Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluation: Topical Products for Inflammatory Skin Diseases

Date of Review: December 2025

Generic Name: Delgocitinib
Generic Name: Sirolimus

Date of Last Review: December 2022
Dates of Literature Search: 09/01/2022 – 8/19/2025
Brand Name (Manufacturer): ANZUPGO (LEO Pharma Inc.)
Brand Name (Manufacturer): HYFTOR (Nobelpharma America, LLC)

Dossier Received: yes

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

Purpose for Class Update:
The purpose of this update is to review recent evidence for topical agents that are Food and Drug Administration (FDA)-approved for inflammatory skin conditions and evaluate place in therapy for 2 new topical medications. Delgocitinib 2% topical cream was recently FDA-approved for moderate-to-severe chronic hand eczema in adults. Sirolimus 0.2% topical gel is FDA-approved for treatment of facial fibroangiomas associated with tuberous sclerosis complex (TSC).

Plain Language Summary:
- Is there any new evidence for different topical medicines (treatments applied to the skin) for skin conditions including psoriasis (scaly plaques), atopic dermatitis (dry, itchy, red skin), and vitiligo (patchy loss of skin color) that would change the current policy of topical medicines for skin conditions?
- Recent evidence shows the most effective medicines to treat atopic dermatitis are topical corticosteroids (i.e. clobetasol, fluocinonide, betamethasone, fluticasone) and topical calcineurin inhibitors (tacrolimus and pimecrolimus).
- A newer medicine, ruxolitinib, is not recommended by the American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma, and Immunology Joint Task Force or Canada's Drug Agency for atopic dermatitis. These organizations say there is not enough evidence to determine if topical ruxolitinib decreases atopic dermatitis flares because it was only evaluated in short-term studies over 4 to 8 weeks.
- For treatment of plaque psoriasis, Canada's Drug Agency supports the use of roflumilast 0.3% cream in people aged 12 years and older.
- Canada's Drug Agency does not recommend ruxolitinib for vitiligo because studies did not show it improved health related quality of life for people who have this skin condition.
- Another new medicine, delgocitinib, was approved by the FDA to treat chronic hand eczema in adults. Chronic hand eczema causes itching and pain. Two 4-month studies showed that when delgocitinib cream is applied to adults with moderate-to-severe hand eczema, symptoms of hand eczema decreased more than when people used a skin cream without medicine. Side effects to delgocitinib were uncommon. The most frequent side effects were application site pain, itching, redness, numbness, and skin infections. There are no studies that compare delgocitinib to other medicines for eczema.

Author: Deanna Moretz, PharmD, BCPS

- The FDA approved a second medicine, sirolimus, for facial angiofibromas (small red or pink bumps on the skin) in people 6 years of age and older with tuberous sclerosis complex. This is a rare condition with very few treatment options. In one small study, sirolimus gel decreased the size and redness of these facial bumps when compared to a gel without any medicine.
- Providers must explain to the Oregon Health Authority why their patient needs topical roflumilast, ruxolitinib, delgocitinib, and sirolimus before Medicaid will pay for it. This process is called prior authorization. Medicaid will pay for some older and less expensive topical medicines, such as topical corticosteroids, without prior authorization.

Research Questions:

1. Is there new evidence regarding the comparative safety and efficacy of topical agents to manage inflammatory skin conditions including plaque psoriasis (PsO), atopic dermatitis (AD), and vitiligo?
2. For adults with moderate-to-severe chronic hand eczema, what is the safety and effectiveness of delgocitinib 2% cream?
3. For patients with facial angiofibroma associated with TSC, what is the safety and effectiveness of sirolimus 0.2% gel?
4. Are there patients based on demographics characteristics (i.e., age, race, ethnicity, gender), socioeconomic status, concomitant medications, or co-morbidities for which one topical agent is more effective or associated with fewer adverse events in treating inflammatory skin diseases?

Conclusions:

Safety And Efficacy of Topical Agents for Management of Eczema, Atopic Dermatitis, Plaque Psoriasis, and Vitiligo

- Since the last review, 3 systematic reviews have evaluated the safety and efficacy of topical agents for management of eczema and AD.[1-3] Six guidelines were updated to guide treatment of mild-to-moderate AD, PsO, and vitiligo with topical agents.[4-9]
- A 2024 Cochrane systematic review and network meta-analysis (NMA) evaluated topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), Janus kinase (JAK) inhibitors, phosphodiesterase-4 (PDE-4) inhibitors, and tapinarof for eczema.[1] This analysis found that potent and very potent TCS, tacrolimus 0.1% and ruxolitinib 1.5% were among the most effective short-term treatments for improving patient-reported symptoms (40 trials, all low confidence) and clinician-reported signs (32 trials, all moderate confidence) of eczema.[1] Local application site reactions were most common with tacrolimus 0.1% (moderate confidence) and crisaborole 2% (high confidence) and least common with TCS (moderate confidence).[1] Skin thinning was not increased with short-term (3 weeks) use of any TCS potency (low confidence) but skin thinning was reported in 0.3% of participants treated with longer-term TCS (over 6 to 60 months).[1]
- A 2023 systematic review and NMA provided the basis for development of American Academy of Allergy, Asthma & Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI) Joint Task Force 2023 guidance on management of AD.[2] The most effective agents for improving AD outcomes are pimecrolimus, tacrolimus, and moderate-potency TCS.[2] Crisaborole was intermediately effective, but with uncertain harm due to low-quality evidence on adverse events.[2] Topical antibiotics are the least effective agents for managing AD.[2] High certainty evidence showed that super-high potency TCS are the best in improving AD severity; tacrolimus (high dose) and high to moderate potency TCS groups 2 to 5 (see **Table 4**) were the best in improving itch severity; pimecrolimus was the best for improving sleep disturbance; and delgocitinib was the best in improving eczema-related quality of life (QoL).[2]
- A 2023 systematic review and meta-analysis evaluated incidence of cancer associated with TCI administration (pimecrolimus and tacrolimus) as part of the 2022 AAAAI/ACAAI guidance update for AD. The absolute risk of any cancer with TCI exposure was not different from controls (absolute risk 4.70 per 1000 with TCI vs 4.56 per 1000 without; odds ratio [OR] 1.03; 95% credible interval [CrI] 0.94 to 1.11; moderate certainty evidence).[3] For all age groups and using data from observational studies and RCTs, the use of pimecrolimus (OR 1.05; 95% CrI 0.94 to 1.15) or tacrolimus (OR 0.99; 95 % CrI 0.89 to 1.09) is likely to have had little to no association with cancer compared with no TCI exposure.[3] For pimecrolimus versus tacrolimus, the finding was similar (OR 0.95; 95% CrI 0.83 to 1.07).[3]

