be tapered and stopped. Rescue treatment, consisting of any locally approved treatments for AD, including topical or systemic medications or phototherapy, could be used after week 2. Patients receiving high-potency TCS as rescue could continue with study drug. If rescue consisted of systemic medications or phototherapy, study drug was temporarily discontinued.

The co-primary endpoints were the proportion of subjects with IGA 0 or 1 (on a 5-point scale) and a reduction in IGA from baseline of 2 points or more at week 16. Three hundred nineteen subjects were randomly assigned to dupilumab once weekly, 106 subjects to dupilumab every other week, and 315 to placebo. At week 16, more patients who received dupilumab once weekly or every other week achieved the co-primary endpoints of IGA 0/1 (39% for both arms), compared to patients who received placebo (12%; ARR = 27%; NNT = 4; $p<0.0001$ for both groups compared to placebo).[4]

Secondary outcomes included the proportion of patients achieving 75% improvement in EASI from baseline to week 16 and proportion of patient achieving IGA 0/1 and 2-point or higher reduction from baseline at week 52. EASI 75 response at week 16 was reported in more patients who received each regimen of dupilumab (once weekly 64%; every other week 69%) than in patients who received placebo (22% $p<0.0001$ for both dupilumab regimens).[4] At week 52 more patients in the dupilumab groups achieved IGA scores of 0/1 and a reduction of greater than 2 points from baseline (once weekly 40%; every other week 36%) compared to placebo (13%; $p<0.0001$ vs. placebo for both dupilumab regimens).[4]

This study has limitations. Over half of the patients had moderate AD (indicated by an IGA score of 3) which is not the true target population for systemic, biologic therapy. Systemic therapy is generally reserved for severe AD, which comprised 48% of the patients (IGA score of 4) enrolled in this study. For some efficacy outcomes, such as the proportion of patients achieving IGA 0/1 and 2 point or higher improvement in IGA from baseline, EASI-75, and peak pruritus NRS improvement of 4 or higher and 3 or higher, the dupilumab every other week group showed greater variability over time compared with the dupilumab once weekly, which might reflect the smaller sample size (33%) of the dupilumab every other week group.[4] Additionally, quantification of the use of concomitant

topical medication was difficult, because there are logistical and technical barriers to accurately and consistently measure leftover content in tubes of TCS across more than 150 study sites.[4] What is needed are studies that compare dupilumab against existing systemic treatments such as methotrexate in people with severe AD or for those who have failed on phototherapy and one other systemic therapy.[45]

Clinical Safety:
The overall incidence of adverse events was similar in the dupilumab and placebo groups in the two SOLO trials. Serious adverse events and adverse events leading to treatment discontinuation were uncommon. The only serious adverse event that was reported in more than 2 patients in any treatment group was a serious exacerbation of AD, which was reported in 2 patients receiving dupilumab every other week and 3 patients receiving placebo in SOLO 1 and in 1 patient receiving weekly dupilumab and 5 patients receiving placebo in SOLO 2.[27] Adverse events categorized as infections or infestations developed in 35% of the patients receiving dupilumab every other week and in 34% of those receiving dupilumab every week, as compared with 28% of those receiving placebo in SOLO 1 and in 28%, 29%, and 32%, respectively, in SOLO 2.[27] The most common adverse events in the two trials were exacerbations of AD, injection-site reactions, and nasopharyngitis. Dupilumab-treated patients had a higher incidence of injection-site reactions, most of which were of mild or moderate severity. Of note, conjunctivitis occurred more frequently in the dupilumab groups than in the placebo groups. The pooled incidence of adverse effects observed at 16 weeks in the SOLO trials are presented in **Table 3**.

Table 3. Adverse Events with Dupilumab Monotherapy compared to Placebo through Week 16[46]

Common Adverse Events	Dupilumab N = 529	Placebo N = 517
Injection-site reactions	51 (10%)	28 (5%)
Conjunctivitis	51 (10%)	12 (2%)
Oral herpes	20 (4%)	8 (2%)
Other herpes simplex infections	10 (2%)	6 (1%)

The LIBERTY AD CHRONOS trial evaluated safety of dupilumab at 52 weeks of therapy. Overall rates of adverse events were similar across the treatment groups during the 52-week treatment period.[4] However, the dupilumab every other week group had higher rates of injection-site reactions than the placebo group (15% vs. 8%, respectively) and the incidence of conjunctivitis was higher in the dupilumab every other week group than in the placebo group (14% vs. 8%, respectively).[4] The incidence of adverse events observed in this 52 week trial are summarized in **Table 4**.

