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OHSU Drug Effectiveness Review Project Summary Report– Atopic Dermatitis

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Date of Last Review: Oct 2020
Literature Search: 05/20/2021-02/14/2022

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

Research Questions:
1. For adults and children, what is the comparative effectiveness of the included interventions (see **Table 2)** for atopic dermatitis (AD)?
2. For adults and children, what are the comparative harms of the included interventions (see **Table 2**) for AD?

Conclusions:
- The February 2022 drug class report on AD by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this review.[1] Evidence for the following informed the DERP report:
    - The immunomodulators azathioprine, cyclosporine, methotrexate, mycophenolate, and omalizumab, which may be prescribed off-label for AD;
    - Crisaborole, tacrolimus, pimecrolimus and dupilumab which have Food and Drug Administration (FDA) approval for AD;
    - The targeted immune modulators (TIMs) with FDA approval for AD, including the topical Janus Kinase (JAK) inhibitor ruxolitinib, the injectable interleukin-13 (IL-13) antagonist tralokinumab, and the oral JAK inhibitor abrocitinib; and
    - The TIM, upadacitinib, which recently received an expanded indication for moderate-to-severe AD.

Off-Label Drugs for Atopic Dermatitis
- Azathioprine improved Six-Area, Six-Sign Atopic Dermatitis (SASSAD) severity scores compared to placebo based on moderate quality evidence from 2 small randomized controlled trials (RCTs).[1] There were no differences between azathioprine and methotrexate over 12 weeks for improvements in the Severity Scoring of Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), and Investigator's Global Assessment (IGA) scales based on moderate quality evidence.[1] More adverse effects (AEs) were reported with azathioprine versus placebo over 12 weeks based on moderate quality evidence, with gastrointestinal (GI) effects (nausea, vomiting, diarrhea, bloating and abdominal pain) more commonly noted with azathioprine.[1] Azathioprine had similar rates of AEs to methotrexate based on moderate quality evidence, except for higher rates neutropenia and lymphopenia observed with azathioprine.[1]
- Seven RCTs with a high risk-of-bias and 2 RCTs with moderate risk of bias which analyzed cyclosporine for treatment of AD were included in the 2022 DERP report.[1] The quality of evidence for the 7 RCTs was downgraded to very low due to small sample sizes (n=24 to 97), lack of blinding, and high attrition rates.[1] Low quality evidence found no differences in efficacy between cyclosporine and methotrexate in pediatric patients.[1] In adults, low quality evidence demonstrated no differences in efficacy between cyclosporine, mycophenolate, or prednisolone.[1] One low quality RCT found cyclosporine was more effective than methotrexate in adults.[1] In one RCT with moderate risk of bias, tacrolimus was superior to cyclosporine in improving SCORAD scores.[1] Three RCTs with high risk of bias favored cyclosporine over placebo but preferred efficacy endpoints like SCORAD, EASI or IGA were not assessed.[1] Regardless of

the comparator group, participants in the cyclosporine groups reported more AEs including hypertension, GI manifestations, and infections.[1] Cyclosporine may have a less favorable safety profile compared with placebo, methotrexate and mycophenolate, based on very low-quality evidence.[1]

- One RCT with low risk of bias compared omalizumab to placebo in pediatric patients with severe AD.[1] Omalizumab was more effective than placebo in improving SCORAD scores based on high quality evidence; however, the improvement fell short of achieving a minimal clinically important difference (MCID).[1] Rates of AEs between omalizumab and placebo were similar based on low-quality evidence.[1] The most commonly reported AEs for both groups were respiratory and GI symptoms.[1]

FDA-Approved Drugs for Atopic Dermatitis

- For the 2022 DERP update, no new studies were identified for crisaborole.[1] Crisaborole is only indicated for management of mild-to-moderate AD, which is not funded by the Oregon Health Plan (OHP).[2,3]
- No new comparative studies to evaluate dupilumab with an FDA-approved therapy were identified for the DERP update.[1] Dupilumab was compared to abrocitinib in one phase 3 RCT, but a statistical analysis was not completed.[4] Upadacitinib was also compared to dupilumab in a clinical trial which assessed the safety and efficacy of upadacitinib for management of moderate-to-severe AD.[5]
- One RCT with moderate risk of bias evaluating the safety and efficacy of pimecrolimus versus topical corticosteroids in infants with mild-to-moderate AD was identified for the DERP report.[1] Both groups reported treatment success defined as an IGA of 0 (clear) or 1 (almost clear) by week 3.[1] High incidences of AEs were reported in both groups, with over 95% of participants in both groups reporting any event by the end of the study period.[1] No new eligible studies were identified for tacrolimus.[1]

New FDA-Approved Drugs for Atopic Dermatitis

- The FDA-approved indication for the oral JAK-1 selective inhibitor abrocitinib is for the treatment of adults with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when the use of those therapies is inadvisable.[6] Four placebo-controlled RCTs with low risk of bias assessed the efficacy of abrocitinib in patients with moderate-to-severe AD.[1] In the phase 3 RCTs, abrocitinib was superior to placebo in achieving IGA response of 0 or 1 and EASI-75 (75% improvement from baseline on the EASI) by week 12 or 16 based on high-quality evidence, with a number needed to treat (NNT) ranging between 2 to 7 for each outcome.[1] In one RCT, abrocitinib 100 mg and 200 mg were similar to dupilumab in achieving EASI-75 response at week 16 based on low-quality evidence; however, the study was not adequately powered to detect differences between the study arms.[1] In all 3 trials, higher rates of GI disorders, acne, herpes, and thrombocytopenia were associated with abrocitinib based on high-quality evidence.[1] One trial found similar rates of AEs between abrocitinib and dupilumab based on moderate quality evidence except dupilumab had higher rates of conjunctivitis.[1]
- The FDA-approved indication for ruxolitinib 1.5% cream is for the short-term treatment of mild-to-moderate AD in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[7] High-quality evidence from 2 placebo-controlled, identical, phase 3 RCTs with low-to-moderate risk of bias showed ruxolitinib was effective in improving EASI and achievement of IGA 0/1 scores in patients with mild-to-moderate AD.[1] No differences were noted between placebo and ruxolitinib in incidence of AEs based on high-quality evidence.[1] Application site-pain was the most frequently reported AE in both ruxolitinib and placebo groups.[1]
- Tralokinumab is FDA-approved for the treatment of moderate-to-severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[8] Four RCTs with low-to-moderate risk-of-bias evaluated the safety and efficacy of tralokinumab in treatment of moderate-to-severe AD.[1] In a phase 2 RCT, improvement in EASI was found with tralokinumab 150 mg and 300 mg doses in combination with topical corticosteroids compared with placebo at 12 weeks based on moderate-quality evidence.[1] In two phase 3 RCTs, tralokinumab monotherapy was superior to placebo in achieving EASI-75 at 12 weeks based on moderate-quality evidence with a NNT ranging from 5 to 9 in each trial.[1] Tralokinumab was superior to placebo in achieving IGA 0/1 at 12 weeks based on low-quality evidence (NNT = 9 to 12) in these trials.[1] The DERP authors downgraded the evidence assessment for IGA outcome due to inconsistency and indirectness.[1] Another trial provided moderate-quality evidence that

tralokinumab, when combined with topical mometasone, was superior to placebo in achieving IGA of 0 to 1 at 16 weeks.[1] Tralokinumab increased the risk of infection-related AEs versus placebo based on low-quality evidence.[1] The most commonly reported AEs reported in more than 5% of participants and occurring more frequently with tralokinumab than placebo were viral upper respiratory tract infections (15.7% vs. 12.2%), upper respiratory tract infections (5.6% vs. 4.8%), and conjunctivitis (5.4% vs. 1.9%).[1]

- Upadacitinib (RINVOQ), an oral JAK-I originally approved for rheumatoid arthritis (RA), received expanded approval for treatment of moderate-to-severe AD in January 2022.[9] Four RCTs with low-to-moderate risk of bias were conducted in adults and adolescents with AD.[1] Upadacitinib was superior to placebo in achieving EASI-75 and IGA 0/1 in 3 RCTs based on high-quality evidence.[1] Upadacitinib was superior to dupilumab in achieving EASI-75 in the fourth trial based on high-quality evidence.[1] Upadacitinib had similar AEs to placebo based on high-quality evidence, except for higher rates of acne observed with upadacitinib.[1] Similar rates of AEs were observed between upadacitinib and dupilumab, except for higher rates of acne, upper respiratory tract infections, and increased creatinine phosphokinase (CPK) observed with upadacitinib based on moderate-quality evidence.[1]

Policy Revisions

- In January 2022, Guideline Note 21 was updated by the Health Evidence Review Commission (HERC) to include vitiligo as an inflammatory skin condition and funded coverage was broadened to include facial involvement for severe inflammatory skin conditions.

Recommendations:

- Update clinical prior authorization (PA) criteria for all drugs used to manage AD to reflect updated 2022 HERC guidance from Guideline Note 21 which now includes facial involvement in the severity assessment of AD (**Appendix 5**) and severe vitiligo as a funded inflammatory skin condition.
- Revise title for topical therapies for AD and psoriasis to “Topical Agents for Inflammatory Skin Conditions”. Add topical ruxolitinib to the clinical PA criteria for “Topical Agents for Inflammatory Skin Conditions” and designate as non-preferred on the Preferred Drug List (PDL).
- Revise title of “Monoclonal Antibodies for Severe Asthma” PA criteria to “Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis”. Add oral abrocitnib and injectable tralokinumab to “Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis” PA Criteria and designate both agents as non-preferred on the PDL (**Appendix 5**).
- Include an assessment of severe AD as an FDA-approved diagnosis for upadacitinib in the clinical PA criteria for “Targeted Immune Modulators for Autoimmune Conditions”(**Appendix 5**).
- After review of costs in the Executive Session, no additional changes were made to PDL.

Summary of Prior Reviews and Current Policy

- The Pharmacy and Therapeutics (P&T) Committee approved revising the PA criteria for topical antipsoriatic drugs to include agents used to manage AD in March 2018. Dupilumab was also made a non-preferred medication on the Practitioner-Managed Prescription Drug Plan (PMPDP) with clinical PA criteria for use in AD. After reviewing 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 topical and systemic medications used to manage AD is presented in **Appendix 1**.
- Over the next 3 years, dupilumab received expanded FDA-approved indications. Dupilumab was presented to the Committee in August 2021 as part of a DERP report focused on TIMs used to treat eosinophilic asthma. The Committee retired the stand-alone dupilumab clinical PA criteria and dupilumab was instead added to the “Monoclonal Antibodies for Severe Asthma” clinical PA criteria. The PA criteria for Topical Atopic Dermatitis and Antipsoriatic Treatments and the Monoclonal Antibodies for Severe Asthma can be reviewed in **Appendix 5**.

- In October 2020, the HERC revised Guideline Note 21 to broaden coverage of severe inflammatory skin diseases, which include psoriasis, AD, lichen planus, Darier disease, pityriasis ruba pilaris, and discoid lupus.[3] Severe forms of these conditions are funded on line 426 and are defined as having functional impairment AND one or more of the following:
    - At least 10% of body surface area (BSA) involved, OR
    - Hand, foot or mucous membrane involvement.

  The definition of functional impairment, previously defined as "inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction", was replaced by an assessment of severe disease using the Dermatology Life Quality Index (DLQI) (score ≥11), Children's Dermatology Life Quality Index (CDLQI) (score ≥13), or severe score on another validated tool.[3] If inflammatory skin conditions do not meet the criteria stipulated in Guideline Note 21, they are not funded by the OHP and are included on lines 482, 504, 532, 541, and 656. The Committee revised the clinical PA criteria for therapies used to treat AD in December 2020 to include an assessment of severe disease using a validated scoring tool such as the DLQI or CDLQI per HERC guidance.
- In January 2022, Guideline Note 21 was updated by the HERC to include vitiligo as an inflammatory skin condition and funded coverage was broadened to include facial involvement for severe inflammatory skin conditions. The revised 2022 Guideline Note 21 is included in **Appendix 3**.