- A 2022 AAAAI/ACAAI Joint Task Force updated 2012 guidance for management of AD in infants, children, and adults.[4] Although moisturization alone may achieve improvement in AD in patient with mild symptoms, and can help improve AD severity and time-to-flare in those with more severe disease, almost all patients will require a prescription anti-inflammatory treatment including TCS, TCIs, or the topical PDE-4 inhibitor, crisaborole. Ruxolitinib, a topical JAK inhibitor, is not recommended by the task force panel because there is insufficient evidence to assess whether topical ruxolitinib reduces AD flares due to imprecision and the short-term (4-8 weeks) nature of the available studies.[4]
- The American Academy of Dermatology (AAD) guidance for management of AD with topical and systemic therapies in adults was updated in 2023.[5,6] For most people with AD, emollients and prescription topical therapies are sufficient to achieve AD control.[5] The use of TCS, TCI, crisaborole, and ruxolitinib for mild to severe AD are all strongly recommended by AAD.[5] Two new strong recommendations supporting the use of tapinarof and roflumilast cream in mild-to-moderate AD are included in the update.
- In May 2025, Canada's Drug Agency (CDA) issued a reimbursement recommendation for the use of the JAK inhibitor, ruxolitinib 1.5% cream, in patients with mild-to-moderate AD.[7] The CDA does not recommend reimbursement for ruxolitinib for treatment of AD in Canadian public drug plans.[7] Evidence from 2 clinical trials showed that ruxolitinib improved the severity of AD compared with placebo in adult and adolescent patients with mild to moderate AD.[7] However, it is unclear if these patients were not adequately controlled with TCS and/or TCI which is the patient population expected to receive ruxolitininb.[7]
- In September 2023, the CDA issued a reimbursement recommendation for roflumilast 0.3% cream, a topical PDE-4 inhibitor, in treatment of PsO for patients aged 12 years and older.[8] Roflumilast may provide an alternative, nonsteroidal topical treatment option for patients living with PsO, including psoriasis in the intertriginous area.[8] CDA Recommendations:
    - Roflumilast should only be covered to treat patients who have a clinical diagnosis of PsO, an Investigator's Global Assessment (IGA) score of at least 2 (mild), an area of PsO appropriate for topical treatment, and an affected body surface area of 2% to 20% (inclusive).[8]
    - Roflumilast should be discontinued if a response has not been demonstrated by 8 weeks. A response to treatment is defined as at least a 2-grade improvement from baseline in IGA score or an IGA score of "clear" or "almost clear" (0 or 1).[8]
- In August 2025, the CDA issued reimbursement recommendations for the use of ruxolitinib for topical treatment of non-segmental vitiligo (NSV) in patients aged 12 years and older.[9] The CDA does not recommend the reimbursement of ruxolitinib in treatment of vitiligo in Canadian public drug plans.[9] Published studies did not show that ruxolitinib led to meaningful improvements in overall health-related quality of life (HRQoL).[9] There is no data on how ruxolitinib compares to other commonly used treatments such as TCS or tacrolimus.[9]
- There is insufficient evidence to evaluate the comparative safety and efficacy of topical agents for treatment of inflammatory skin conditions in specific subpopulations based on demographic characteristics, socioeconomic status, concomitant medications, or co-morbidities.

Efficacy and Safety of Delgocitinib in Management of Chronic Hand Eczema

- Delgocitinib is a JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) inhibitor available as 2% topical cream in the United States (U.S.).[10] The medication received FDA-approval in July 2025 for the treatment of moderate-to-severe chronic hand eczema in adults who have had inadequate response to, or for whom TCS therapies are not advisable.[10]
- Two phase 3 studies, DELTA 1 and DELTA 2, provide data that support the FDA-approval of delgocitinib.[11] These studies were double-blind, placebo-controlled, multi-center RCTs conducted over 16 weeks in adults with moderate-to-severe chronic hand eczema and are described in detail in **Table 4**.[11]
- The primary endpoint of each trial was the Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) treatment success, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) at week 16 with a 2-step or greater improvement from baseline.[11] At week 16, a greater proportion of delgocitinib-treated patients versus cream vehicle patients had IGA-CHE treatment success (19.7% vs. 9.9%; difference, 9.8%; 95% confidence interval [CI] 3.6 to 16.1; $p<0.0055$ in DELTA 1 and 29.1% vs. 6.9%; difference, 22.2%; 95% CI 15.8 to 28.5; $p<0.0001$ in DELTA 2; moderate-quality evidence).[11]

- Most adverse events were mild to moderate and not considered related to trial treatment.[11] In both trials, the most frequently reported adverse events reported in <1% of the delgocitinib-treated group included application site pain, paresthesia, pruritis, erythema, and bacterial skin infections.[11]
- Draft recommendations from CDA suggest that delgocitinib be reimbursed for the treatment of moderate-to-severe chronic hand eczema in adults for whom TCS are inadequate or are not advisable, only if specific conditions are met:
    - adults (≥18 years) with moderate-to-severe chronic hand eczema as defined by an IGA-CHE score of 3-4 and who have had an adequate trial (with a documented refractory disease), documented intolerance, or are ineligible for high-potency TCS.[12]
    - Response should be assessed at 12 weeks with renewal for patients who demonstrate either a ≥ 2-step improvement of IGA-CHE or a score of 0 to 1 (clear/almost clear).[12]

Efficacy and Safety of Sirolimus for Facial Angiofibromas

- Low-quality-evidence from one double-blind, randomized trial (n=62) showed that sirolimus improved response rate in people with angiofibroma after 12 weeks of treatment compared to placebo (60% in the sirolimus group vs. 0% with placebo; p<0.001).[13] A 6-category scale was used to evaluate changes in angiofibroma size and color with the following categories: markedly improved, improved, slightly improved, unchanged, slightly aggravated, and aggravated.[13] It is not clear how this scale was developed and validated.[14] There is insufficient evidence to evaluate whether sirolimus improves quality of life; the Dermatology Life Quality Index (DLQI) and Children's DLQI (CDLQI) were evaluated as secondary outcomes and neither outcome achieved statistical significance compared to placebo.[13]
- In a 104-week, open-label safety trial, the most common adverse reactions associated with sirolimus application were application site irritation (31%), dry skin (28%), acne (20%), pruritus (9%), eye irritation (9%), erythema (7%), acneiform dermatitis (6%), contact dermatitis (5%), solar dermatitis (1%), and photosensitivity reaction (1%).[15]