Table 4. Adverse Events with Dupilumab Every Other Week compared to Placebo through Week 52[4]

Adverse Events	Dupilumab N = 110 (%)	Placebo N = 315 (%)
≥ 1 adverse event	97 (88%)	266 (84%)
≥ 1 Serious Adverse Event	4 (4%)	16 (5%)
Nasopharyngitis	25 (23%)	61 (19%)
Injection-site reactions	16 (15%)	24 (8%)
Conjunctivitis	15 (14%)	25 (8%)
Any herpes infections	8 (7%)	25 (8%)

Look-alike / Sound-alike Error Risk Potential: None reported

Table 4. Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	Interleukin-4 Receptor Antagonist
Absorption	Bioavailability: 64%
Distribution and Protein Binding	Volume of Distribution: 4.6 liters
Half-Life	Not Available
Elimination	Monoclonal antibodies are primarily degraded into small peptides and amino acids by catabolism

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Symptom improvement
2) Quality of life
3) Serious adverse events
4) Study withdrawal due to adverse event

Primary Study Endpoint:
1) Percentage of patients with IGA score 0/1 and reduction of ≥ 2 points from baseline at week 16

Table 5. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
Simpson EL, et al. [27] SOLO 1 Phase 3, DB, PG, MC, RCT N=671	1. Dupilumab 600 mg x 1 followed by 300 mg/week, SC 2. Dupilumab 600 mg x1 followed by 300 mg SC every other week alternating with placebo 3. Placebo SC weekly Duration: 16 weeks	Demographics: -Mean age: 39 y -Male: 58% -White: 67% - Mean AD duration: 28 y - Mean EASI: 31 -IGA score 4: 48% -Previous topical corticosteroids: 32% -Previous immunosuppressant: 26% -Median-affected BSA: 57% Key Inclusion Criteria: -Age 18 y or older -Moderate-to-severe AD (IGA 3 or 4), inadequately controlled by topical treatment -EASI score ≥ 16 -Chronic AD ≥ 3 years -AD involvement ≥ 10% BSA involvement -Pruritus NRS ≥ 3 Key Exclusion Criteria: -Treatment with an investigational drug -Treatment with immunomodulating drugs (corticosteroids, cyclosporine, azathioprine, etc.) or phototherapy 4 weeks before study enrollment.	ITT: 1.223 2.224 3.224 PP: 1.197 2.208 3.184 Attrition at week 52: 1.26 (12%) 2.16 (7%) 3.40 (18%)	Primary Endpoint: IGA score of 0/1 and reduction of ≥ 2 points from baseline at week 16 1.83 (37%) 2.85 (38%) 3.23 (10%) RR and CI NR P < 0.001 for 1 and 2 compared to placebo Secondary Endpoint: Secondary outcomes at week 16: EASI 75 1. 117 (52%) 2. 115 (51%) 3. 33 (15%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo EASI 90 1.74 (33%) 2.80 (36%) 3.17 (8%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo Improvement in pruritus NRS ≥ 4 from baseline to week 16 1. 81 (40%) 2. 86 (40%) 3. 24 (12%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo	27%/4 28%/4 37%/3 36%/3 25%/4 28%/4 28%/4 28%/4	Outcome: AEs ≥ 1 1. 150 (69%) 2. 167 (73%) 3. 145 (65%) SAEs ≥ 1 1. 2 (1%) 2. 7 (3%) 3. 11 (5%) Discontinuation due to AEs 1. 4(2%) 2. 4 (2%) 3. 2 (1%) Exacerbation of AD: 1. 21 (10%) 2. 30 (13%) 3. 67 (30%) Infections and Infestations: 1. 74 (34%) 2. 80 (35%) 3. 63 (28%) Nasopharyngitis: 1. 25 (11%) 2. 22 (10%) 3. 17 (8%) Conjunctivitis 1. 7 (3%) 2. 11 (5%) 3. 2 (1%) Injection Site Reactions 1. 41 (19%)	NA NA NA NA NA NA	**Overall Trial Rating: Good Quality** **Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized 1:1:1 via centralized IVRS and stratified according to IGA score 3 or 4 and region. Baseline characteristics balanced Performance Bias: LOW. Blinded, coded kits containing dupilumab or placebo were used to mask the assigned treatment. All patients received injections every week by investigators to maintain blinding. Detection Bias: HIGH. All investigators were blinded to treatment. However, unblinding may have occurred due to large differences in efficacy between treatment groups or percentage of injection site reactions. Attrition Bias: LOW. Higher attrition rate in placebo group compared to dupilumab groups. LOCF after rescue treatment, subject considered a non-responder. Reporting Bias: LOW. Protocol available in supplementary appendix. All outcomes reported as stated a priori. CI were NR for outcomes giving uncertain estimate of precision. Funded by Sanofi and Regeneron Pharmaceuticals. **Applicability**: Patient: Children not evaluated although AD is more prevalent in pediatrics. Adults had median EASI score of 30 with median affected BSA of 57%, indicating severe disease. Intervention: 2 doses of dupilumab were appropriate based on results from Phase 2 trials Comparator: Placebo administered at same frequency as dupilumab to maintain blinding. Placebo suitable to assess efficacy. Outcomes: IGA score and EASI validated and used to evaluate AD in other trials. Setting: 160 global study sites. Proportion from the US was NR.