Background

Atopic dermatitis is chronic skin disorder characterized by pruritus and recurrent eczematous lesions accompanied by inflammation with a relapsing and remitting pattern.[10] The cause is unknown, but may be due to genetics or immunologic dysfunction.[11] Many patients also have allergic asthma, allergic rhinoconjunctivitis, food allergies, and other immediate hypersensitivity (type 1) allergies.[12] Although it may affect all age groups, AD is most common in children. The disease affects 15-20% of children in developed countries.[13] Estimated prevalence of AD for adults in the United States (U.S.) is 10%.[13] Both sexes are affected, and the prevalence varies among races and ethnic groups.[14] For example, in the U.S., the prevalence is higher among Black children (19.3%) than among White children (16.1%).[15] 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.[16] AD can persist into adulthood in about one-third of affected individuals.[17] Itching, sleep deprivation, and social embarrassment due to visible lesions can have substantial effects on the quality of life.[18]

Therapy for AD is selected according to the clinical stage of disease (mild, moderate, or severe), the extent and location of body-surface area involved, age, co-existing conditions and medications being taken by the patient, the severity of pruritus, the degree to which quality of life is impaired, and the goals of the patient.[19,20] For all disease stages, general measures include care with frequent application of an emollient to maintain the skin's epidermal barrier, avoidance of triggers, and anti-inflammatory therapy with a topical corticosteroid or a topical calcineurin inhibitor (e.g., pimecrolimus or tacrolimus) as needed.[11] The use of topical corticosteroid and topical calcineurin inhibitor therapies in AD is supported by The American College of Dermatology's 2014 guideline[21] and 2004 guidance from the National Institute for Health and Care Excellence.[22] 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 topical corticosteroid 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.[23] Topical calcineurin inhibitors are considered a second-line option in both adults and children with AD who have not responded to topical corticosteroid or when those treatments are not advisable.[23] The main rationale for topical calcineurin inhibitor 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. All topical preparations can sting, but there is evidence that this is even more of a problem with topical calcineurin inhibitor preparations. Furthermore, FDA labeling for tacrolimus and pimecrolimus include boxed warnings regarding a theoretical risk for skin cancers and lymphoma associated with topical calcineurin inhibitor administration.[24,25]

Patients with severe AD that cannot be controlled with topical corticosteroid or topical calcineurin inhibitor therapy can be treated with short-term, narrow band ultraviolet B (UVB) phototherapy or systemic immunomodulators such as cyclosporine, azathioprine, methotrexate, mycophenolate and 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,[26] and can increase the risk of infections and cancer.[27] Cyclosporine nephrotoxicity can be irreversible, and this risk increases with longer durations of treatment.[26] As a result, treatment with cyclosporine for AD is typically limited to one year. National Institute for Health and Care Excellence (NICE) Guidance from 2004 recommends systemic corticosteroids, phototherapy, and systemic immunosuppressants as "treatments of last resort" in AD patients.[22] 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.[28]

Two additional agents with novel mechanisms of action are included in AD treatment algorithms. Crisaborole is a topical phosphodiesterase 4 (PDE4) inhibitor approved for mild-to-moderate AD in adults and children aged 3 months and older.[2] PDE4 is a regulator of inflammation, and intracellular inflammatory cell PDE4 activity is increased in AD.[29] Crisaborole is available as an ointment that is applied twice daily. Dupilumab is an injectable IL-4 antagonist monoclonal antibody approved as systemic therapy for moderate-to-severe AD refractory to topical treatments in children aged 6 years and older and adults.[30] The Canadian Agency for Drugs and Technologies in Health (CADTH) published updated recommendations for the use of dupilumab in atopic dermatitis April 2020.[31] Dupilumab should be initiated in patients with moderate-to-severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable.[31] Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.[31] Within the past year, 3 new TIMs have received FDA-approval for management of AD. These therapies will be discussed later in this report.

Clinical studies have utilized several scales for defining the severity of AD, including the SCORAD index, the EASI, IGA, and SASSAD severity score. The SCORAD index was developed in 1993 by the European Task Force on Atopic Dermatitis and is the most widely referenced AD scoring instrument in literature.[32] The SCORAD has been validated for content and construct validity, interobserver reliability, and sensitivity to change in 26 different publications.[32] The SCORAD tool incorporates clinician estimates of disease extent and severity and subjective patient assessment of itching and sleep loss.[33] The extent of AD is graded using a percentage score by the clinician for specific areas of the body (head/neck, upper limbs, lower limbs, trunk and back). 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).[33] 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. Combining extent, severity, and symptoms results in a total SCORAD score ranging between 1 to 100 and categorized as mild (<25), moderate (26-49), and severe (>50).[33]

The EASI was adapted from the Psoriasis Area and Severity Index in 1998.[32] The EASI assesses the severity of, and body surface area affected by, AD symptoms including erythema, induration/papulation/edema, excoriations, and lichenification.[34] Each symptom is graded systematically for specific anatomical regions (the head, trunk, arms and legs) and summarized in a composite score. EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of AD.[34] An EASI score of 7 or lower is considered to indicate mild disease, 8 to 21 moderate disease, 22 to 50 severe disease, and 51 to 72 very severe disease.[12] EASI outcomes are measured as a percentage improvement in EASI score from baseline as EASI 50, 75, or 90. A limitation often cited is the EASI's intermediate interobserver reliability, especially compared to SCORAD scale.[32]

The IGA is a clinician-reported outcome measure that has been used to evaluate severity of AD at a given point in time.[35] This measure was used to evaluate clinical response to treatment in studies evaluating new AD therapies.[36,37] 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."[38] 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.[35] 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).

The SASSAD score was created in 1998 by the British Association of Dermatologists.[32] The SASSAD severity score is obtained by grading 6 signs (erythema, exudation, excoriation, dryness, cracking and lichenification) each on a scale of 0 (absent), 1 (mild), 2 (moderate), or 3 (severe) at each of 6 sites; arms, hands, legs, feet, head, neck and truck.[39] As with many other tested atopic eczema scoring indices, the SASSAD index is subject to significant interobserver variation, reflecting the difficulties in reliably assessing eczema severity objectively.[40] It is not commonly used as an outcome measurement in the literature or in clinical practice as there are better options for scales in terms of simplicity and validity.[32]

Table 1 summarizes the 4 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.[16] Quality of life in AD patients is assessed by the DLQI, a 10 question tool used to asses impact of AD on itch, embarrassment, clothing, work/school, and relationships.[41] Questions are rated on a 0 to 3 scale, for a total score between 0 and 30; higher scores indicate poorer quality of life.[41] A similar tool, the CDLQI is used in children aged 4 to 16 years.[42]

Table 1. Assessment of Atopic Dermatitis Severity in Clinical Trials[33,34,39,43]

	SCORAD	**EASI**	**IGA/ISGA**	**SASSAD**
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 (IGA) *or* 0 to 5 (ISGA) Score of 0 or 1 indicates disease clearing	Range: 0 to 108 Higher scores indicate more severe disease
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 - absent 1 - mild 2 - moderate 3 - severe	5 (IGA) or 6 (ISGA) 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 (ISGA)	3 point scale used to assess 6 domains; erythema, exudation, excoriation, dryness, cracking, and lichenification: 0 - absent 1 - mild 2 - moderate 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	Proportionate values assigned to 4 separate body regions: • Upper limbs (20%) • Lower limbs (40%) • Trunk (30%) • Head/Neck (10%)	Not Used	Scores from 6 different body areas are added together for final score: • Head/Neck • Trunk • Hand • Feet • Arms

	4= more than 4 affected sites			• Legs
Additional Assessments	Patient assessment of itching and sleep loss on a 0 to 10 VAS	None	None	None
Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; ISGA = Investigator's Static Global Assessment; SASSAD=Six-Area, Six-Sign Atopic Dermatitis; SCORAD = Severity Scoring of Atopic Dermatitis; VAS = Visual Analog Scale				

Methods:
The February 2022 drug class report on AD by the DERP at the Center for Evidence-based Policy at OHSU was used to inform recommendations for this drug class.[1] The original report is available to P&T Committee members upon request.

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

Summary Findings:
The 2022 DERP systematic review and meta-analysis on drugs to treat to AD was an update of the 2017 DERP report completed in 2017. The 2017 DERP report focused on comparative evidence for dupilumab, crisaborole, pimecrolimus, and tacrolimus.[38] Oral immunomodulators (azathioprine and cyclosporine) and the monoclonal antibody omalizumab, which are prescribed off-label for AD, were not included in the original report. For the 2022 report, DERP investigators conducted a systematic review based on RCTs published from January 2017 through August 2021.[1] Adults and children with moderate-to-severe AD using FDA-approved agents, off-label agents, and investigational therapies were evaluated. Forty-seven new documents met inclusion criteria and 6 RCTs were carried forward from the 2017 DERP report.[1] Outcomes included response to treatment (IGA), disease symptoms (EASI score, SCORAD, percentage of BSA affected, quality of life [DLQI]), AEs, and serious adverse events (SAEs).[1]

Three new TIMs have received FDA-approval for AD management. These include the topical JAK inhibitor ruxolitinib (OPZELURA; September 2021)[7]; the injectable IL-13 antagonist tralokinumab (ADBRY; December 2021)[8]; and the oral JAK inhibitor abrocitinib (CIBINQO; January 2022).[6] Manufacturer's prescribing information for each of these products is presented in **Appendix 4**. In addition, upadacitinib (RINVOQ), an oral JAK inhibitor originally approved for rheumatoid arthritis (RA), received expanded approval for AD management in January 2022.[9] Additional TIMs currently under investigation for AD include the oral JAK inhibitor baricitinib, currently approved for RA treatment, and 2 new injectable IL-13 antagonists, lebrikizumab and nemolizuamb. Lastly, a novel neurokinin-1 receptor antagonist, tradipitant, is being studied for AD. These pipeline agents will not be discussed in-depth as they have not yet received FDA approval for management of AD. Drug information for the AD drugs included in the DERP report are summarized in **Table 2.**

Table 2. Drug Information for the Atopic Dermatitis Drugs Summarized in the DERP Report

Generic Name	Brand Name	Mechanism of Action	Dosage Formulations	FDA Indication	FDA-Approved Ages
Off-Label Drugs for AD					
Azathioprine[44]	Generics; IMURAN	Immunosuppressant	Oral Tablet	--	--
Cyclosporine[45]	Generics; NEORAL, SANDIMMUNE	Immunosuppressant	Oral Capsules and Solution	--	--
Omalizumab[46]	XOLAIR	Monoclonal Antibody	Subcutaneous Injection	--	--
FDA-Approved Drugs for AD					
Crisaborole[2]	EUCRISA	PDE4 Inhibitor	2% Ointment	Mild-to-Moderate AD	≥ 3 months
Dupilumab[30]	DUPIXENT	IL-4 Antagonist	Subcutaneous Injection	Moderate-to-Severe AD	≥ 6 years
Pimecrolimus[24]	ELIDEL	Calcineurin Inhibitor	1% Cream	Mild-to-Moderate AD	≥ 2 years
Tacrolimus[25]	PROTOPIC	Calcineurin Inhibitor	0.03% Ointment 0.10% Ointment	Moderate-to-Severe AD	≥ 2 years ≥ 15 years
New FDA-Approved Drugs for AD					
Abrocitinib[6]	CIBINQO	JAK Inhibitor	Oral Tablets	Moderate-to-Severe AD	≥ 18 years
Ruxolitinib[7]	OPZELURA	JAK Inhibitor	1.5% Cream	Mild-to-Moderate AD	≥ 12 years
Tralokinumab[8]	ADBRY	IL-13 Antagonist	Subcutaneous Injection	Moderate-to-Severe AD	≥ 18 years
Upadacitinib[9]	RINVOQ	JAK Inhibitor	Oral Extended-Release Tablets	Moderate-to-Severe AD	≥ 12 years

Abbreviations: AD = Atopic Dermatitis; DERP = Drug Effectiveness Review Project; FDA = Food and Drug Administration; IL= Interleukin; JAK = Janus Kinase; PDE4 = Phosphodiesterase 4