Expanded Indications and New Formulations

- In September 2025, ruxolitinib cream was FDA-approved for topical short-term and non-continuous chronic treatment of mild-to-moderate AD in non-immunocompromised patients aged 2 years and older.[16] The prescribing information recommends adults use no more than one 60 gram tube per week and in children no more than one 60 gram tube per 2 weeks.[16] Ruxolitinib cream should not be applied to more than 20% of body surface area (BSA).[16] Prior to this approval, ruxolitinib was FDA-approved for topical treatment of NSV and AD in patients aged 12 years and older.[16]
- A new formulation of roflumilast 0.05% cream received FDA-approval in October 2025. This product is indicated for topical treatment of mild-to-moderate AD in pediatric patients aged 2 to 5 years of age.[17]
- In May 2025, roflumilast 0.3% topical foam received an expanded indication for treatment of PsO in patients at least 12 years of age.[18] Prior to this expanded indication, roflumilast 0.3% foam was FDA-approved for the treatment of seborrheic dermatitis in patients at least 9 years of age.[18]
- Roflumilast 0.15% cream was FDA-approved in July 2024 for the treatment of mild-to-moderate AD in people aged 6 years of age and older.[17] Prior to this approval, roflumilast 0.3% cream was FDA-approved for topical treatment of PsO in patients aged 6 years and older.[17]
- Tapinarof cream received an expanded FDA-approved indication for the topical treatment of AD in adults and children aged 2 years and older in December 2024.[19] Prior to this approval, tapinarof was FDA-approved for the topical treatment of PsO in adults.[19]

Recommendations:

- Revise prior authorization (PA) criteria for the "Topical Agents for Inflammatory Skin Conditions" to include expanded indications for ruxolitinib cream, ruxolitinib foam, roflumilast cream, sirolimus gel, and tapinarof cream.
- Maintain delgocitinib cream and make sirolimus topical gel non-preferred on the preferred drug list (PDL).
- After review of drug costs in executive session, no changes to the PDL were recommended.

Summary of Prior Reviews and Current Policy

- The Pharmacy and Therapeutics (P & T) committee reviewed the topical agents for inflammatory skin conditions at the December 2022 meeting. The PA criteria for "Topical Agents for Inflammatory Skin Conditions" were revised to include use of ruxolitinib in patients aged 12 years and older for those meeting Health Evidence Review Commission (HERC) guidance for severe nonsegmental vitiligo (NSV) or those having hand, foot, face, or mucous membrane involvement. Topical roflumilast and tapinarof were designated as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP). The PA criteria were revised to include roflumilast and tapinarof and limit their use to:
    - Individuals meeting HERC guidance for severe PsO or those having hand, foot, face, or mucous membrane involvement and,
    - FDA-approved ages (12 years or greater for roflumilast or age of 18 years or greater for tapinarof) and,
    - History of inadequate response to at least 2 moderate-to-high potency TCS for at least 4 weeks.
- After evaluation of costs in the executive session, tazarotene gel was designated as nonpreferred.
- The PDL status for topical medications used for inflammatory skin conditions is provided in **Appendix 1.** Calcipotriene and calcipotriene/betamethasone are designated as preferred topical agents on the PMPDP and do not require PA authorization. Both TCIs used to treat atopic dermatitis (pimecrolimus and tacrolimus) are preferred but require PA to ensure appropriate utilization in FDA-approved populations (**Appendix 8**). Non-preferred topical agents include anthralin, calcitriol, coal tar, crisaborole, tazarotene, and ruxolitinib, which require PA to ensure appropriate utilization in inflammatory skin conditions funded by HERC.

Background:

Atopic Dermatitis

Atopic dermatitis or eczema is a chronic skin disorder characterized by pruritus, recurrent lesions, and inflammation with a relapsing and remitting pattern.[20] The cause is unknown, but may be due to genetics or immunologic dysfunction.[21] Many patients with AD also have allergic asthma, allergic rhinoconjunctivitis, food allergies, or other immediate hypersensitivity (type 1) allergies.[22] Although it may affect all age groups, AD is most common in children. The disease affects 15-20% of children in developed countries.[23] Estimated prevalence of AD for adults in the United States (U.S.) is 10%.[23] Both sexes are affected, and the prevalence varies among races and ethnic groups.[24] For example, in the U.S., the prevalence is higher among Black children (19.3%) than among White children (16.1%).[25] Onset of AD is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the condition during the first year of life and 90% by the age of 5 years.[26] Atopic dermatitis can persist into adulthood in about one-third of affected individuals.[27] Itching, sleep deprivation, and social embarrassment due to visible lesions can have substantial effects on the quality of life in people with AD.

Therapy for AD is selected according to the clinical stage of disease (mild, moderate, or severe), the extent and location of body surface area (BSA) 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.[28,29] The National Institute for Health and Care Excellence (NICE) has developed an assessment for the severity of atopic dermatitis as outlined in Table 1.

Table 1. **NICE Holistic Assessment of Atopic Eczema**[30]

Skin Description	**Physical Severity**	**Impact on Quality of Life and Psychosocial Wellbeing**
Clear	Normal skin, no evidence of active AD	No impact on quality of life
Mild	Areas of dry skin, infrequent itching (with or without small areas of redness).	Little impact on everyday activities, sleep, and psychosocial wellbeing

Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening).	Moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep.
Severe	Widespread areas of dry skin, incessant itching, redness (with or with excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation).	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep.
Abbreviations: AD = atopic dermatitis; NICE = National Institute for Health and Care Excellence		

For all AD 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 TCS or a TCI as needed.[21] The use of TCS and TCI therapies in AD is supported by The American College of Dermatology's 2014 guideline.[31] Topical corticosteroids are recommended for individuals who have failed to respond to good skin care and regular use of emollients alone. However, prolonged use of TCS can result in telangiectasia, increased hair, skin tears, easy bruising, poor wound healing, acne, rosacea, and atrophic skin changes, which can be permanent.[32] TCIs are a second-line option in both adults and children with AD who have not responded to TCS therapy or when those treatments are not advisable.[32] Unlike TCS, TCIs do not cause skin atrophy and are, therefore, of particular value in delicate skin areas such as the face, neck, and skin folds. Side effects to TCIs include application site pain, which may be more frequent compared to other topical preparations. FDA labeling for tacrolimus and pimecrolimus also includes boxed warnings regarding a theoretical risk for skin cancers and lymphoma associated with long-term TCI administration.[33,34] Additional agents FDA-approved for AD include topical PDE-4 inhibitors, JAK inhibitors, and aryl hydrocarbon receptor agonists (see **Table 3**).