		-Treatment with biologic agents -Treatment with a live vaccine 12 weeks prior to study - 2 visits per week to a tanning booth within 4 weeks of study enrollment				2. 19 (8%) 3. 13 (6%)	NA	
Simpson EL, et al[27] SOLO 2 Phase 3, DB, MC, RCT N=708	1. Dupilumab 600mg x 1 followed by 300 mg/week, SC 2. Dupilumab 600mg x1 followed by 300 mg SC every other week alternating with placebo 3. Placebo Duration: 16 weeks	Demographics: -Mean age: 35 y -Male: 57% -White: 70% - Mean AD duration: 25 y -Mean EASI: 29 -IGA score 4: 48% -Previous corticosteroids: 33% -Previous immunosuppressant: 31% -Median-affected BSA: 53% Key Inclusion Criteria: -See SOLO 1 Key Exclusion Criteria: -See SOLO 1	ITT: 1.239 2.233 3.236 PP: 1.221 2.220 3.190 Attrition: 1.18 (8%) 2.13 (6%) 3.46 (19%)	Primary Endpoint: IGA score of 0/1 and reduction of ≥ 2 points from baseline 1.87 (36%) 2.84 (36%) 3.20 (8%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo Secondary Endpoint: Secondary outcomes at week 16: EASI 75 1. 115 (48%) 2. 103 (44%) 3. 28 (12%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo EASI 90 1.73 (31%) 2.70 (30%) 3.17 (7%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo Improvement in pruritus NRS ≥ 4 from baseline to week 16 1. 87 (38%) 2. 79 (35%) 3. 21 (10%)	28%/4 28%/4 36%/3 32%/3 24%/5 23%/5 28%/4	Outcome: AEs ≥ 1 1. 157 (66%) 2. 154 (65%) 3. 168 (72%) SAEs ≥ 1 1. 8 (3%) 2. 4 (2%) 3. 13 (6%) Discontinuation due to AEs 1. 3 (1%) 2. 2 (1%) 3. 5 (2%) Exacerbation of AD 1. 38 (16%) 2. 32 (14%) 3. 81 (35%) Infections and Infestations 1. 68 (29%) 2. 65 (28%) 3. 76 (32%) Nasopharyngitis 1. 20 (8%) 2. 20 (8%) 3. 22 (9%) Conjunctivitis 1. 9 (4%) 2. 9 (4%)	NA NA NA NA NA NA	**Overall Trial Rating: Good Quality** **Risk of Bias (low/high/unclear)**: Selection Bias: see SOLO 1 Performance Bias: see SOLO 1 Detection Bias: see SOLO 1 Attrition Bias: see SOLO 1 Reporting Bias: see SOLO 1 **Applicability**: Patient: see SOLO 1 Intervention: see SOLO 1 Comparator: see SOLO 1 Outcomes: see SOLO 1 Setting: see SOLO 1