1. Off-Label Drugs for Atopic Dermatitis

Azathioprine

Azathioprine is FDA-approved as an adjunct for the prevention of rejection in renal transplantation and to reduce symptoms of rheumatoid arthritis.[44] The off-label use of azathioprine for AD is recommended in compendial resources.[47] Two placebo-controlled RCTs with moderate risk of bias met inclusion criteria. These RCTs evaluated azathioprine 1 mg to 2.5 mg/kg/day versus placebo in adults with moderate-to-severe AD over 12 weeks in 2002 and 2006.[1] An additional single-blind, RCT with moderate risk of bias published in 2011 compared azathioprine 1.5 mg to 2.5 mg/kg/day to methotrexate 10 mg to 22.5 mg per week over 24 weeks in adults (n=41) who had previously failed cyclosporine therapy.[1] Participants (n=35) from the 2011 RCT could enroll in an open-label, extension study to provide comparative data between azathioprine and methotrexate over 5 years of follow-up.[1] By the end of the 5-year study period only 7 participants were still receiving methotrexate and 4 participants were receiving azathioprine, with the remainder switching to topical therapy (n=15), lost to follow-up (n=5) or discontinued therapy (n=5).[1] All 3 RCTs had small sample sizes ranging from 37 to 61 adults with short durations of treatment.[1] The primary outcome was the change in SASSAD severity score at the end of treatment for the older studies and the SCORAD scale for the 2011 RCT. Compared with placebo, moderate-quality evidence showed azathioprine improved SASSAD severity scores in the 2 small RCTs (n=37 and n=61).[1] Moderate-quality evidence showed there was no difference between azathioprine and methotrexate over 12 weeks for improvements in the SCORAD, EASI, and IGA assessments.[1] Low quality-evidence showed azathioprine was superior to placebo for improvements in quality of life assessed by the DLQI.[1] Moderate-quality evidence revealed more reported AEs with azathioprine versus placebo over 12 weeks, with GI effects (nausea, vomiting, diarrhea, bloating and abdominal pain) more commonly noted with azathioprine.[1] Moderate-quality evidence showed azathioprine had similar AEs to methotrexate with higher rates of neutropenia and lymphopenia observed with azathioprine.[1]

Cyclosporine

Cyclosporine is FDA-approved for prophylaxis of organ rejection in kidney, liver, and heart allogenic transplants and treatment of rheumatoid arthritis and plaque psoriasis.[45] The off-label use of cyclosporine for AD is included in compendial resources.[47] Seven RCTs with a high risk-of-bias and 2 RCTs with moderate risk-of-bias which analyzed cyclosporine for treatment of AD were identified for the 2022 DERP report.[1] Two RCTs compared cyclosporine with methotrexate 7.5 mg to 15 mg per week, 4 separate RCTs evaluated cyclosporine versus mycophenolate, prednisolone, topical tacrolimus, or topical betamethasone, and 3 RCTs compared cyclosporine with placebo. Doses of cyclosporine ranged from 3 mg to 5 mg/kg/day. The quality of the evidence was downgraded to very low due to small sample sizes (n=24 to 97), lack of blinding, and high attrition rates.[1] Most of the studies were conducted over 6 to 24 weeks. One noninferiority RCT comparing cyclosporine with mycophenolate was conducted over 48 weeks. None of the studies were conducted in the U.S.[1]

Five RCTs published after 2000 used SCORAD changes as the primary endpoint.[1] Very low-quality evidence from one RCT comparing cyclosporine with methotrexate in pediatric patients, and another RCT in adults, found no difference in SCORD score changes between the 2 drugs.[1] Very low-quality evidence from one RCT found no difference in SCORAD score improvements between cyclosporine and mycophenolate over 48 weeks.[1] Another low-quality RCT comparing cyclosporine with prednisolone found similar efficacy for both treatments for the primary outcome of changes in the SCORAD score.[1] The attrition rate for this RCT was 39%, so findings from this trial should be carefully interpreted.[1] Very low-quality evidence from one RCT showed differences in the SCORAD score favored tacrolimus over cyclosporine.[1] In one RCT with high risk-of-bias, no differences in AD symptoms were identified between cyclosporine and topical betamethasone.[1] Three RCTs with high risk of bias favored cyclosporine over placebo; but preferred efficacy outcomes such as SCORAD, EASI or IGA were not assessed.[1] Regardless of the comparator group, participants in the cyclosporine groups reported more AEs including hypertension, GI manifestations, and infections.[1] Very low-quality evidence demonstrated placebo, methotrexate and mycophenolate may have a more favorable safety profile compared with cyclosporine.[1] Given the moderate-to-high risk of bias in these studies, caution is warranted when interpreting the findings.[1]

Omalizuamb

Omalizumab is FDA-approved for treatment of moderate-to-severe persistent asthma, nasal polyps, and chronic idiopathic urticaria.[46] According the prescribing information, omalizumab Is not indicated for allergic conditions or other forms of urticaria.[46] Evidence for the off-label use of omalizumab in AD is not included in compendial resources. [47] In the 2022 DERP report, one RCT with low risk-of-bias comparing omalizumab to placebo in pediatric patients (n=62) with severe AD over 24 weeks is described.[4] High-quality evidence shows the change in SCORAD score at 24 weeks was improved with omalizumab compared with placebo (adjusted mean difference [MD] of -8.3 points; 95% confidence interval [CI] -15.1 to -1.1).[1] However, the change in SCORAD score did not achieve the MCID of -8.7 points.[1] Low-quality evidence showed quality of life was improved in the omalizumab group compared with placebo (mean score difference of -3.5; 95% CI -6.5 to -0.5), and did achieve the MCID of -3.3 defined by investigators.[1] Low-quality evidence revealed AEs between omalizumab and placebo were similar.[1] The most commonly reported AEs for both groups were respiratory and GI symptoms.[1]

2. FDA-Approved Drugs for Atopic Dermatitis

Crisaborole

The 2017 DERP report stated there is inadequate evidence to assess the relative efficacy and safety of crisaborole compared with topical calcineurin inhibitor and topical corticosteroid treatments.[38] For the 2022 DERP update, no new studies were identified for crisaborole.[1] Crisaborole is only indicated for management of mild-to-moderate AD, which is not funded by the OHP.[2,3]

Dupilumab

In the 2017 DERP report, results from 6 placebo-controlled trials were pooled to assess the likelihood of achieving an IGA response of 0 or 1 in participants with moderate-to-severe AD treated with dupilumab.[1] The pooled risk ratio (RR) for this outcome was 4.10 (95% CI 3.10 to 5.42; p<0.01).[1] The overall incidence of AEs was similar between dupilumab and placebo groups.[38] Serious adverse events and AEs leading to treatment discontinuation were uncommon.[38] There is insufficient evidence to compare dupilumab with topical calcineurin inhibitor monotherapy, systemic cyclosporine or phototherapy. No new comparative studies to evaluate dupilumab with an FDA-approved therapy were identified for the DERP update.[1] Dupilumab was compared to abrocitinib in 1 RCT, but a statistical analysis was not completed.[4] Upadacitinib was also compared to dupilumab in a trial that assessed the safety and efficacy of upadacitinib in management of moderate-to-severe AD.[5] The results of this trial will be discussed in the upadacitinib section.

Pimecrolimus and Tacrolimus

The 2017 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.[38] Short-term improvement in symptoms was modestly better with tacrolimus compared to pimecrolimus, using a symptom scale, reduction in the percentage of BSA affected, and ratings of pruritus.[38] The DERP meta-analysis of the comparative topical calcineurin inhibitor trials did not show a difference between pimecrolimus and tacrolimus in withdrawal of therapy due to AEs (pooled RR 1.16; 95% CI 0.43 to 3.14; I^2 = 0%).[38]

In the 2022 DERP update, one RCT with moderate risk of bias evaluating the safety and efficacy of pimecrolimus versus topical corticosteroids over 5 years in infants with mild-to-moderate disease was identified.[1] Both groups reported improvement treatment success defined as an IGA of 0 or 1 by week 3.[1] High incidences of AEs were reported in both groups, with over 95% of participants in both groups reporting any event by the end of the study period.[1] No new eligible studies were identified for tacrolimus in the recent DERP update.[1]

3. New FDA-Approved Drugs for Atopic Dermatitis

Abrocitinib

Four phase 3 placebo-controlled trials with low risk of bias assessed the safety and efficacy of abrocitinib, an oral JAK-1 selective inhibitor, for treatment of moderate-to-severe AD.[1] One study was a phase 2 dose-finding trial, while the others 4 studies were phase 3 RCTs. Two RCTs included adults, 2 RCTs included participants 12 years or older weighing at least 40 kilograms (kg), and one RCT included adolescents aged 12 to 17 years who weighed at least 25 kg. Study sample sizes ranged from 267 to 838 participants and were conducted over 12 to 16 weeks.[1] Moderate-to-severe AD was defined as an IGA of 3 or more, EASI score of 16 or more, and involving a total BSA of at least 10%.[1] Participants enrolled in the RCTs had either an inadequate response to 4 weeks of topical calcineurin inhibitors or topical corticosteroids or were unable to receive topical treatments within 12 months of the study.[1] Participants were permitted to use oral antihistamines and non-medicated emollients as adjunctive therapy during the trials.[1]

Abrocitinib demonstrated superior efficacy over placebo in achieving IGA response of 0 or 1 and EASI-75 by week 12 or 16 based on high-quality evidence from the phase 3 trials.[1] In one RCT, moderate-quality evidence showed both doses of abrocitinib were similar to dupilumab in achieving EASI-75 response at week 16; however, the study was not powered to detect significant differences between the 2 study arms.[4] A summary of study characteristics and primary outcome data is presented in **Table 3.**

Table 3. Study Characteristics and Results: Abrocitinib for Moderate-to-Severe Atopic Dermatitis

-Author -Trial Name -DERP Risk-of-Bias Assessment	-Study Design -Participant Description -Duration	Product, Dose, Frequency	Primary Outcome or Co-Primary Outcomes	Adverse Effects
Gooderham et al.[48] NCT02780167 Low	▪ Phase 2b ▪ DB, MC, PC, RCT ▪ n=267 ▪ Adults 18-75 yo ▪ 12 weeks	1. ABRO 10 mg po daily (n=46) 2. ABRO 30 mg po daily (n=45) 3. ABRO 100 mg po daily (n=54) 4. ABRO 200 mg po daily (n=48) 5. Oral Placebo daily (n=52)	**Proportion of participants who achieved IGA of 0 or 1** 1. ABRO 10 mg: 10.9% (n=5; NS) 2. ABRO 30 mg: 8.9% (n=4; NS) 3. ABRO 100 mg: 29.6% (n=16; p<0.001) 4. ABRO 200 mg: 43.8% (n=21; p<0.001) 5. Placebo: 5.8% (n=3)	**Total TEAEs for all study arms:** 16.5% (n=44) ▪ Worsening AD: 7.5% ▪ Eczema: 2.2% ▪ Abdominal pain: 0.7%
Simpson et al.[49] JADE MONO-1 Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=387 ▪ Adults and adolescents ≥12 yo and weight ≥ 40 kg) ▪ 12 weeks	1. ABRO 100 mg po daily (n=156) 2. ABRO 200 mg po daily (n=154) **3.** Oral Placebo daily (n=77)	**Proportion of participants who achieved IGA response of 0 or 1** 1. ABRO 100 mg: 24% (n=37) Difference vs. placebo: 15.8% (95% CI 6.8 to 24.8; p<0.0001; NNT=7) 2. ABRO 200 mg: 44% (n=67) Difference vs. placebo: 36.0% (95% CI 26.2 to 46.57; p<0.0001; NNT=3) 3. Placebo: 8% (n=6) **Proportion of participants who achieved EASI-75** 1. ABRO 100 mg: 40% (n=62) Difference vs. placebo: 27.9% (95% CI 17.4 to 38.3; p<0.0001; NNT=4) 2. ABRO 200 mg: 63% (n=96) Difference vs. placebo: 51.0% (95% CI 40.5 to 61.5; p<0.0001; NNT=2) 3. Placebo: 12% (n=9)	**Percent of patients reporting SAEs** 1. ABRO 100 mg: 3% (n=5) 2. ABRO 200 mg: 3% (n=5) 3. Placebo: 4% (n=3)
Silverberg et al.[50] JADE MONO-2 Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=391 ▪ Adults and adolescents ≥ 12 yo and weight ≥ 40kg ▪ 12 weeks	1. ABRO 100 mg po daily (n=158) 2. ABRO 200 mg po daily (n=155) **3.** Oral Placebo daily (n=78)	**Proportion of participants who achieved IGA response** 1. ABRO 100 mg: 28.4% (n=44) Difference vs. placebo: 19.3% (95% CI 9.6 to 29.0; p<0.001; NNT=6) 2. ABRO 200 mg: 38.1% (n=59) Difference vs. placebo: 28.7% (95% CI 18.6 to 38.8; p<0.001; NNT=4) 3. Placebo: 9.1% (n=7) **Proportion of participants who achieved EASI-75**	**Percent of patients reporting SAEs** 1. ABRO 100 mg: 3.2% (n=5) 2. ABRO 200 mg: 1.3% (n=2) 3. Placebo: 1.3% (n=1)