Another topical JAK inhibitor, delgocitinib, recently received FDA approval for management of moderate-to-severe chronic hand eczema in adults.[10] Hand eczema that persists for more than 3 months or recurs 2 or more times within a 12-month time frame is considered chronic.[35] The condition is characterized by extremely itchy, painful, inflamed, dry scaly patches of skin on the hands and wrist that can flake, crack, and bleed.[35] These symptoms can impact quality of life and the ability to complete activities of daily living. Chronic hand eczema is often associated with occupations that involve frequent hand washing, exposure to chemicals, or working in wet environments including health care workers, food handlers, dental technicians, metal workers, cleaners, florists, and hairdressers.[35] Other risk factors include development of AD in childhood, persistent/severe AD, cold/dry weather conditions, and decreased indoor humidity.[35] Chronic hand eczema can be sub-classified as irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema, vesicular hand eczema, hyperkeratotic eczema, and protein contact dermatitis/contact urticaria.[35] The 1-year prevalence of hand eczema is at least 9.1% in the general global population (6.4% in men and 10.5% in women).[36]

The European Society of Contact Dermatitis guidance (2021) recommends the use of protective gloves, hand washing in lukewarm (not hot) water, switching from hand washing with soap to alcohol disinfection when hands are not visibly dirty (as alcohol is less irritating than soap), thoroughly rinsing and drying hands after washing, and application of emollients to prevent hand eczema.[35] Initial treatment for moderate-to-severe hand eczema is short-term use of TCS or tacrolimus ointment.[35] Patients with severe or recalcitrant hand eczema that does not respond to TCS may require systemic therapies, including oral corticosteroids, oral immunosuppressants, retinoids or phototherapy.[35]

Symptom scores are designed to specifically assess improvement in chronic hand eczema symptoms (itching, pain, redness, scaling, edema) and are presented in **Table 2**.

Table 2. Assessments for Treatment of Chronic Hand Eczema

Tool	Description
Hand Eczema Severity Index (HECSI)[37,38]	The HECSI is a clinician assessment that evaluates the extent and severity of hand eczema symptoms. Scoring ranges from 0 (clear) to 360 (severe) based upon location involvement and severity of erythema, induration/papulation, vesicles, fissures, scaling and edema. HECSI-75 denotes 75% improvement in the HECSI score from baseline, which is considered clinically significant.
Investigators Global Assessment of Chronic Hand Eczema (IGA-CHE)[39]	IGA-CHE is a clinician assessment for severity of the subject's global disease stage at a given time point and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). Scoring is based upon intensity of erythema, scaling, hyperkeratosis, vesiculation, edema, and fissures.
Hand Eczema Symptom Diary (HESD)[40,41]	The HESD is a 6-item patient-reported instrument designed to assess the severity of chronic hand eczema. Six signs and symptoms (itch, pain, cracking, redness, dryness, and flaking) over the previous 24 hours are rated on an 11-point scale (0 = no symptoms and 10 = severe symptoms). Total score is an average of the 6 signs and symptoms.
Hand Eczema Symptom Diary (HESD) Itch Score[10]	The HESD is a patient-reported instrument to assess itching severity associated with chronic hand eczema over the previous 24 hours. Itch severity is rated on an 11-point scale (0 = no itching and 10 = severe itching).
Hand Eczema Symptom Diary (HESD) Pain Score[10]	The HESD is a patient-reported instrument to assess pain severity associated with chronic hand eczema over the previous 24 hours. Pain severity is rated on an 11-point scale (0 = no pain and 10 = severe pain).

Clinical studies have utilized several scales for defining the severity of AD, including the Scoring Atopic Dermatitis (SCORAD) scale, Eczema Area and Severity Index (EASI), and Investigators Global Assessment (IGA).[22] The SCORAD has been validated for content and construct validity, interobserver reliability, and sensitivity to change in 26 different publications.[42] The SCORAD tool incorporates clinician estimates of disease extent and severity and subjective patient assessment of itching and sleep loss.[43] 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).[43] 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).[43]

The EASI was adapted from the Psoriasis Area and Severity Index in 1998.[42] The EASI assesses severity and body surface area affected by AD including erythema, induration, papulation, excoriations, and lichenification.[44] Each symptom is graded in 4 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.[44] An EASI score of 7 or lower indicates mild disease, 8 to 21 moderate disease, 22 to 50 severe disease, and 51 to 72 very severe disease.[22] EASI outcomes are measured as a percentage improvement in EASI score from baseline as EASI 50, 75, or 90.

The IGA is a clinician-reported outcome measure used to evaluate severity of AD at a given point in time.[45] 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."[46] 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.[45] 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).

Plaque Psoriasis

Plaque psoriasis (PsO) is a chronic, immune-mediated inflammatory disorder of the skin which affects about 3% of the U.S. adult population.[47] Plaque psoriasis is characterized by erythematous scaly patches or plaques that occur commonly on extensor surfaces, but it can also affect the intertriginous areas, palms, soles of the feet, and nails.[48] The onset generally occurs between 20 and 30 years of age.[47] Approximately 1% of children are affected by psoriasis, typically with onset during adolescence.[49] A 2020 population-based cross-sectional study sampled the U.S. civilian population and estimated psoriasis prevalence as highest in White individuals at 3.6%, followed by other racial/ethnic groups (non-Hispanic, including multiracial) at 3.1%, Asian individuals at 2.5%, Hispanic individuals (including Mexican American and other Hispanic individuals) at 1.9%, and Black individuals at 1.5%.[47]

The development of psoriasis is complex and appears to be influenced by many factors, including genetic changes, local trauma, infections, certain drugs (such as beta-blockers, lithium, chloroquine, and non-steroidal anti-inflammatory drugs), endocrine factors, sunlight, alcohol, smoking, and stress.[50] Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 5% of BSA and has little to no impact on quality of life or function.[48] Mild PsO is not a funded condition per HERC Guideline Note 21.[51] An estimated 20% of patients with PsO have moderate-to-severe disease, defined as greater than 10% of BSA.[47]