				RR and CI NR P < 0.0001 for 1 and 2 compared to placebo	25%/4	3. 1 (<1%) <u>Injection Site Reactions</u> 1. 31 (13%) 2. 32 (14%) 3. 15 (6%)	NA	
Blauvelt A et al[4] LIBERTY AD CHRONOS Phase 3, DB, PC, PG, MC N=740	1. Dupilumab 600mg x 1 followed by 300 mg/week, SC +TCS 2. Dupilumab 600mg x1 followed by 300 mg SC every other week alternating with placebo +TCS 3. Placebo + TCS Duration: 52 weeks - Primary outcome assessment at 16 weeks	<u>Demographics</u>: -Mean age: 36 y -Male: 60% -White: 66% -AD duration: 27 y -Mean EASI score: 30 -IGA score 4: 48% -Average BSA %: 55 <u>Key Inclusion Criteria</u>: -Aged 18 y or older -AD ≥ 3 y -Inadequate response to TCS (with or w/o TCI) or systemic treatment 6 mos prior to screening -IGA score ≥ 3 -EASI score ≥ 16 <u>Key Exclusion Criteria</u>: -≥ 30% of total lesional surface located on areas of body unable to be treated with medium or high potency TCS -immunosuppressive or immunomodulating drugs or phototherapy for AD within 4 weeks before baseline - biologics, within 6 months prior to screening	<u>ITT</u>: 1.319 2.106 3.315 <u>PP</u>: 1.270 2.89 3.264 <u>Attrition</u>: 1.49 (15%) 2.17 (16%) 3.51 (16%)	<u>Primary Endpoints</u>: IGA score of 0/1 and reduction of ≥ 2 points from baseline to week 16 IGA Score 0/1 1.125 (39%) 2.41 (39%) 3.39 (12%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo <u>Secondary Endpoints:</u> EASI 75 at week 16: 1. 204 (64%) 2. 73 (69%) 3. 73 (23%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo Improvement in pruritus NRS ≥ 4 from baseline to week 16: 1. 150 (51%) 2. 60 (59%) 3. 59 (20%) RR and CI NR P < 0.0001 for 1 and 2 compared to placebo EASI 75 at week 52: 1.73 (64%) 2.70 (65%) 3.17 (22%) RR and CI NR	27%/4 27%/4 41%/3 46%/3 31%/4 39%/3 42%/3 43%/3	Outcome: <u>≥ 1 AE</u> 1.261 (83%) 2. 97(88%) 3. 266(84%) <u>≥ 1 SAE</u> 1. 9 (3%) 2. 4 (4%) 3. 5 (16%) <u>D/C due to AEs</u> 1. 9(3%) 2. 2 (2%) 3. 24 (8%) <u>Infections and Infestations</u> 1. 166(63%) 2. 63 (57%) 3. 182 (58%) <u>Nasopharyngitis</u> 1. 60 (19%) 2. 25 (23%) 3. 61 (19%) <u>Conjunctivitis</u> 1. 61 (19%) 2. 15 (14%) 3. 25 (8%) <u>Injection Site Reactions</u> 1. 60 (19%) 2. 16 (15%) 3. 24 (8%)	NA NA NA NA NA NA NA	**Overall Trial Rating: Good** **Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: LOW. Patients assigned 3:1:3 via IVRS. Stratified by baseline AD severity (IGA 3 or 4) and geographic region (Asia Pacific, eastern Europe, North America, and western Europe). Similar baseline demographics. <u>Performance Bias</u>: LOW. Patients given dupilumab every other week received matching placebo in the weeks when dupilumab was not given. Blinded study drug kits with a medication numbering system were used. Placebo was provided in identical syringes. <u>Detection Bias</u>: LOW. The study remained blinded to all individuals (including patients, investigators, and study personnel) until the time of prespecified unblinding, except for the statistician who provided the randomization sequence, and independent data monitoring committee members. <u>Attrition Bias</u>: LOW. Attrition rate over 52 weeks was similar across all treatment groups. <u>Reporting Bias</u>: UNCLEAR. Study was funded by Sanofi and Regeneron Pharmaceuticals Inc. The funders participated in the conception and design of the study, analysis and interpretation of the data, and drafting and critical revision of the report. Conflicts of interest were declared for all 31 authors, 16 of whom had a financial conflict with the commercial sponsors. **Applicability**: <u>Patient</u>: Children not evaluated although AD is more prevalent in pediatrics. Subjects had