			1. ABRO 100 mg: 44.5% (n=69) Difference vs. placebo: 33.9% (95% CI 23.3 to 44.4; p<0.001; NNT=3) 2. ABRO 200 mg: 61% (n=94) Difference vs. placebo: 50.5% (95% CI 40 to 60.9; p<0.001; NNT=2) 3. Placebo: 10.4% (n=8)	
Beiber et al.[4] JADE COMPARE	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=838 ▪ Adults aged ≥ 18 yo ▪ 16 weeks	1. ABRO 100 mg po daily (n=238) 2. ABRO 200 mg po daily (n=226) 3. Dupilumab 600 mg SC x 1 dose, then 300 mg SC every other week (n=243) **4.** Oral Placebo daily (n=131)	**Proportion of participants who achieved IGA response of 0 or 1** 1. ABRO 100 mg: 36.6% (n=86) Difference vs. placebo: 23.1% (95% CI 14.7 to 31.4; p<0.001; NNT=5) 2. ABRO 200 mg: 48.4% (n=106) Difference vs. placebo: 34.8% (95% CI 26.1 to 43.5 ; p<0.001; NNT=3) 3. Dupilumab 300 mg: 36.5% (n=88) Difference vs. ABRO: NR 4. Placebo: 14% (n=18) **Proportion of participants who achieved EASI-75** 1. ABRO 100 mg: 58.7% (n=138) Difference vs. placebo: 31.9% (95% CI 22.2 to 41.6; p<0.001; NNT=4) 2. ABRO 200 mg: 70.3% (n=154) Difference vs. placebo: 43.2% (95% CI 33.7 to 52.7; p<0.001; NNT=3) 3. Dupilumab 300 mg: 58.1% (n=140) Difference vs. ABRO: NR 4. Placebo: 27.1% (n=35)	**Percent of patients reporting SAEs** 1. ABRO 100 mg: 2.5% (n=6) 2. ABRO 200 mg: 0.9% (n=2) 3. Dupilumab 300 mg: 0.8% (n=2) 4. Placebo: 3.8% (n=5)
Eichenfield et al.[51] JADE TEEN Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=273 ▪ Adolescents aged ≥12 to 17 yo and weight ≥ 25 kg ▪ 12 weeks	1. ABRO 100 mg po daily (n=92) 2. ABRO 200 mg daily (n=91) **3.** Oral Placebo daily (n=90)	**Proportion of participants who achieved IGA score improvement** 1. ABRO 100 mg: 41.6% (n=37) Difference vs. placebo: 16.7% (95% CI 3.5 to 29.9; p<0.05; NNT=6) 2. ABRO 200 mg: 46.2% (n=43) Difference vs. placebo: 20.6% 3. (95% CI 7.3 to 33.9; p<0.05; NNT=5) 4. Placebo: 24.5% (n=23) **Proportion of participants who achieved EASI-75** 1. ABRO 100 mg: 68.5% (n=61)	**Percent of patients reporting SAEs** 1. ABRO 100 mg: 0% 2. ABRO 200 mg: 1.1% (n=1) 3. Placebo: 2.1% (n=2)

			Difference vs. placebo: 26.5% (95% CI 13.1 to 39.8; p<0.05; NNT=4) 2. ABRO 200 mg: 72% (n=67) Difference vs. placebo: 29.4% (95% CI 16.3 to 42.5; p<0.05; NNT=4 **3.** Placebo: 41.5% (n=39)	
Abbreviations: ABRO=abrocitinib; AD=atopic dermatitis; CI=confidence interval; DB=double blind; DERP=Drug Effectiveness Review Project; EASI= Eczema Area and Severity Index; IGA=Investigator's Global Assessment; kg=kilogram; MC=multi-center; mg=milligrams; N=number; NNT = number needed to treat; NR=not reported; NS=not significant; PC=placebo controlled; PO=oral; RCT=randomized controlled trial; SAEs=serious adverse events; SC=subcutaneous; TEAEs=treatment-emergent adverse effects; yo=years old				

One notable AE associated with abrocitinib is a transient drop in platelets during the first few weeks of treatment.[1] The thrombocytopenia appears to be dose-related and no participants discontinued clinical trials due to this AE.[1] In the phase 3 trials, high-quality evidence showed abrocitinib had higher rates of GI disorders, acne, herpes infections, headache, and thrombocytopenia compared with placebo.[1] One RCT demonstrated abrocitinib had similar AEs to dupilumab based on moderate-quality evidence; however dupilumab had higher rates of conjunctivitis.[1] As with other JAK inhibitors, abrocitinib prescribing information has a FDA black boxed warning regarding the risk of serious opportunistic infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis associated with abrocitinib administration.[6] Adverse events occurring in 1.5% or more of abrocitinib patients compared with placebo in clinical studies are described in **Table 4.**

Table 4. Adverse Events Reported In Clinical Trials Of Abrocitinib Compared With Placebo[6]

Adverse Event	Abrocitinib 200 mg (n=590)	Abrocitinib 100mg (n=608)	Placebo (n=342)
Nausea	14.5%	6.0%	2.1%
Nasopharyngitis	8.7%	12.4%	7.9%
Headache	7.8%	6.0%	3.5%
Acne	4.7%	1.6%	0.0%
Herpes Simplex	4.2%	3.3%	1.8%
Vomiting	3.2%	1.5%	0.9%
Increased blood creatinine phosphokinase	2.9%	2.3%	1.5%
Dizziness	2.9%	1.8%	0.9%
Urinary Tract Infection	2.2%	1.7%	1.2%
Upper Abdominal Pain	1.9%	0.6%	0.0%
Thrombocytopenia	1.5%	0.0%	0.0%

The FDA-approved indication for abrocitinib is for the treatment of adults with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when the use of those therapies is inadvisable.[6] The recommended starting abrocitinib dose is 100 mg orally once daily.[6] Abrocitinib should be avoided in patients with severe renal impairment, end-stage renal disease, or severe hepatic impairment.[6] If patients are taking strong inhibitors of CYP2C19, the recommended dose is 50 mg or 100 mg once daily.[6] Use of abrocitinib is not advised if patients are taking a moderate to strong inhibitor of both CYP2C19 and CYP2C9.[6] Antiplatelet therapies except for aspirin 81 mg per day or less are contraindicated during the first 3 months of treatment.[6] Laboratory monitoring is recommended due to potential changes in platelets, lymphocytes, and lipids.[6]

Ruxolitinib

Ruxolitinib is selective inhibitor of JAK1 and JAK2. Three RCTs analyzed the safety and efficacy of topical ruxolitinib for people with mild-to-moderate AD. One study was a phase 2, dose-finding RCT with low risk-of-bias, and 2 identical phase 3 RCTs with moderate risk-of-bias compared ruxolitinib with placebo in adolescents and adults with mild-to-moderate AD.[1] Sample sizes ranged from 307 to 631 participants.[1] Study durations were short, ranging from 4 weeks to 8 weeks.[1] Criteria for study enrollment was similar across the RCTs: diagnosis of AD for least 2 years; IGA score of 2 or 3; and total BSA involvement of up to 20%.[1] Study details and primary outcome results are presented in **Table 5**. Adverse events reported during clinical trials are summarized in **Table 6**.

The primary end point of the Phase 2 study was mean percentage change from baseline in EASI score at week 4 in patients treated with ruxolitinib 1.5% cream twice daily versus patients treated with placebo twice daily.[52] Ruxolitinib 1.5% cream twice daily demonstrated a greater mean percentage change from baseline in EASI scores versus placebo at week 4 (71.6% vs. 15.5%; 95% CI not reported; p<0.0001).[52] No significant differences in EASI improvement at week 4 were observed between ruxolitinib 1.5% and triamcinolone.[52]

In the phase 3 RCTs, high-quality evidence demonstrated a greater proportion of patients treated with ruxolitinib cream (both 0.75% and 1.5% strengths) achieved IGA-treatment success (defined as a score of 0 or 1 with ≥2-grade improvement in IGA from baseline) versus placebo (p<0.0001 for all comparisons).[53] High-quality evidence indicated there were no differences between placebo and ruxolitinib in AE incidence rates.[1] Application site pain was the most frequently reported AE in both ruxolitinib and placebo groups.[1] There are insufficient data on ruxolitinib long-term safety and potential adverse effects due to systemic absorption.[1]

Table 5. Study Characteristics and Results: Topical Ruxolitinib for Mild-to-Moderate Atopic Dermatitis

-Author -Trial Name -DERP Risk-of-Bias Assessment	-Study Design -Participant Description -Duration	Product, Dose, Frequency	Primary Outcome	Adverse Effects
Kim et al.[52] NCT03011892 Low	▪ Phase 2 ▪ DB, MC, PC, RCT ▪ n=307 ▪ Adults 18 to 70 yo ▪ 4 weeks	1. RUX 0.15% QD (n=51) 2. RUX 0.5% QD (n=51) 3. RUX 1.5% QD (n=52) 4. RUX 1.5% BID (n=50) 5. Triamcinolone 0.1% BID (n=51) 6. Placebo BID (n=52)	**Mean percentage change in EASI at week 4:** 1. RUX 0.15%: 45.4% (Statistics NR) 2. RUX 0.5%: 52.2% (Statistics NR) 3. RUX 1.5% QD: 67% RUX vs. Vehicle p<0.0001 RUX vs. Triamcinolone: NS 4. RUX 1.5% BID: 71.6% RUX vs. Vehicle p<0.0001 RUX vs. Triamcinolone: NS 5. Triamcinolone 0.1% BID: 59.8% 6. Placebo BID: 15.5%	**Patients with TEAEs** 1. RUX 0.15% QD: 37.3% 2. RUX 0.5% QD: 21.6% 3. RUX 1.5% QD: 33.3% 4. RUX 1.5% BID: 24% 5. Triamcinolone 0.1% BID: 33.3% 6. Placebo BID: 32.7%
Papp et al.[53] TRuE-AD1 Moderate	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=631 ▪ Adults and adolescents ≥ 12 yo ▪ 8 weeks	1. RUX 0.75% BID (n=252) 2. RUX 1.5% BID (n=253) 3. Placebo BID (n=126)	**Proportion of participants who achieved IGA score of 0 or 1 and ≥2 point improvement** 1. RUX 0.75%: 50.0% (n=126) Difference vs. placebo: 34.9% (95% CI 26.1 to 43.7; p<0.0001; NNT=3) 2. RUX 1.5%: 53.8% (n=136) Difference vs. placebo: 38.9%	**Patients with SAES (combined study analysis)** 1. RUX 0.75%: 0.8% (n=4) 2. RUX 1.5%: 0.6% (n=3) 3. Placebo: 0.8% (n=2)

			(95% CI 30.3 to 47.4; p<0.0001; NNT=3) 3. Placebo: 15.1% (n=19) **Proportion of participants who achieved EASI-75** 1. RUX 0.75%: 56.0% (n=142) Difference vs. placebo: 31.4% (95% CI 21.7 to 41.1; p<0.0001; NNT=4) 2. RUX 1.5%: 62.1% (n=158) Difference vs. placebo: 37.5% (95% CI 27.8 to 47.1; p<0.0001;NNT=3) 3. Placebo: 24.6% (n=31)	**Patients with TEAEs (combined study analysis)** **1.** RUX 0.75%: 26.5% (n=132) 2. RUX 1.5%: 29% (n=145) 3. Placebo: 33.2% (n=83) **Discontinuation due to TEAEs (combined study analysis)** 1. RUX 0.75%: 0.8% (n=4) 2. RUX 1.5%: 0.8% (n=4) **3.** Placebo: 3.2% (n=8)
Papp et al.[53] TRuE-AD2 Moderate	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ n=618 ▪ Adults and adolescents ≥ 12 yo ▪ 8 weeks	1. RUX 0.75% BID (n=248) 2. RUX 1.5% BID (n=246) 3. Placebo BID (n=124)	**Proportion of participants who achieved IGA score of 0 or 1 and ≥2 point improvement** 1. RUX 0.75%: 39.0% (n=91) Difference vs. placebo: 31.3% 95% CI 23.4 to 39.2; p<0.0001; NNT=4) 2. RUX 1.5%: 51.3% (n=117) Difference vs. placebo: 43.7% (95% CI 35.6 to 51.8; p<0.0001; NNT=3) 3. Placebo: 7.6% (n=9) **Proportion of participants who achieved EASI-75** 1. RUX 0.75%: 51.5% (n=128) Difference vs. placebo: 37.1% (95% CI 28.1 to 42.6; p<0.0001; NNT=3) 2. RUX 1.5%: 61.8% (n=140) Difference vs. placebo: 47.4% (95% CI 38.5 to 56.4; p<0.0001; NNT=3) 3. Placebo: 14.4% (n=17)	**See Above**
Abbreviations: AD=atopic dermatitis; BID=twice daily; CI=confidence interval; DB=double blind; DERP=Drug Effectiveness Review Project; EASI= Eczema Area and Severity Index; IGA=Investigator's Global Assessment; MC=multi-center; N=number; NNT=number needed to treat; NR=not reported; NS=not significant; PC=placebo controlled; QD=once daily; RCT=randomized controlled trial; RUX=ruxolitinib; SAEs=serious adverse events; TEAEs=treatment-emergent adverse effects; yo=years old				