According to the 2021 American Academy of Dermatology/National Psoriasis Foundation (AAD/NPF) guidance, first-line topical agents to treat mild-to-moderate PsO include: TCS, anthralin, vitamin D analogues (e.g., calcipotriene, calcitriol), retinoids (e.g., tazarotene), TCIs, or salicylic acid.[52] Recently approved topical agents for treatment of PsO include roflumilast and tapinarof.[17,19] The relative efficacy of roflumilast and tapinarof compared with TCS regimens is unclear. High potency TCS are usually prescribed for the initial treatment of plaques in sites at low risk for corticosteroid-induced skin atrophy (e.g., nonfacial, no intertriginous plaques) because of their rapid efficacy and wide availability. Moderate-to-severe PsO may need to be treated with systemic TIMs including PDE-4 inhibitors, tumor necrosis factor (TNF) inhibitors, interleukin (IL)-12/23 antagonists, IL-23 antagonists, or IL-17 antagonists.[53] The TIMs may be added for patients with moderate-to-severe PsO not controlled by other therapies.[53]

In clinical trials assessing treatments for PsO, symptom improvement is often evaluated using the Psoriasis Area and Severity Index (PASI). The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head, arms and legs, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[54,55] It does not consider symptoms affecting hands, feet, face or genitals. Because the PASI scale is not linear, small changes in BSA involvement can result in a significant improvement of the overall score without change in other symptoms.[54] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, an improvement of 100%, indicating complete disease clearance, is considered more clinically significant.[55] This tool is rarely used in clinical practice to assess psoriasis severity due to the substantial amount of time required to complete the scoring.[52] The Physician Global Assessment (PGA) is a scoring system that assesses degree of erythema, induration, and scaling.[52] There are several different versions of the PGA, with most severity scores ranging from 0 to 4 or 0 to 5.[52] Higher scores indicate more severe disease. The PGA is also used in research, but not frequently used in clinical practice.[52] The Investigator Global Assessment (IGA) has also been used to measure the severity of PsO based on skin thickening and hyperpigmentation in clinical trials.[56] Similar to the PGA, the IGA is a 5 point scale ranging from 0 (clear), 1 (almost clear), 2 (mild symptoms), 3 (moderate symptoms) to 4 (severe symptoms).[56] Response to therapy is indicated by an IGA score of 0 or 1 plus at least a 2-grade improvement from baseline.[56]

Vitiligo

Vitiligo is a chronic autoimmune disorder and is the most frequent cause of skin depigmentation worldwide with an estimated global prevalence of 1%.[57] It usually begins after birth and has an average age of onset of about 20 years.[58] This condition can be psychologically devastating and stigmatizing, especially in dark skinned individuals.[57] Vitiligo is clinically characterized by the development of white macules due to the loss of functioning melanocytes in the skin or hair,

or both.[57] Two forms of the disease are recognized: segmental vitiligo (SV) and NSV.[59] Non-segmental vitiligo is characterized by symmetrical and bilateral white patches.[57] The most commonly affected sites are the fingers, wrists, axillae, groin, mouth, eyes and genitalia.[60] Different NSV clinical subtypes have been described, including generalized, mucosal, acrofacial, and universal, all with a bilateral distribution.[57] In contrast, SV is less common than NSV and usually has asymmetrical, one-sided or band-shaped distribution.[57] Segmental vitiligo accounts for 5–16% of overall vitiligo cases and tends to occur at a younger age, before age 30 years in 87% of cases and before age 10 years in 41% of cases.[57]

Many studies support the association of vitiligo with thyroid disorders and other associated autoimmune diseases, such as rheumatoid arthritis, psoriasis, adult-onset diabetes mellitus, Addison's disease, pernicious anemia, alopecia areata, and systemic lupus erythematosus.[57] Almost one-third of people with vitiligo have a positive family history of the disease.[57] Several corresponding relevant genes associated with both vitiligo and other pigmentary, autoimmune and autoinflammatory disorders have now been identified.[61] They are involved in immune regulation, melanogenesis and apoptosis.[61]

The diagnosis of vitiligo is based upon the finding of acquired, amelanotic, non-scaly, chalky-white macules with distinct margins in a typical distribution: periorificial, lips and tips of distal extremities, penis, segmental and areas of friction.[61] The diagnosis of vitiligo does not usually require confirmatory laboratory tests.[61] A skin biopsy or other tests are not necessary except to exclude other disorders.[61] The diagnosis of vitiligo may be facilitated by the use of a Wood's lamp, a hand-held ultraviolet irradiation device that emits ultraviolet A rays.[61] It helps identify focal melanocyte loss and detect areas of depigmentation that may not be visible to the naked eye, particularly in pale skin.[61] Under the Wood's light, the vitiligo lesions emit a bright blue-white fluorescence and appear sharply demarcated.[61]

Treatment of vitiligo aims to halt disease spread and facilitate repigmentation.[62] Choice of treatment depends on several factors including: the subtype of the disease, the extent, distribution and activity of disease as well as the patient's age, phototype, effect on quality of life and motivation for treatment.[61] The face, neck, trunk and mid-extremities respond best to therapy, while the lips and distal extremities are more resistant to treatment.[61] The 2021 British Association of Dermatologists (BAD) guidance recommends high potency or very high potency TCS or topical tacrolimus as first-line treatment.[63] Commonly prescribed TCS include betamethasone dipropionate, betamethasone valerate, clobetasol dipropionate and fluticasone propionate.[63] Use of TCS or tacrolimus ointment to treat vitiligo is off-label.[64] Topical tacrolimus, as monotherapy or in combination with phototherapy, is just as effective as TCS therapy but has a safer side-effect profile.[63] Second-line treatments consist of narrowband ultraviolet B or psoralen ultraviolet A phototherapy and systemic steroid treatment.[63] Third-line treatment consists of surgical grafting techniques.[63] Despite the autoimmune nature of vitiligo, there is insufficient evidence to support the use of immunosuppressive therapies in managing vitiligo.[63] Phototherapy has been a mainstay of treatment for vitiligo for several years.[58] Phototherapy is typically administered 3 times per week and is more effective if initiated early on in the disease.[65] It is used as first-line therapy in extensive disease. It can be used in combination with TCS or topical tacrolimus.[63] The JAK inhibitor, ruxolitinib 1.5% cream, is FDA-approved for the treatment of nonsegmental vitiligo in patients aged 12 years and older.[16]