		-live vaccine 12 weeks before enrollment - regular use (more than 2 visits per week) of a tanning booth within 4 weeks before baseline		P < 0.0001 for 1 and 2 compared to placebo IGA score of 0/1 and reduction of ≥ 2 points from baseline to week 52: 1. 108 (40%) 2. 32 (36%) 3. 33 (13%) RR and CI NR P < 0.001 for 1 and 2 compared to placebo	27%/4 23%/5			median EASI score of 30 with median affected BSA of 55%, indicating severe disease. However, 52% of patients had an IGA score of 3, indicating moderate AD. Intervention: 2 doses of dupilumab were appropriate based on results from Phase 2 trials over 52 weeks provided longer assessment time to assess safety and efficacy. Comparator: Dupilumab studied in combination with TCS/TCI therapies, standard of care for AD. Outcomes: IGA score and EASI validated and used to evaluate AD in other trials. Setting: 161 sites in 14 countries including Australia, Canada, Czech Republic, Hungary, Italy, Japan, the Netherlands, New Zealand, Poland, Romania, South Korea, Spain, the UK, and the US.

Abbreviations: AD = atopic dermatitis; AE = adverse effect; ARR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DB = double blind; D/C = discontinuation; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ITT = intention to treat; IVRS = interactive voice response system; LOCF = last observation carried forward; MC= multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NRS = numerical rating scale; PC = placebo-controlled; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SC = subcutaneous; SAE = serious adverse effect; TCS = topical corticosteroid; TCI = topical calcineurin inhibitors; y = years

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
CRISABOROLE	EUCRISA	TP	OINT. (G)	N
DUPILUMAB	DUPIXENT	SQ	SYRINGE	
PIMECROLIMUS	ELIDEL	TP	CREAM (G)	
TACROLIMUS	PROTOPIC	TP	OINT. (G)	
TACROLIMUS	TACROLIMUS	TP	OINT. (G)	

Appendix 2: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DUPIXENT safely and effectively. See full prescribing information for DUPIXENT.

DUPIXENT® (dupilumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. (1)

DOSAGE AND ADMINISTRATION

- Administer by subcutaneous injection. (2.1)
- The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield (3)

CONTRAINDICATIONS

Known hypersensitivity to DUPIXENT or any of its excipients. (4)

WARNINGS AND PRECAUTIONS

- *Hypersensitivity*: If a systemic hypersensitivity reaction occurs, discontinue DUPIXENT immediately and initiate appropriate therapy. (5.1)
- *Conjunctivitis and Keratitis*: Patients should report new onset or worsening eye symptoms to their healthcare provider. (5.2)
- *Comorbid Asthma*: Advise patients with comorbid asthma not to adjust or stop their asthma treatment without consultation with their physicians. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Live Vaccines: Avoid use of live vaccines with DUPIXENT. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2017

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, keroderma 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, keroderma 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 #17

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. Is the drug topical tacrolimus, pimecrolimus or crisaborole?	**Yes:** Go to #10	**No:** Go to #13
10. 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 #11
11. 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 #12	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. 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
13. Is the drug dupilumab?	**Yes:** Go to #14	**No:** Go to #17
14. What is the age of the patient? • Dupilumab injection is FDA approved for patients 18 years of age and older	**Age 17 years or younger**: Pass to RPh. Deny; medical appropriateness.	**Ages 18 years and older:** Go to #15
15. Is the medication being prescribed by or in consultation with a dermatologist or allergist?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
16. 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
17. 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 length of treatment.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *3/18 (DM); 9/17; 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *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 December 27, 2017.