The FDA-approved indication for ruxolitinib 1.5% cream is for the short term and non-continuous treatment of mild-to-moderate AD in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with other topical prescription therapies or when those therapies are not advisable.[7] Treatments for mild-to-moderate AD are not funded by HERC.[3] Use of ruxolitinib with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.[7] The cream should be applied twice daily to affected areas of up to 20% of body surface area.[7] As with other JAK inhibitors, the label for topical ruxolitinib has a FDA black boxed warning regarding the risk of serious infections, mortality, MACE, and thrombosis associated with JAK inhibitor administration for inflammatory conditions.[7] Adverse events occurring in 1% or more of ruxolitinib patients compared with vehicle placebo in clinical studies are described in **Table 6.**

Table 6. Adverse Events Reported With Ruxolitinib In Clinical Trials compared with Placebo[7]

Adverse Event	Ruxolitinib (n=499)	Vehicle (n=250)
Nasopharyngitis	27%	33%
Bronchitis	3%	1%
Ear Infection	1%	0%
Decreased Eosinophil Count	1%	0%
Urticaria	1%	0%
Diarrhea	1%	<1%
Folliculitis	1%	0%
Tonsillitis	1%	0%
Rhinorrhea	1%	<1%

Tralokinumab

Tralokinumab is an IL-13 antagonist formulated for subcutaneous injection. Four placebo-controlled RCTs with low-to-moderate risk of bias assessed the safety and efficacy of tralokinumab for treatment of moderate-to-severe AD.[1] One dose-finding phase 2 trial and phase 3 RCTs enrolled participants diagnosed with moderate-to-severe AD with an EASI score of 12 or greater, IGA of 3 or more, and BSA involvement of 10% or more.[1] In the phase 2 trial, enrollees continued topical corticosteroids and could use rescue therapy as long it was not as systemic agent or topical calcineurin inhbitor.[1] In 2 of the phase 3 studies, ECZTRA 1 and ECZTRA 2, participants were permitted to use emollients twice daily, rescue topical corticosteroid therapy, and systemic glucocorticoids.[1] Patients who received rescue treatment (systemic and topical) were labeled as nonresponders by the investigators.[54] In the third phase 3 trial, ECZTRA 3, tralokinumab was combined with topical mometasone 0.1% cream as needed in patients with similar characteristics as those enrolled in ECZTRA 1 and ECZTRA 2. Studies were conducted over 12 to 16 weeks with relatively large sample sizes (n=340 to 800). Additional study details and results are presented in **Table 7**.

The primary endpoints for all studies were achievement of an IGA of 0 to 1 and improvement of EASI by 75% or more over 12 to 16 weeks. In the phase 2 RCT, EASI was improved with tralokinumab 150 mg and 300 mg doses in combination with topical corticosteroids compared with placebo at 12 weeks based on moderate-quality evidence.[1] In the ECZTRA 1 and ECZTRA 2 trials, there was moderate-quality evidence that showed tralokinumab monotherapy was superior to placebo in achieving EASI-75 at 12 weeks.[1] Tralokinumab was superior to placebo in achieving IGA 0 or 1 at 12 weeks based on low-quality evidence from these trials.[1] The DERP authors downgraded the evidence assessment for IGA outcome due to inconsistency and indirectness.[1] In ECZTRA 3, moderate-quality evidence demonstrated tralokinumab combined with topical mometasone was superior to placebo in achieving IGA of 0 to 1 and EASI-75 at 16 weeks.[1]

Table 7. Study Characteristics and Results: Tralokinumab for Moderate-to-Severe Atopic Dermatitis

-Author -Trial Name -DERP Risk-of-Bias Assessment	-Study Design -Participant Description -Duration	Product, Dose, Frequency	Co-Primary Outcomes	Adverse Effects
Wollenberg et al.[55] NCT02347176 Moderate	▪ Phase 2 ▪ DB, MC, PC, RCT ▪ n=204 ▪ Adults aged 18 -75 yo ▪ 12 wks	1. TRAL 45 mg SC every 2 wks (n=50) 2. TRAL 150 mg SC every 2 wks (n=51) 3. TRAL 300 mg SC every 2 wks (n=52) 4. Placebo every 2 wks (n=51)	**Change in EASI score from baseline to week 12** 1. TRAL 45 mg: -13.67 (NS) MD vs placebo: NS 2. TRAL 150 mg: -15.14 MD vs placebo: -4.36 (95% CI -8.22 to -0.51; p<0.05) 3. TRAL 300 mg: - 15.72 MD vs placebo: -4.94 (95% CI -8.76 to -1.13; p<0.05) 4. Placebo: -10.78 **Proportion of participants who achieved IGA score of 0 or 1** 1. TRAL 45 mg: 11.6% (n=6) Difference vs placebo: NS 2. TRAL 150 mg: 19.5% (n=10) Difference vs placebo: 7.7 (95% CI -6.1 to 21.5; NS) 3. TRAL 300 mg: 26.7% (n=13) Difference vs placebo: 14.8 (95% CI 0 to 29.7; NS) 4. Placebo: 11.8% (n=6)	**Patients with TEAEs** 1. TRAL 45 mg: 24% (n=12) 2. TRAL 150 mg: 17.6% (n=9) 3. TRAL 300 mg: 11.5% (n=6) 4. Placebo: 17.6% (n=9)
Wollenberg et al.[54] ECZTRA 1 Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ N=802 ▪ Adults ≥ 18 yo ▪ 16 wks	1. TRAL 300 mg SC every 2 wks after 600 mg LD (n=601) 2. Placebo SC every 2 wks (n=197) • Monotherapy	**Proportion of participants who achieved IGA score of 0 or 1** 1. TRAL 300 mg: 15.8% (n=95) 2. Placebo: 7.1% (n=14) Difference: 8.6% (95% CI 4.1 to 13.1; p=0.002; NNT=12) **Proportion of participants who achieved EASI-75** 1. TRAL 300 mg: 25.0% (n=150) 2. Placebo: 12.7% (n=25) Difference: 12.1% (95% CI 6.5 to 17.7; p<0.001; NNT=9)	**Patients with SAES** 1. TRAL 300 mg: 3.9% (n=24) 2. Placebo: 5.6% (n=11)
Wollenberg et al.[54] ECZTRA 2	▪ Phase 3 ▪ DB, MC, PC, RCT	1. TRAL 300 mg SC every 2 weeks after 600 mg LD (n=591)	**Proportion of participants who achieved IGA score of 0 or 1**	**Patients with SAEs** 1. TRAL 300 mg: 1.68% (n=10)

Low	▪ N=794 ▪ Adults ≥ 18 yo ▪ 16 wks	2. Placebo SC every 2 wks (n=201) • Monotherapy	1. TRAL 300 mg: 22.2% (n=131) 2. Placebo: 10.9% (n=22) Difference: 11.1% (95% CI 5.8 to 16.4; p<0.001; NNT=9) **Proportion of participants who achieved EASI-75** 1. TRAL 300 mg: 33.2% (n=196) 2. Placebo: 11.4% (n=23) Difference: 21.6% (95% CI 15.8 to 27.3; p<0.001; NNT=5)	2. Placebo: 3% (n=6)
Silverberg et al.[56] ECZTRA 3 Low	▪ Phase 3 ▪ DB, MC, PC, RCT ▪ N=380 ▪ Adults ▪ 16 wks	1. TRAL 300 mg SC every 2 weeks after 600 mg LD (n=253) 2. Placebo SC every 2 weeks (n=127) • Both arms continued a topical corticosteroid during the study	**Proportion of participants who achieved IGA score of 0 or 1** 1. TRAL 300 mg: 38.9% (n=98) 2. Placebo: 26.2% (n=33) Difference: 12.4% (95% CI 2.9 to 21.9; p<0.001; NNT=4) **Proportion of participants who achieved EASI-75** 1. TRAL 300mg: 56.0% (n=141) 2. Placebo: 35.7% (n=45) Difference: 20.2% (95% CI 9.8 to 30.6; p<0.001; NNT=5)	**Patients with SAEs** 1. TRAL 300 mg: 0.8% (n=2) 2. Placebo: 3.2% (n=4)

Abbreviations: AD=atopic dermatitis; BID=twice daily; CI=confidence interval; DB=double blind; DERP=Drug Effectiveness Review Project; EASI= Eczema Area and Severity Index; IGA=Investigator's Global Assessment; LD=loading dose; MC=multi-center; MD=mean difference; N=number; NNT= number needed to treat; NR=not reported; NS=not significant; PC=placebo controlled; QD=once daily; RCT=randomized controlled trial; SAEs=serious adverse events; SC=subcutaneous; TEAEs=treatment-emergent adverse effects; TRAL=tralokinumab; wks=weeks; yo= years old

Low-quality evidence demonstrated tralokinumab increased the risk of infection-type AEs over placebo.[1] Most AEs were mild to moderate. The most commonly reported AEs reported in more than 5% of participants and occurring more frequently with tralokinumab than placebo were viral upper respiratory tract infections, upper respiratory tract infections, and conjunctivitis.[1] The most frequently reported AEs in tralokinumab clinical trials are summarized in **Table 8**.[8]

Table 8. Adverse Events Reported in Clinical Trials with Tralokinumab and Placebo[8]

Adverse Reaction	Tralokinumab Monotherapy		Tralokinumab Combined with Mometasone	
	Tralokinumab (n=1180)	Placebo (n=388)	Tralokinumab (n=243)	Placebo (n=123)
Upper respiratory infection	23.8%	20.4%	30.0%	15.4%
Conjunctivitis	7.5%	3.1%	13.6%	4.9%
Injection Site Reactions	7.4%	4.1%	11.1%	0.8%
Eosinophilia	1.4%	0.5%	1.2%	0%

Tralokinumab is FDA-approved for the treatment of moderate-to-severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[8] The recommended dose is an initial subcutaneous dose of 600 mg followed by 300 mg

administered every other week.[8] For patients below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment, the dose can be adjusted to 300 mg every 4 weeks.[8]

Upadacitinib

Upadacitinib is a selective JAK-1 inhibitor which is FDA-approved for management of RA in adults and treatment of moderate-to-severe AD in patients aged 12 years and older.[9] Four RCTs with low-to-moderate risk of bias were conducted in adults and adolescents with AD.[1] The phase 2 RCT was a dose-ranging study in patients with an AD diagnosis for at least 2 years, EASI score of 12 or greater, and total BSA involvement of at least 10%. Two identical phase 3 RCTs were placebo-controlled and an additional head-to-head phase 3 trial included dupilumab as an active comparator. In all 3 of the phase 3 RCTs participants had a confirmed moderate-to-severe AD diagnosis with an IGA score of 3 or more, EASI score of 16 or more, and total BSA involvement of least 10%.[1]

In one placebo-controlled phase 3 RCT, patients were randomized to upadacitinib 15 mg or 30 mg in combination with topical corticosteroid therapy in adults (18 to 75 years of age) and adolescents (12 to 17 years of age) with moderate-to-severe AD.[57] Rescue therapy was permitted with topical calcineurin inhibitors or crisaborole.[57] In the MEASURE UP 1 and MEASURE UP 2 RCTs, no additional therapies were allowed, although rescue therapy was permitted beginning at week 4.[58] These trials were conducted during the COVID-19 pandemic, so accommodations were made for site disruptions and remote visits.[1] In the HEADS UP trial, participants had to be candidates for systemic therapy which was defined as having an inadequate response to topical treatments, documented use of systemic treatment, or topical treatments were otherwise medically inadvisable.[5] Rescue therapy could be administered at any time per investigator discretion.[5]

Upadacitinib was superior to placebo in achieving EASI-75 and IGA 0 or 1 in 3 clinical trials based on high-quality evidence.[1] Upadacitinib was superior to dupilumab in achieving EASI-75 (NNT = 10) in the HEADS UP trial based on high-quality evidence.[1] Study details and results are presented in **Table 9**.