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an inherited neurocutaneous disorder of cellular proliferation with produces benign tumors that affect the skin.[66] Brain involvement in people with TSC may be associated with seizures, cognitive deficits, and neurodevelopmental disorders including autism.[14] This condition arises due to mutations in either the TSC1 or TSC2 genes, which are responsible for overactivation of the mammalian target of rapamycin (mTOR) protein, which gives rise to noncancerous growths in multiple organs.[67,68] It is estimated the TSC affects approximately 1 per 6,000 to 10,000 individuals.[66] Males and females are affected in equal numbers, and the disorder occurs in all races and ethnic groups.[14] Expression of the disease varies substantially among individuals and within

families.[14] Some individuals with TSC may demonstrate only dermatologic features, while others may develop more serious neurologic or systemic manifestations.[68]

The dermatologic features of TSC include hypopigmented macules, angiofibromas, Shagreen patches, and fibrous forehead plaques.[14] Angiofibromas begin to appear as early as within the first 2 years of life, and by adolescence angiofibromas are present in approximately 80% of patients with TSC.[14] The lesions may begin as erythematous macules and then mature into pink to red, or red to brown, papules or papulonodules, which may coalesce into plaques.[14] Angiofibromas typically develop over the central face and cheeks and may cause hemorrhage, obstruction of facial orifices, and disfigurement, which can lead to emotional distress.[14] When not prominent, the skin lesions do not require treatment. However, closer surveillance and intervention is recommended for skin lesions that rapidly change in size or number and for those that cause pain, bleeding, functional impairment, or social problems.[14]

Rapidly changing, disfiguring, or symptomatic TSC-associated skin lesions should be treated as appropriate for the lesion and clinical context, using approaches such as surgical excision, cryotherapy, dermabrasion, laser treatments, or application of a topical mTOR inhibitor (sirolimus).[66] The surgical and laser procedures may be performed several times to reduce recurrence of the lesions, may be painful, and may have poor treatment outcomes due to lesion recurrence and scarring.[67] Larger angiofibromas may be recalcitrant to topical treatment and may benefit from laser therapy.[69] Some clinicians have suggested that topical sirolimus may be effective as pretreatment for larger fibrous angiofibromas to reduce the aggressiveness of ablative therapy.[69] Due to the rarity of TCS, the evidence for the standard of care for treating facial angiofibromas is limited, and no guidelines have been published.

Sirolimus, also known as rapamycin, is a naturally occurring macrolide antifungal and mTOR inhibitor.[67] The oral formulation of sirolimus (RAPAMUNE) was approved by the FDA for prophylaxis of organ rejection in 1999.[70] Topical sirolimus has been studied in a range of concentrations for the treatment of angiofibromas in tuberous sclerosis and has been prescribed or compounded “off-label” since 2006.[67] More details about the FDA approval of the 0.2% gel formulation of sirolimus are presented below. The Oregon Health Evidence Review Commission recommends that treatment of hemangiomas of the skin and subcutaneous tissue are funded when they are ulcerated, infected, currently hemorrhaging, or function-threatening (e.g., eyelid hemangioma) as outlined in Guideline Note 13.[71] Otherwise, hemangiomas are not funded.[71] HERC will be assessing the inclusion of angiofibromas in Guideline Note 13 at their December meeting.

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

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

Systematic Reviews:

Cochrane: Topical Anti-Inflammatory Treatments for Eczema

A 2024 Cochrane systematic review and NMA evaluated the efficacy and safety of topical anti-inflammatory eczema treatments.[1] Literature was searched through June 2023 and 291 RCTs (n=45,846) met inclusion critiera.[1] Participants had eczema that was not clinically infected and was not diagnosed as contact dermatitis, seborrheic eczema, or hand eczema.[1] Interventions included topical anti-inflammatory treatments (i.e., TCS, TCI, JAK inhibitors, PDE-4 inhibitors, and tapinarof).[1] The non-TCS, FDA-approved topical anti-inflammatory agents for management of eczema and AD are presented in **Table 3.** The TCS are classified as mild, moderate, potent or very potent. A summary of TCS classified by potency is presented in **Table 4**.

RCTs included in the systematic review compared therapies to no treatment/vehicle or another topical anti-inflammatory agent.[1] Primary outcomes included the clinician assessments: EASI, SCORAD, and IGA and patient-reported symptoms of eczema.[1] Secondary outcomes included health-related quality of life (QoL) based upon the Dermatology Life Quality Index (DLQI), long-term control of eczema, local adverse effects (application site reactions, pigmentation changes, skin thinning/atrophy), and withdrawal due to adverse effects.[1]

Table 3. FDA-Approved Topical Agents for Inflammatory Skin Conditions[64]

Generic Drug Name	Brand Name	Mechanism of Action	Minimum Age	Indication (Severity)
Crisaborole 2% ointment	EUCRISA	PDE-4 Inhibitor	3 months	Atopic Dermatitis (Mild-to-Moderate)
Roflumilast 0.05% cream Roflumilast 0.15% cream Roflumilast 0.3% cream Roflumilast 0.3% foam Roflumilast 0.3% foam	ZORYVE	PDE-4 Inhibitor	2 to 5 years 6 years 6 years 9 years 12 years	Atopic Dermatitis (Mild-to-Moderate) Atopic Dermatitis (Mild-to-Moderate) Plaque Psoriasis Seborrheic Dermatitis Plaque Psoriasis
Delgocitinib 2% cream	ANZUPGO	JAK Inhibitor	18 years	Chronic Hand Eczema (Moderate-to-Severe)
Ruxolitinib 1.5% cream	OPZELURA	JAK Inhibitor	12 years 12 years	Atopic Dermatitis (Mild-to-Moderate) Nonsegmental Vitiligo
Pimecrolimus 1% cream	ELIDEL	TCI	2 years	Atopic Dermatitis (Mild-to-Moderate)
Tacrolimus 0.03% ointment	PROTOPIC	TCI	2 years	Atopic Dermatitis (Moderate-to-Severe)
Tacrolimus 0.1% ointment	PROTOPIC	TCI	18 years	Atopic Dermatitis (Moderate-to-Severe)
Tapinarof 1% cream	VTAMA	Aryl Hydrocarbon Receptor Agonist	2 years 18 years	Atopic Dermatitis Plaque Psoriasis
Abbreviations: FDA = Food and Drug Administration; JAK = Janus kinase; PDE-4 = phosphodiesterase; TCI = topical calcineurin inhibitor				