Exclusion List

- Deny payment for drug claims for drugs that are only FDA-approved for indications that are not covered by the Oregon Health Plan (OHP).
- Other exclusionary criteria are in rules at: www.oregon.gov/OHA/healthplan/pages/pharmacy-policy.aspx

Excerpt from OAR 410-121-0147 Exclusions and Limitations (DMAP Pharmaceutical Services Program)
1) The following items are not covered for payment by the Division of Medical Assistance Programs (DMAP) Pharmaceutical Services Program: (a) Drug products for diagnoses below the funded line on the Health Services Commission Prioritized List or an excluded service under Oregon Health Plan (OHP) coverage; (b) Home pregnancy kits; (c) Fluoride for individuals over 18 years of age; (d) Expired drug products; (e) Drug products from non-rebatable manufacturers, with the exception of selected oral nutritionals, vitamins, and vaccines; (f) Active Pharmaceutical Ingredients (APIs) and Excipients as described by Centers for Medicare and Medicaid (CMS); (g) Drug products that are not assigned a National Drug Code (NDC) number; (h) Drug products that are not approved by the Food and Drug Administration (FDA); (i) Drug products dispensed for Citizen/Alien-Waived Emergency Medical client benefit type; (j) Drug Efficacy Study Implementation (DESI) drugs (see OAR 410-121-0420); (k) Medicare Part D covered drugs or classes of drugs for fully dual eligible clients (see OAR 410-121-0149, 410-120-1200, & 410-120-1210).

<u>NOTE:</u> Returns as "70 – NDC NOT COVERED"

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. For what reason is it being rejected?		
3. "70" NDC Not Covered (Transaction line states "Bill Medicare"	**Yes:** Go to the Medicare B initiative in these criteria.	**No:** Go to #2B
4. "70" NDC Not Covered (Transaction line states "Bill Medicare or Bill Medicare D"	**Yes:** Informational Pa to bill specific agency	**No:** Go to #2C

Approval Criteria		
5. "70" NDC Not Covered (due to expired or invalid NDC number)	**Yes:** Informational PA with message "The drug requested does not have a valid National Drug Code number and is not covered by Medicaid. Please bill with correct NDC number."	**No:** Go to #2D
6. "70" NDC Not Covered (due to DME items, excluding diabetic supplies) (Error code M5 –requires manual claim)	**Yes:** Informational PA (Need to billed via DME billing rules) 1-800-336-6016	**No:** Go to #2E
7. "70" NDC Not Covered (Transaction line states "Non-Rebatable Drugs")	**Yes:** Pass to RPh. Deny (Non-Rebatable Drug) with message "The drug requested is made by company that does not participate in Medicaid Drug Rebate Program and is therefore not covered"	**No:** Go to #2F
8. "70" NDC Not Covered (Transaction line states "DESI Drug")	**Yes:** Pass to RPh. Deny (DESI Drug) with message, "The drug requested is listed as a "Less-Than-Effective Drug" by the FDA and not covered by Medicaid."	**No:** Pass to RPh. Go to #3

Approval Criteria		
9. RPh only: "70" NDC Not Covered (Drugs on the Exclusion List) All indications need to be evaluated to see if they are above the line or below the line.	**Above:** Deny with yesterday's date (Medically Appropriateness) and use clinical judgment to APPROVE for 1 month starting today to allow time for appeal. Message: "Although the request has been denied for long term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."	**Below:** Deny. Not funded by the OHP. Message: "The treatment for your condition is not a covered service on the Oregon Health Plan."

If the MAP desk notes a drug is often requested for a covered indication, notify Lead Pharmacist so that policy changes can be considered for valid covered diagnoses.