High-quality evidence showed upadacitinib had similar AEs to placebo with higher rates of acne observed with upadacitinib.[1] Moderate-quality evidence showed similar rates of AEs between upadacitinib and dupilumab with higher rates of acne, upper respiratory tract infections, and increased creatinine phosphokinase (CPK) observed with upadacitinib.[1]

Table 9. Study Characteristics and Results: Upadacitinib for Moderate-to-Severe Atopic Dermatitis

-Author -Trial Name -DERP Risk-of-Bias Assessment	-Study Design -Participant Description -Duration	Product, Dose, Frequency	Co-Primary Outcomes	Adverse Effects
Guttman-Yassky et al.[59] NCT02925117 Low	• Phase 2 • DB, MC, PC, RCT • N=167 • Adults ≥ 18 yo • 16 wks	1. UPAD 7.5 mg po once daily (n=42) 2. UPAD 15 mg po once daily (n=42) 3. UPAD 30 mg po once daily (n=42) 4. Placebo po once daily (n=41)	**Percentage improvement in EASI** 1. UPAD 7.5 mg: 39% Difference vs placebo: 16% (95% CI 1.4 to 31; p=0.03) 2. UPAD 15 mg: 62% Difference vs placebo: 39% (95% CI 24 to 54; p<0.001) 3. UPAD 30 mg: 74% Difference vs placebo: 51% (95% CI 36 to 67; p<0.001)	**Patients with SEAS** 1. UPAD 7.5 mg: 4.8% (n=2) 2. UPAD 15 mg: 2.4% (n=1) 3. UPAD 30 mg: 0% 4. Placebo: 2.5% (n=1)

			4. Placebo: 23%	
Reich et al.[57] AD Up Low	• Phase 3 • DB, MC,PC, RCT • N=901 • Adolescents and Adults ≥ 12 yo • 16 wks	1. UPAD 15 mg po once daily + TCS (n=300) 2. UPAD 30 mg po once daily + TCS (n=297) 3. Placebo po once daily + TCS (n=304)	**Proportion of participants who achieved EASI-75** 1. UPAD 15 mg: 65% (n=194) Difference vs placebo: 38.1% (95% CI 30.8 to 45.4; p<0.0001; NNT=3) 2. UPAD 30 mg: 77% (n=229) Difference vs placebo: 50.6% (95% CI 43.8 to 57.4; p<0.0001; NNT=2) **3.** Placebo: 26% (n=80) **Proportion of participants who achieved IGA score of 0 or 1** 1. UPAD 15 mg: 40% (n=119) Difference vs placebo: 28.5% (95% CI 22.1 to 34.9; p<0.0001; NNT=4) 2. UPAD 30 mg: 59% (n=174) Difference vs placebo: 47.6% (95% CI 41.1 to 54.0; p<0.0001; NNT=3) 3. Placebo: 11% (n=33)	**Patients with SEAS** 1. UPAD 15 mg: 2% (n=7) 2. UPAD 30 mg: 1% (n=4) 3. Placebo: 9% (n=3)
Guttman-Yassky et al.[58] Measure Up 1 Low	• Phase 3 • DB, MC, PC, RCT • N=847 • Adults and adolescents aged ≥ 12 yo • 16 wks	1. UPAD 15 mg po once daily (n=281) 2. UPAD 30mg po once daily (n=285) 3. Placebo po once daily (n=281)	**Proportion of participants who achieved EASI-75** 1. UPAD 15 mg: 69.6% (n=196) Difference vs placebo: 53.3% (95% CI 46.4 to 60.2; p<0.0001; NNT=2) 2. UPAD 30 mg: 79.7% (n=227) Difference vs. placebo: 63.4% (95% CI 57.1 to 69.8; p<0.0001; NNT=2) 3. Placebo: 16.3% (n=46) **Proportion of participants who achieved IGA score of 0 or 1** **1.** UPAD 15 mg: 48.1% (n=135) Difference vs placebo: 39.8% (95% CI 33.2 to 46.4; p<0.0001; NNT=3) **2.** UPAD 30 mg: 62% (n=177) Difference vs placebo: 53.6% (95% CI 47.2 to 60.0; p<0.0001; NNT=2) **3.** Placebo: 8.4% (n=24)	**Patients with SEAS** 1. UPAD 15 mg: 2% (n=6) 2. UPAD 30 mg: 3% (n=8) 3. Placebo: 8% (n=3)
Guttman-Yassky et al.[58] Measure Up 2 Low	• Phase 3 • DB, MC, PC, RCT • N=836	1. UPAD 15 mg po once daily (n=276) 2. UPAD 30mg po once daily (n=282) 3. Placebo po once daily (n=278)	**Proportion of participants who achieved EASI-75** 1. UPAD 15 mg: 60.1% (n=166) Difference vs placebo: 46.9% (95% CI 39.9 to 53.9; p<0.0001; NNT=3)	**Patients with SEAS** 1. UPAD 15 mg: 2% (n=5) 2. UPAD 30 mg: 3% (n=7) 3. Placebo: 8% (n=3)

	• Adults and adolescents ≥ 12 yo • 16 wks		2. UPAD 30 mg: 72.9% (n=206) Difference vs placebo: 59.6% (95% CI 53.1 to 66.2; p<0.0001; NNT=2) 3. Placebo: 13.3% (n=37) **Proportion of participants who achieved IGA score of 0 or 1** 1. UPAD 15 mg: 38.8% (n=107) Difference vs placebo: 34% (95% CI 27.8 to 40.2; p<0.0001; NNT=3) 2. UPAD 30 mg: 52% (n=147) Difference vs placebo: 47.4% (95% CI 41.0 to 53.7; p<0.0001; NNT=3) 3. Placebo: 4.7% (n=13)	
Blauvelt et al.[5] HEADS Up Moderate	• Phase 3 • DB, AC, MC, RCT • N=692 • Adults ≥ 18 yo • 16 wks	1. UPAD 30 mg po once daily (n=348) 2. Dupilumab 300 mg SC every 2 weeks after 600 mg LD (n=344)	**Proportion of participants who achieved EASI-75** UPAD 30 mg: 71% (n=247) Dupilumab 300 mg: 61.1% (n=210) Difference: 10% (95% CI 2.9 to 17.0; p=0.006; NNT=10)	**Patients with SEAS** 1. UPAD 30 mg: 2.9% (n=10) 2. Dupilumab 300 mg: 1.2% (n=4)

Abbreviations: AC=active-comparator; AD=atopic dermatitis; BID=twice daily; CI=confidence interval; DB=double blind; DERP=Drug Effectiveness Review Project; EASI= Eczema Area and Severity Index; IGA=Investigator's Global Assessment; LD=loading dose; MC=multi-center; MD=mean difference; N=number; NNT=number needed to treat; NR=not reported; NS=not significant; PC=placebo controlled; po=oral; RCT=randomized controlled trial; SAEs=serious adverse events; SC=subcutaneous; TCS=topical corticosteroid; TEAEs=treatment-emergent adverse effects; UPAD=upadacitinib; wks=weeks; yo= years old

Summary

Current therapies for moderate-to-severe AD include topical creams, oral products and subcutaneous injections. Older therapies such as azathioprine and cyclosporine are effective, but carry risk of significant AEs including systemic immunosuppression.[1] Azathioprine showed mixed long-term efficacy with many participants discontinuing treatment over time due to AEs.[1] Studies for cyclosporine highlighted there is insufficient high-quality comparative evidence with other oral immunomodulators (methotrexate, mycophenolate, prednisolone).[1] Topical tacrolimus and pimecrolimus have demonstrated superiority to placebo and therapeutic equivalence.[1] Topical ruxolitinib showed good efficacy in achieving EASI-75 and IGA 0 or 1 for managing mild-to-moderate AD, which is not funded by OHP. The oral JAK-inhibitors, abrocitinib and upadacitinib, showed effective response rates in EASI-75 and IGA 0 or 1 in patients with moderate-to-severe AD. Tralokinumab, an injectable IL-13 antagonist, was shown to be superior to placebo in short-term trials. Further published studies are needed to demonstrate safety of ruxolitinib, abrocitinib, and tralokinumab with long-term use beyond 52 weeks.

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59. Guttman-Yassky E, Thaci D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *Journal of Allergy & Clinical Immunology.* 2020;145(3):877-884.

Appendix 1: Current Preferred Drug List

Atopic Dermatitis PDL Class (Topical Products)

Generic	Brand	Route	Form	PDL
pimecrolimus	ELIDEL	TOPICAL	CREAM (G)	Y
pimecrolimus	PIMECROLIMUS	TOPICAL	CREAM (G)	Y
tacrolimus	PROTOPIC	TOPICAL	OINT. (G)	Y
tacrolimus	TACROLIMUS	TOPICAL	OINT. (G)	Y
crisaborole	EUCRISA	TOPICAL	OINT. (G)	N
ruxolitinib phosphate	OPZELURA	TOPICAL	CREAM (G)	N

Asthma Biologics (Select Systemic Products)

Generic	Brand	Route	Form	PDL
dupilumab	DUPIXENT PEN	SUBCUT	PEN INJCTR	N
dupilumab	DUPIXENT SYRINGE	SUBCUT	SYRINGE	N
tralokinumab-ldrm	ADBRY	SUBCUT	SYRINGE	N
abrocitinib	CIBINQO	ORAL	TABLET	

Targeted Immune Modulators (Select Systemic Products)

Generic	Brand	Route	Form	PDL
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1946 to February Week 1, 2022, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to February 16, 2022

1. Dermatitis, Atopic/	22299
2. Eczema/	11785
3. Calcineurin Inhibitors/	4191
4. Pimecrolimus.mp.	889
5. Tacrolimus/	16993
6. Crisaborole.mp.	124
7. Dupilumab.mp.	1100
8. exp Janus Kinase Inhibitors/	896
9. abrocitinib	40
10. ruxolitinib	1734
11. tralokinumab	97
12. upadacitinib	204
13. baricitinib	541
14. lebrikizumab	96
15. nemolizuamb	57
16. 1 or 2	32181
17. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	23863
18. 16 and 17	505
19. limit 19 to (english language and humans and yr="2020 -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"))	85

Appendix 3: Prioritized List Guideline Note

Extracted from the January 1, 2022 Prioritized List
Searchable Prioritized List 2022

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE
Lines 426,482,504,532,541,656

Inflammatory skin conditions included in this guideline are:

A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus
G) Vitiligo

The conditions above are included on Line 426 if severe, defined as having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following:

- At least 10% of body surface area involved
- Hand, foot, face, or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 482, 504, 532, 541 and 656.
For severe psoriasis, first line agents include topical agents, phototherapy and methotrexate. Second line agents include other systemic agents and oral retinoids and should be limited to those who fail, or have contraindications to, or do not have access to first line agents. Biologics are included on this line only for the indication of severe plaque psoriasis; after documented failure of first line agents and failure of (or contraindications to) a second line agent.

For severe atopic dermatitis/eczema, first-line agents include topical moderate- to high- potency corticosteroids and narrowband UVB. Second line agents include topical calcineurin inhibitors (e.g. pimecrolimus, tacrolimus), topical phosphodiesterase (PDE)-4 inhibitors (e.g. crisaborole), and oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids). Use of the topical second line agents (e.g. calcineurin inhibitors and phosphodiesterase (PDE)-4 inhibitors) should be limited to those who fail or have contraindications to first line agents. Biologic agents are included on this line for atopic dermatitis only after failure of or contraindications to at least one agent from each of the following three classes: 1) moderate to high potency topical corticosteroids, 2) topical calcineurin inhibitors or topical phosphodiesterase (PDE)-4 inhibitors, and 3) oral immunomodulator therapy.