Trials were mainly conducted in high-income countries (n=243) especially Europe and North America.[1] Adults were included in most of the RCTs with only 31 RCTs limited to children aged less than 12 years.[1] Male and female participants and multiple ethnic groups were present in most RCTs, but trials populations were mainly White participants.[1] Trials were primarily industry-funded (97%) and evaluated short-term (3 weeks) outcomes.[1] Most RCTs (89%) had a high risk of bias due to selective reporting, due to absence of prospective trial registration/protocol availability.[1] Other issues included insufficient information for allocation concealment, risk for contamination in within-participant trials, poor reporting of participants included in outcome analyses, exclusions from analysis for potentially inappropriate reasons such as adverse events, and trials with high proportions of randomized participants missing from analyses.[1] Certainty of evidence was assessed using the Confidence In Network Meta-Analysis (CINeMA) approach.[1] The CINeMA approach considers 6 domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.[72]

Patient-reported eczema symptoms were assessed in 40 RCTs (n=6,482) and most commonly reported a 4-point improvement in the Peak Pruritus Numerical Rating Scale (PPNRS).[1] High potency TCS (OR 5.99; 95% CI 2.83 to 12.69), tacrolimus 0.1% (OR 6.27; 95% CI 1.19 to 32.98), and ruxolitinib 1.5% (OR 5.64; 95% CI 1.26 to 25.25) were ranked as the most effective agents.[1] Mild potency TCS (OR 1.35; 95% CI 0.51 to 3.53), roflumilast 0.15% (OR 1.03; 95% CI 0.12 to 9.23), and crisaborole 2% (OR 1.15; 95% CI 0.17 to 7.71) were ranked as the least effective agents to relieve itching.[1] Confidence intervals were wide and overlapping for most comparisons, and CINeMA ratings were low except for roflumilast 0.15%, which was rated as moderate certainty of evidence.[1] Evidence certainty was downgraded for within-trial bias in all CINeMA ratings, and some were also downgraded for imprecision and heterogeneity.[1]

Clinician-reported eczema symptoms were reported in 32 RCTs (n=4,121) and commonly included EASI-75.[1] High potency TCS (OR 8.15; 95% CI 4.90 to 13.57), tacrolimus 0.1% (OR 8.06; 95% CI 3.30 to 19.67), ruxolitinib 1.5% (OR 7.72; 95% CI 4.92 to 12.10) and delgocitinib 0.5% (OR 7.61; 95% CI 3.72 to 15.58) were ranked as most effective agents to achieve EASI-75.[1] Mild TCS (OR 2.22; 95% CI 0.74 to 6.64), roflumilast 0.15% (OR 2.43; 95% CI 0.88 to 6.70), crisaborole 2% (OR 2.98; 95% CI 1.42 to 6.26) and tapinarof 1% (OR 2.45; 95% CI 1.00 to 6.02) were ranked as least effective agents.[1] Confidence intervals were wide and overlapping for most comparisons, but CINeMA ratings were moderate or high for most interventions.[1] CINeMA downgrades were most commonly made for within-trial bias, but also imprecision and heterogeneity.[1]

The NMA included 140 RCTs (n=23,383) which reported clear or almost clear eczema on a 6-point IGA (0 or 1, respectively).[1] High potency TCS (OR 5.00; 95% CI 3.80 to 6.58), medium potency TCS (OR 8.34; 95% CI 4.73 to 14.67), ruxolitinib 1.5%, (OR 9.34; 95% CI 4.80 to 18.18), delgocitinib 0.5% (OR 10.08, 95% CI 2.65 to 38.37), delgocitinib 0.25% (OR 6.87; 95% CI 1.79 to 26.33), and tacrolimus 0.1% (OR 5.06; 95% CI 3.59 to 7.13) were ranked as most effective agents to achieve clear or almost clear skin.[1] Mild potency TCS (OR 1.38; 95% CI 0.94 to 2.02), roflumilast 0.15% (OR 2.43; 95% CI 0.65 to 9.01), crisaborole 2% (OR 2.14; 95% CI 1.22 to 3.76), tacrolimus 0.03% (OR 3.53; 95% CI 2.60 to 4.80), and pimecrolimus 1% (OR 2.39; 95% CI 1.78 to 3.21) were ranked as least effective agents.[1] Confidence intervals were wide and overlapping for most comparisons, and CINeMA ratings were low or moderate for most interventions.[1] The CINeMA downgrades were most commonly made for within-trial bias.[1] In a sensitivity analysis of low risk of bias data (12 trials, n=1,639), potent TCS and the JAK inhibitors delgocitinib 0.5% and delgocitinib 0.25% ranked as most effective, while pimecrolimus 1%, and roflumilast 0.15%, were the least effective agents.[1]

The NMA included 83 trials (n=18,992) reporting tolerability events, burning, stinging and/or irritation reactions.[1] Tacrolimus 0.1% and 0.03%, pimecrolimus 1%, and crisaborole 2% were ranked as most likely to cause application site reactions.[1] The mild to medium potency TCS were least likely to cause application site reactions.[1] Confidence intervals were wide for most comparisons, and CINeMA ratings were low or moderate for most interventions, but high for crisaborole 2%.[1] CINeMA downgrades were most commonly made for within-trial bias and imprecision.[1]

The NMA included 25 trials (n=3,691; 36 events) reporting skin thinning, atrophy, striae and/or telangiectasia.[1] On these short-term trials there was no significant increase in odds of skin thinning/atrophy with mild to medium potency TCS, tacrolimus 0.1%, or pimecrolimus 1% compared with vehicle.[1] CINeMA ratings were low for all comparisons, due to within-trial bias and imprecision.[1] Longer-term data over 6 to 60 months for this outcome were insufficient for NMA but were reported for TCS versus TCI in 3 trials, showing an increase in long-term skin thinning with TCS (6 events in 2044 participants with TCS versus 0 events in 2025 participants with TCI; p = 0.031).[1] The 3 included trials evaluated high potency TCS versus tacrolimus 0.1% over 6 months follow-up, moderate potency TCS versus pimecrolimus 1% over 1-year follow-up and mild/medium potency TCS versus pimecrolimus 1% over 5 years follow-up.[1] The 3 trials were all funded by TCI manufacturers and included treatment of both facial and non-facial areas affected by eczema.[1] The trial authors did not comment on reversibility of the skin thinning changes nor did they provide details about location and nature of the identified changes.[1]

Due to insufficient data, an NMA was not possible for HRQoL, long-term symptom control or longer-term outcome assessment for any of the above outcomes.[1] The NMA of pigmentary changes (8 trials of TCS and a PDE-4 inhibitor, n=1,786; 3 events) did not show any significant increase in odds of pigmentation changes compared to vehicle, with low confidence for mild, medium or high potency TCS and moderate confidence for crisaborole 2%.[1] The NMA of withdrawal due to short-term adverse events (11 trials of TCS, TCI, JAK inhibitors and other interventions, n=2,404) did not show any significant increase in odds of withdrawal compared to vehicle with any intervention, with low confidence.[1] Long-term safety data is lacking.[1]