Exclusion List		
Drug Code	**Description**	**DMAP Policy**
DCC = 1	Drugs To Treat Impotency/ Erectile Dysfunction	Impotency Not Covered on OHP List
DCC = B	Fertility Agents	Fertility Treatment Not Covered on OHP List
DCC = D	Diagnostics	DME Billing Required
DCC= F, except HSN = 018751 002111 002112 002070 002113 016924	Weight Loss Drugs	Weight Loss Not Covered on OHP List except In cases of co-morbidity. Exceptions are Prior Authorized
DCC= Y	Ostomy Supplies	DME Billing Required
HIC3= B0P	Inert Gases	DME Billing Required

HIC3= L1C	Hypertrichotic Agents, Systemic/Including Combinations	Cosmetic Indications Not Covered on OHP List
HIC3= Q6F	Contact Lens Preparations	Cosmetic Indications Not Covered on OHP List
HIC3=X1C	IUDs	DME Billing Required
HIC3=D6C	Alosetron Hcl	IBS Not Covered on OHP List
HIC3=D6E	Tegaserod	IBS Not Covered on OHP List
HIC3=L1D	Hyperpigmentation Agents	
Drug Code	**Description**	**DMAP Policy**
HIC3=L3P	Astringents	
HIC3=L4A	Topical Antipruritic Agents	
HIC3=L5A; Except HSN= 002466, 002557 006081 (Podophyllin Resin)	Keratolytics	Acne, Warts, Corns/Calluses; Seborrhea Are Not Covered on OHP List
HIC3=L5B	Sunscreens	Cosmetic Indications, Acne, Warts, Corns/Callouses; Diaper Rash, Seborrhea Are Not Covered on OHP List
HIC3=L5C	Abrasives	Cosmetic Indications, Acne, Warts, Corns/Callouses; Diaper Rash, Seborrhea Are Not Covered on OHP List
HIC3=L5E	Anti Seborrheic Agents	Seborrhea Not Covered on OHP List
HIC3=L5G	Acne Agents	Acne Not Covered on OHP List
HIC3=L5H	Acne Agents, Topical	Acne Not Covered on OHP List
HIC3=L6A; Except HSN = 002577 002576 002574 002572 (Capsaicin)	Irritants	Acne, Seborrhea, Sprains Not Covered on OHP List
HIC3=L7A	Shampoos	Cosmetic Indications, Seborrhea, Not Covered on OHP List

HIC3=L8A	Deodorants	Cosmetic Indications Not Covered on OHP List
HIC3=L8B	Antiperspirants	Cosmetic Indications Not Covered on OHP List
HIC3=L9A	Topical Agents, Misc	Cosmetic Indications, Acne, Warts, Corns/Callouses; Diaper Rash, Seborrhea, are Not Covered on OHP List
HIC3=L9B	Vit A Used for Skin	Acne Not Covered on OHP List
HIC3=L9C	Antimelanin Agents	Pigmentation Disorders Not Covered on OHP List
HIC3=L9D	Topical Hyperpigmentation Agent	Pigmentation Disorders Not Covered on OHP List
HIC3=L9F	Topical Skin Coloring Dye Agent	Cosmetic Indications Not Covered on OHP List
HIC3=L9I	Topical Cosmetic Agent; Vit A	Cosmetic Indications Not Covered on OHP List
HIC3=L9J	Hair Growth Reduction Agents	Cosmetic Indications Not Covered on OHP List
Drug Code	**Description**	**DMAP Policy**
HIC3=Q5C	Topical Hypertrichotic Agents	Cosmetic Indications Not Covered on OHP List
HIC3=Q6R, Q6U, Q6D	Antihistamine-Decongestant, Vasoconstrictor and Mast Cell Eye Drops	Allergic Conjunctivitis Not Covered on OHP List
HIC3= U5A, U5B, U5F & S2H plus HSN= 014173	Herbal Supplements “ Natural Anti-Inflammatory Supplements” - Not Including Nutritional Supplements such as: Ensure, Boost, Etc.	
HSN = 004045 + ROA = TOPICAL	Clindamycin Topical	Acne Not Covered on OHP List
HSN=003344	Sulfacetamide Sodium/Sulfur Topical	Acne Not Covered on OHP List
HSN=008712, 004022 + ROA=TOPICAL	Erythromycin Topical	Acne Not Covered on OHP List

HSN=025510	Rosacea	Acne Not Covered on OHP List
TC=93; Except HSN = 002363 (dextranomer) 002361 (zno)	Emollients/Protectants	Cosmetic Indications, Acne, Warts, Corns/Callouses; Diaper Rash, Seborrhea, Psoriasis Are Not Covered on OHP List

P&T Review: *3/18; 2/23/06*
Implementation: *TBD; 5/1/16; 9/1/06; 1/1/12*