ICD-10-CM Q82.8 (Other specified congenital malformations of skin) is included on Line 426 only for Darier disease.

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CIBINQO™ (abrocitinib) tablets, for oral use
Initial U.S. Approval: 2022

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), and THROMBOSIS

See full prescribing information for complete boxed warning.

- **Increased risk of serious bacterial, fungal, viral and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Discontinue treatment with CIBINQO if serious or opportunistic infection occurs. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative latent TB test. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death, with another JAK inhibitor vs. TNF blockers in rheumatoid arthritis (RA) patients. CIBINQO is not approved for use in RA patients. (5.2)**
- **Malignancies have occurred with CIBINQO. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs. TNF blockers in RA patients. (5.3)**
- **MACE has occurred with CIBINQO. Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients. (5.4)**
- **Thrombosis has occurred with CIBINQO. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs. TNF blockers. (5.5)**

INDICATIONS AND USAGE

CIBINQO is a Janus kinase (JAK) inhibitor indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. (1)

Limitation of Use: CIBINQO is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

DOSAGE AND ADMINISTRATION

- For recommended testing, evaluations and procedures prior to CIBINQO initiation, see Full Prescribing Information. (2.1)
- Recommended dosage is 100 mg orally once daily. (2.2)
- 200 mg orally once daily is recommended for those patients who are not responding to 100 mg once daily. (2.2)
- Moderate renal impairment: 50 mg once daily or 100 mg once daily for those patients who are not responding to 50 mg once daily. (2.3)
- CYP2C19 poor metabolizer: 50 mg once daily or 100 mg once daily for those patients who are not responding to 50 mg once daily. (2.4)
- For dosage modifications for certain adverse reactions, see Full Prescribing Information. (2.6)

DOSAGE FORMS AND STRENGTHS

CIBINQO Tablets: 50 mg, 100 mg, and 200 mg (3)

CONTRAINDICATIONS

Antiplatelet therapies except for low-dose aspirin (≤81 mg daily), during the first 3 months of treatment. (4)

WARNINGS AND PRECAUTIONS

- Laboratory Abnormalities: Laboratory monitoring is recommended due to potential changes in platelets, lymphocytes, and lipids. (5.6)
- Immunizations: Avoid use of live vaccines prior to, during, and immediately after CIBINQO treatment. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (≥1%) in subjects receiving 100 mg and 200 mg include:: nasopharyngitis, nausea, headache, herpes simplex, increased blood creatinine phosphokinase, dizziness, urinary tract infection, fatigue, acne, vomiting, oropharyngeal pain, influenza, gastroenteritis.
Most common adverse reactions (≥1%) in subjects receiving either 100 mg or 200 mg also include: impetigo, hypertension, contact dermatitis, upper abdominal pain, abdominal discomfort, herpes zoster, and thrombocytopenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong inhibitors of CYP2C19: The recommended dose is 50 mg daily or 100 mg once daily for those patients who are not responding to 50 mg once daily. (2.5, 7.1)
- Moderate to strong inhibitors of both CYP2C19 and CYP2C9, or strong CYP2C19 or CYP2C9 inducers: Avoid concomitant use. (7.1)
- P-gp substrate where small concentration changes may lead to serious or life-threatening toxicities: Monitor or titrate dosage of P-gp substrate. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)
- Renal Impairment: Avoid use in patients with severe renal impairment or end-stage renal disease. (8.6)
- Hepatic Impairment: Avoid use in patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2022

Opzelura™
(ruxolitinib) cream 1.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OPZELURA cream safely and effectively. See full prescribing information for OPZELURA cream.

OPZELURA™ (ruxolitinib) cream, for topical use
Initial U.S. Approval: 2011

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving Janus kinase inhibitors for inflammatory conditions. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.2)**
- **Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.3)**
- **Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.4)**
- **Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.5)**

INDICATIONS AND USAGE

OPZELURA is a Janus kinase (JAK) inhibitor indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. (1)

Limitation of Use

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended. (1)

DOSAGE AND ADMINISTRATION

- Apply a thin layer twice daily to affected areas of up to 20% body surface area. Do not use more than 60 grams per week. (2)
- For topical use only. (2)
- Not for ophthalmic, oral, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Cream: 1.5% ruxolitinib (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *Serious Infections:* Serious bacterial, mycobacterial, fungal and viral infections have occurred. Regularly monitor patients for infection and manage it promptly. (5.1)
- *Non-melanoma Skin Cancers.* Basal cell and squamous cell carcinoma have occurred. Perform periodic skin examinations during treatment and following treatment as appropriate. (5.3)
- *Thrombosis.* Thromboembolic events have occurred. (5.5)
- *Thrombocytopenia, Anemia and Neutropenia:* Thrombocytopenia, anemia and neutropenia have occurred. Perform CBC monitoring as clinically indicated (5.6).

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥1%) are nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Incyte Corporation at 1-855-463-3463 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ADBRY™ (tralokinumab-ldrm) injection, for subcutaneous use
Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------

ADBRY is an interleukin-13 antagonist indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. ADBRY can be used with or without topical corticosteroids. (1)

----------DOSAGE AND ADMINISTRATION----------

- Prior to ADBRY initiation, complete all age appropriate vaccinations as recommended by current immunization guidelines (2.1)
- The recommended dosage of ADBRY is an initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week. A dosage of 300 mg every 4 weeks may be considered for patients below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment. (2.2)
- Administer by subcutaneous injection. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 150 mg/mL solution in a single-dose prefilled syringe with needle guard. (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to tralokinumab-ldrm or any excipients in ADBRY. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity: Hypersensitivity reactions, including anaphylaxis, and angioedema have occurred after administration of ADBRY. Discontinue ADBRY in the event of a hypersensitivity reaction. (5.1)
- Conjunctivitis and Keratitis: Patients should report new onset or worsening eye symptoms to their healthcare provider. (5.2)
- Parasitic (Helminth) Infections: Treat patients with pre-existing helminth infections before initiating treatment with ADBRY. If patients become infected while receiving ADBRY and do not respond to anti-helminth treatment, discontinue treatment with ADBRY until the infection resolves. (5.3)
- Risk of Infection with Live Vaccines: Avoid use of live vaccines. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 1%) are upper respiratory tract infections, conjunctivitis, injection site reactions, and eosinophilia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LEO Pharma Inc. at 1-877-494-4536 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 01/2022

Topical Agents for Inflammatory Skin Disease

Goal(s):

- Restrict dermatological drugs only for funded OHP diagnoses. Treatments are funded on the OHP for severe inflammatory skin diseases including: psoriasis, atopic dermatitis, lichen planus, Darier disease, pityriasis rubra pilaris, discoid lupus and vitiligo. Treatments for mild or moderate psoriasis, mild or moderate atopic dermatitis, 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 targeted immune modulators for psoriasis or atopic dermatitis which are subject to separate clinical PA criteria.

Covered Alternatives:

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

Table 1. FDA-Approved Ages or Topical Atopic Dermatitis Drugs

Drug	Minimum Age
Crisaborole	3 months
Pimecrolimus	2 years
Ruxolitinib	12 years
Tacrolimus 0.03%	2 years
Tacrolimus 0.1%	16 years

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for mild or moderate inflammatory skin conditions?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the request for treatment of severe inflammatory skin disease? Severe disease is defined as:[1] • Having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: 1. At least 10% body surface area involved OR 2. Hand, foot, face , or mucous membrane involvement	**Yes:** Go to #4	**No:** Pass to RPh; deny, not funded by the OHP
4. Is the diagnosis psoriasis?	**Yes:** Go to #8	**No:** Go to #5
5. Is the diagnosis atopic dermatitis?	**Yes:** Go to #6	**No:** Go to #10
6. Does the patient meet the age requirements per the FDA label (Table 1)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Does the patient have a documented contraindication, intolerance or failed trials of at least 2 first line agents (i.e. topical corticosteroids or tacrolimus) indicated for the treatment of severe AD? *Note ruxolitinib, 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 or contraindications (if applicable): 1._____(dates) 2._____(dates) Approve for length of treatment; maximum 6 months.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the requested product preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #9
9. 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 Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Approve for length of treatment; maximum 1 year.
10. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.*	**If funded, and clinic provides supporting literature:** Approve for 1 year.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *6/22 (DM); 12/20; 10/20; 7/19; 5/19; 3/18; 9/17; 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *7/1/22; 1/1/2021, 11/1/20; 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 and moderate 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 March 1, 2022.

Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis

Goal(s):

- Restrict use of targeted immune modulators 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 or for patients with severe atopic dermatitis.
- Restrict use for conditions not funded by the OHP (e.g., chronic urticaria, mild-to-moderate atopic dermatitis).

Length of Authorization:

- Up to 12 months

Requires PA:

- Targeted immune modulators with indications for severe asthma or severe atopic dermatitis (see **Table 2** below) for pharmacy and provider-administered claims.
- This PA does not apply to topical agents for inflammatory skin conditions which are 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
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Armonair (fluticasone propionate)	232 mcg BID
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
Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID

AirDuo Digihaler (fluticasone/salmeterol)	232/14 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	232/14 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 2. FDA-approved Indications and Ages

Generic Name/ BRAND NAME	Eosinophilic Asthma	Moderate to Severe Allergic Asthma	Difficult To Treat, Severe Asthma*	Hypereosinophilic Syndrome (HES)	Eosinophilic Granulomatosis with Polyangiitis (EGPA)	Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	Atopic Dermatitis (AD)
Abrocitinib CIBINQO							≥18 years
Benralizumab FASENRA	≥12 years						
Dupilumab DUPIXENT	≥6 years (or with oral corticosteroid dependent asthma)					≥18 years	≥6 years
Mepolizumab NUCALA	≥6 years			≥ 12 years	≥18 years	≥18 years	
Omalizumab XOLAIR		≥6 years				≥18 years	
Reslizumab CINQAIR	≥18 years						
Tezepelumab TEZSPIRE			≥ 12 years				
Tralokinumab ADBRY							≥18 years

Difficult to treat, severe asthma is defined as asthma with poor symptom control on high-dose inhaled corticosteroid-long acting beta agonist (ICS-LABA) or maintenance oral corticosteroids (OCS).

Table 3. Abrocitinib Dosing Adjustments for Atopic Dermatitis

Assessment	Recommended Dose
CYP2C19 Poor Metabolizer	50 mg once daily
GFR 30 to 60 mL/min	50 mg once daily
GFR < 30 mL/min	Use is not recommended
Severe hepatic impairment (Child-Pugh Class C)	Use is not recommended

Table 4. FDA-Approved Dosing for Monoclonal Antibodies Used to Treat Severe Asthma Phenotypes

Generic Name	Brand Name	Asthma Indication	Initial Dose and Administration Route	Maintenance Dose and Administration Route
Benralizumab	FASENRA	Severe asthma with an eosinophilic phenotype	30 mg SC every 4 weeks for the first 3 doses	30 mg SC every 8 weeks
Dupilumab	DUPIXENT	Add on maintenance treatment for moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	Pediatrics (6 to 11 yo)**:** An initial loading dose is not necessary Adults and Adolescents ≥ 12 yo : 400 mg to 600 mg SC x 1 dose	Ages 6 – 11 yo (weight 15 to 30 kg) 100 mg SC every 2 weeks OR 300 mg SC every 4 weeks Adults and Adolescents ≥ 12 yo: 200 to 300 mg SC every 2 weeks
Mepolizumab	NUCALA	Severe asthma with an eosinophilic phenotype	N/A	Ages ≥ 6 – 11 yo: 40 mg SC every 4 weeks Ages ≥ 12 yo: 100 mg SC every 4 weeks
Omalizumab	XOLAIR	Moderate to severe persistent asthma and positive allergy testing	N/A	75 to 375 mg SC every 2 to 4 weeks based on weight and serum IgE levels
Reslizumab	CINQAIR	Severe asthma with an eosinophilic phenotype	N/A	3 mg/kg IV infusion every 4 weeks
Tezepelumab	TEZSPIRE	Severe asthma	N/A	210 mg SC every 4 weeks

Abbreviations: IgE = immunoglobulin E; IV = intravenous; kg = kilogram; mg = milligram; N/A = Not Applicable; SC = subcutaneous; yo = years old

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP-funded diagnosis? Note: chronic idiopathic urticaria and mild-to-moderate atopic dermatitis are not OHP-funded conditions	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
3. Is the request for an FDA-approved indication and age (**Table 2**)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. 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 #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the diagnosis Severe Atopic Dermatitis (AD)? Severe disease is defined as:[1] • Having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: ○ At least 10% body surface area involved, or ○ Hand, foot, face, or mucous membrane involvement	**Yes:** Go to #7	**No:** Go to #14
7. Is the medication being prescribed by or in consultation with a dermatologist, allergist, or a provider who specializes in care of atopic dermatitis?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for abrocitinib?	**Yes:** Go to #9	**No:** Go to # 13

Approval Criteria		
9. Are baseline labs (platelets, lymphocytes, lipids) documented? *Note: Abrocitinib therapy should not be initiated if platelet count is < 150,000/mm^3, absolute lymphocyte count is < 500/mm^3, absolute neutrophil count is < 1,000/mm^3, or hemoglobin is < 8 g/dL	**Yes:** Go to # 10 Document Lab and Date Obtained: Platelets:_____ Lymphocytes:_____ Lipids:_____ Hemoglobin:	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the patient currently taking other targeted immune modulators or oral immunosuppressants?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
11. If the patient has renal or hepatic impairment has the dose been adjusted as described in Table 3?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. If the patient taking a strong CYP2C19 inhibitor (e.g., fluvoxamine, fluoxetine), or CYP2C9 inhibitor (e.g., fluconazole, amiodarone) or CYP2C9 inducer (e.g,rifampin, phenobarbital), or CYP2C19 inducer (carbamazepine) or antiplatelet agent has the abrocitinib dose been adjusted in Table 3 or has the interacting drug been discontinued if necessary? *Note: agents with antiplatelet properties (NSAIDs, SSRIs, etc.) should not be used during the first 3 months of abrocitinib therapy. Do not use aspirin at doses ≥ 81 mg/day with abrocitinib during the first 3 months of therapy.	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
13. 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
14. Is the request for eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) 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 for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #15
15. Is the request for the treatment of a patient with hypereosinophilic syndrome (HES) with a duration of 6 months or greater without an identifiable non-hematologic secondary cause?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #16
16. Is the request for treatment of nasal polyps?	**Yes:** Go to # 17	**No:** Go to #19
17. Is the prescriber an otolaryngologist, or allergist who specializes in treatment of chronic rhinosinusitis with nasal polyps?	**Yes:** Go to # 18	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
18. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
19. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #20	**No:** Pass to RPh. Deny; medical appropriateness.
20. Has the patient experienced one of the following: • at least 4 asthma exacerbations requiring systemic corticosteroids in the previous 12 months OR • taking continuous oral corticosteroids at least the equivalent of prednisolone 5 mg per day for the previous 6 months OR • 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, tiotropium)?	**Yes:** Go to #21 Document number asthma exacerbations over the previous 12 months or oral corticosteroid dose over the previous 6 months or number of hospitalizations or ED visits in the past 12 months _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
21. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #22	**No:** Pass to RPh. Deny; medical appropriateness.
22. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, or tezepelumab etc.,)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #23
23. Is the request for tezepelumab?	**Yes:** Approve for up to 12 months.	No: Go to # 24

Approval Criteria		
24. 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 #25
25. If the request is for asthma with an eosinophilic phenotype, can the prescriber provide documentation of one of the following biomarkers: • severe eosinophilic asthma, confirmed by blood eosinophil count ≥150 cells/µL OR • fractional exhaled nitric oxide (FeNO)≥ 25 ppb in the past 12 months?	**Yes:** Approve up to 12 months, based on dosing outlined in Table 4. Document eosinophil count (or FeNO date):_____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew therapy for eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps (CRSwNP), or hypereosinophilic syndrome (HES)?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #4	**No:** Go to #5

Renewal Criteria		
4. Have the patient's symptoms improved with targeted immune modulator 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.
5. 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 #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. 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.

1. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports.* http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed March 1, 2022.
2. National Institute for Health and Care Excellence (NICE) Guidance. Mepolizumab for Treating Severe Eosinophilic Asthma. https://www.nice.org.uk/guidance/ta671 February 2021.
3. National Institute for Health and Care Excellence (NICE) Guidance. Dupilumab for Treating Severe Asthma with Type 2 Inflammation. https://www.nice.org.uk/guidance/ta751 December 2021
4. Global Initiative for Asthma. Global strategy for asthma management and prevention (2021 update). 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf

P&T Review: *6/22 (DM); 8/21; 10/20; 7/19; 7/18; 7/16*
Implementation: *7/1/22; 1/1/22; 9/1/21; 8/19/19, 8/15/18, 8/16*

Targeted Immune Modulators for Autoimmune Conditions

Goal(s):

- Restrict use of targeted immune modulators to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators for autoimmune conditions (both pharmacy and physician-administered claims)

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. Approved and Funded Indications for Targeted Immune Modulators

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo			aGVHD ≥ 2 yo
Adalimumab (HUMIRA) and biosimilars	≥18 y	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo (Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥5 yo (Humira) ≥18 yo (biosimilars)		Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo			NOMID DIRA
Apremilast (OTEZLA)				≥18 yo	≥18 yo				Oral Ulcers associated with BD ≥ 18 yo
Baricitinib (OLUMIANT)						≥18 yo			COVID ≥ 18 yo (hospitalized)
Brodalumab (SILIQ)				≥18 yo					
Canakinumab (ILARIS)			≥2 yo						FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4 yo HIDS ≥ 4 yo MKD ≥ 4 yo FMF ≥ 4 yo

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
									Stills Disease
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo			Nr-axSpA ≥ 18 yo
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥4 yo (biosimilars)	≥18 yo	≥18 yo			
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo		≥2 yo active polyarticular course		≥2 yo	≥18 yo	≥18 yo (Simponi)		
Guselkumab (TREMFYA)				≥18 yo	≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Ixekizumab (TALTZ)	≥ 18 yo			≥6 yo	≥18 yo				Nr-axSpA ≥ 18 yo
Risankizumab-rzaa (SKYRIZI)				≥18 yo	≥ 18 yo				
Rituximab (RITUXAN) and biosimilars						≥18 yo			CLL ≥18 yo DLBCL≥6 mo BL≥6 mo BLL≥6 mo B-AL≥6 mo NHL ≥18 yo GPA ≥2yo MPA ≥ 2 yo Pemphigus Vulgaris ≥18 yo (Rituxan only)
Sarilumab (KEVZARA)						≥18 yo			
Secukinumab (COSENTYX)	≥18 yo			≥6 yo	≥2 yo				ERA ≥ 4 yo Nr-AxSpA ≥18 yo
Tildrakizumab-asmn (ILUMYA)				≥18 yo					
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo			CRS ≥2 yo GCA ≥18 yo SSc-ILD ≥18 yo
Tofacitinib (XELJANZ)	≥18 yo		≥2 yo		≥18 yo	≥18 yo	≥18 yo		

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
			active polyarticular course						
Upadacitinib (RINVOQ)	≥18 yo				≥18 yo	≥18 yo	≥18 yo	≥ 12 yo	
Ustekinumab (STELARA)		≥ 18 yo		≥6 yo	≥18 yo		≥18 yo		
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo		

Abbreviations: aGVHD = acute Graft Versus Host Disease; BD = Behcet's Disease; BL = Burkitt Lymphoma; BLL = Burkitt-like Lymphoma; B-AL = mature B-cell acute leukemia; CLL = Chronic Lymphocytic Leukemia; COVID = Covid-19 infection; CRS = Cytokine Release Syndrome; DIRA = Deficiency of Interleukin-1 Receptor Antagonist; DLBCL = Diffuse Large B-Cell Lymphoma; ERA = Enthesitis-Related Arthritis; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; HS: Hidradenitis Suppurativa; MKD = Mevalonate Kinase Deficiency; mo = months old; MPA = Microscopic Polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; Nr-axSpA = Non-Radiographic Axial Spondyloarthritis; SSc-ILD = Systemic Sclerosis-Associated Interstitial Lung Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP? Notes: A. Mild-to-moderate psoriasis is unfunded, severe psoriasis is funded. B. Mild Hidradenitis Suppurativa (HS) is unfunded, moderate-to-severe HS (e.g., Hurley Stage II or III) is funded.	**Yes:** Go to # 3	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
3. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?* *(Note: this requirement does not apply to requests for apremilast.)	**Yes:** Go to # 4	**No:** Pass to RPh. Deny; medical appropriateness. If patient meets all other criteria, pharmacist may approve once for up to 3 months to allow time for screening for ongoing therapy to avoid interruptions in care.
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to # 5
5. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives. Go to #6	**No:** Go to # 6
6. Is the request for a medication and corresponding diagnosis indicated according to the “Other” column of table 1? AND Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to # 7
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to # 8	**No:** Go to # 9

Approval Criteria		
8. Is this a request for a preferred agent OR if the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® branded product or an Enbrel® branded product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to # 10	**No**: Go to #12
10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involvement; OR • Hand, foot, face, or mucous membrane involvement?	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
11. Has the patient failed to respond or had inadequate response to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); AND • At least one other topical agent: calcipotriene, tazarotene, anthralin; AND • Phototherapy; AND • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; AND • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for a drug FDA-approved for atopic dermatitis as defined in Table 1? Note: only *severe* atopic dermatitis is funded by the OHP.	**Yes:** Go to # 13	**No**: Go to #15
13. Is the atopic dermatitis severe in nature, which has resulted in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involvement; or • Hand and, foot, face, or mucous membrane involvement?	**Yes:** Go to # 14	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
14. 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
15. Is the diagnosis rheumatoid arthritis, juvenile idiopathic arthritis, or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 16	**No:** Go to # 19

Approval Criteria		
16. Has the patient failed to respond or had inadequate response to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; OR • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® branded product or an Enbrel® branded product for at least 3 months? AND • Is the patient on concurrent DMARD therapy with plans to continue concomitant use?	**Yes:** Go to # 17 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
17. Is the request for tofacitinib, baricitinib, or upadacitinib?	**Yes:** Go to # 18	**No:** Approve for up to 6 months
18. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus OR cyclosporine? Note: Tofacitinib, baricitinib, and upadacitinib may be used concurrently with methotrexate or other nonbiologic DMARD drugs. Tofacitinib, baricitinib, or upadacitinib are not recommended to be used in combination with other JAK inhibitors, biologic DMARDs, azathioprine, or cyclosporine.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve baricitinib or upadacitinib for up to 6 months. Approve tofacitinib for up to 6 months at a maximum dose of 10 or 11 mg daily for Rheumatoid Arthritis OR 10 mg twice daily for 8 weeks then 5 or 10 mg twice daily for Ulcerative Colitis
19. Is the request for adalimumab in an adult with moderate-to-severe Hidradenitis Suppurativa (HS)?	**Yes:** Go to # 20	**No:** Go to # 21

Approval Criteria		
20. Has the patient failed to respond, had inadequate response, or do they have an intolerance or contraindication to a 90 day trial of conventional HS therapy (e.g. oral antibiotics)? Note: Treatment of moderate-to-severe HS with adalimumab is funded on the Prioritized List of Health Services per Guideline Note 198 OHA Prioritized List	**Yes:** Approve for up to 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness**.**
21. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 22	**No:** Go to # 24
22. Has the patient failed to respond or had inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy?	**Yes:** Go to #23	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
23. Is the request for a preferred product or has the patient tried and failed a 3 month trial of a Humira® product?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
24. Is the diagnosis for an FDA approved diagnosis and age as outlined in Table 1, and is the requested drug rituximab for *induction or maintenance* of remission?	**Yes:** Approve for length of treatment.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for treatment of psoriatic arthritis, plaque psoriasis, or rheumatoid arthritis?	**Yes:** Go to # 6	**No:** Go to # 2
2. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #3	**No:** Go to #4

Renewal Criteria		
3. Have the patient's symptoms improved with upadacitinib 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.
4. Is the request for continuation of adalimumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to # 5	**No:** Go to # 6
5. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: • a reduction of 25% or more in the total abscess and inflammatory nodule count, AND • no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been adherent to both biologic and DMARD therapy (if DMARD therapy has been prescribed in conjunction with the biologic therapy)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *6/22(DM); 10/21; 10/20; 2/20; 5/19; 1/19; 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *7/1/22; 1/1/22; 1/1/2021; 7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/2*