In summary, the NMA ranked potent and/or very potent TCS, tacrolimus 0.1% and ruxolitinib 1.5% among the most effective short-term treatments for improving patient-reported symptoms (40 trials, all low confidence) and clinician-reported signs (32 trials, all moderate confidence) of eczema.[1] For IGA assessment, ruxolitinib 1.5%, delgocitinib 0.5% or 0.25%, high/medium potency TCS and tacrolimus 0.1% were ranked as most effective (140 trials, all moderate confidence).[1] Local application site reactions were most common with tacrolimus 0.1% (moderate confidence) and crisaborole 2% (high confidence) and least common with TCS (moderate confidence).[1] Skin thinning was not increased with short-term use of any TCS potency (low confidence), but skin thinning was reported in 6/2044 (0.3%) participants treated with longer-term TCS (over 6–60 months).[1] Data from almost 300 trials suggest that high potency TCS, JAK inhibitors and tacrolimus 0.1% are among the most effective topical treatments for eczema.[1] Local reactions were most common with tacrolimus 0.1% and crisaborole and least common with TCS.[1]

Topical Treatments for Atopic Dermatitis

A 2023 systematic review and NMA provided the basis for development of AAAAI/ACAAI Joint Task Force 2022 guidance on management of AD.[2] Literature was searched through September 5, 2022 for RCTs addressing topical therapies to manage AD.[2] Of the 219 included RCTs (n=43,123), 156 included children, 59 included only adults, 67 included both children and adults, and 4 did not report age data.[2] The mean age was 18.5 years (range of means 0.35-49 years), and a median 53% were female (range of proportions 0-78%); most studies addressed patients with mild-to-moderate AD.[2] Individual outcomes of most studies had low risk of bias.[2] Limitations from missing outcome data were the most frequent issue.[2] Interventions of interest included TCS, TCIs, JAK inhibitors, PDE-4 inhibitors), antibiotics, prescription moisturizers, and tapinarof.[2] The TCS were stratified by U.S. classification of potency with TCS groups 1 and 2 classified as super-high and high potency, TCS groups 3, 4, and 5 classified as medium potency, and TCS groups 6 and 7 classified as low potency (see **Table 4** for specific TCS products).[2]

Table 4. Potency Of Topical Corticosteroid Preparations Using United States Classification[3]

Potency Group	Corticosteroid	Strength	Formulation
Lowest Potency (Group 7)	Hydrocortisone Base and Hydrocortisone Acetate	0.5%, 1.0%, 2.0%	cream, ointment, gel, lotion, solution
Low Potency (Group 6)	Alcometasone dipropionate	0.05%	cream, ointment
	Betamethasone valerate	0.05%	lotion
	Desonide	0.05%	cream
	Fluocinolone acetonide	0.01%	cream, oil, shampoo, solution
	Triamcinolone acetonide	0.1%	cream
Medium-Low Potency (Group 5)	Betamethasone dipropionate	0.05%	lotion
	Betamethasone valerate	0.1%	cream
	Betamethasone valerate	0.01%	cream, lotion
	Desonide	0.05%	lotion, ointment
	Fluocinolone acetonide	0.025%	cream

	Flurandrenolide	0.05%	cream
	Fluticasone propionate	0.05%	cream
	Hydrocortisone butyrate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Prednicarbate	0.1%	cream
	Triamcinolone acetonide	0.1%	lotion
Medium Potency (Group 4)	Betamethasone valerate	0.12%	foam
	Desoximetasone	0.05%	cream
	Fluocinolone acetonide	0.025%	ointment
	Fluocinolone acetonide	0.2%	cream
	Flurandrenolide	0.05%	ointment
	Halcinonide	0.025%	cream
	Hydrocortisone probutate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Mometasone furoate	0.1%	cream, lotion, solution
	Prednicarbate	0.1%	ointment
Medium-High Potency (Group 3)	Amcinonide	0.1%	cream, lotion
	Betamethasone valerate	0.1%	ointment
	Diflorasone diacetate	0.05%	cream
	Fluocinonide	0.05%	cream
	Fluticasone propionate	0.005%	ointment
	Halcinonide	0.1%	ointment, solution
	Triamcinolone acetonide	0.5%	cream
	Triamcinolone acetonide	0.1%	ointment
High Potency (Group 2)	Amcinonide	0.1%	ointment
	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	cream, lotion
	Betamethasone dipropionate, unaugmented (Diprosone®)	0.05%	cream, ointment
	Desoximetasone	0.25%	cream, ointment, spray
	Desoximetasone	0.05%	gel
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.05%	cream, gel, ointment, solution
	Halcinonide	0.1%	cream
	Mometasone furoate	0.1%	ointment
	Triamcinolone acetonide	0.5%	ointment
Super-High Potency (Group 1)	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	gel, ointment
	Clobetasol propionate	0.05%	cream, foam, gel, lotion, ointment, shampoo, spray
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.1%	cream
	Flurandrenolide	4 mcg/cm^2	tape
	Halobetasol propionate	0.05%	cream, ointment

A total of 187 RCTs (n=34,926) assessed the effects of topical interventions on AD severity compared with placebo or standard care.[2] The NMA results are presented using SCORAD results (0-103, higher score indicates greater severity):

- Most effective: Group 1 TCS (mean difference [MD] -17.81; CrI -21.32 to -14.30; high certainty evidence).[2]
- Intermediate superior efficacy: high-dose tacrolimus (MD −13.05; 95% CrI −15.15 to −10.95; high-certainty evidence), TCS group 2 (MD −13.82; 95% CrI −18.74 to −8.89; high-certainty evidence), TCS group 3 (MD −11.57; 95% CrI −14.80 to −8.37; high-certainty evidence), and TCS group 4 (MD −12.26; 95% CrI −15.02 to −9.50; high-certainty evidence).[2]
- Intermediate inferior efficacy: pimecrolimus (MD −7.23; 95% CrI −8.76 to −5.72; high-certainty evidence), low-dose tacrolimus (MD −9.38; 95% CrI −11.22 to −7.55; moderate-certainty evidence), TCS group 5 (MD −8.46; 95% CrI −10.90 to −6.03; high-certainty evidence), TCS group 6/7 (MD −4.68; 95% CrI −7.10 to −2.29; moderate-certainty evidence), combination TCS group 5 and pimecrolimus (MD −10.45; 95% CrI −18.64 to −2.20; moderate-certainty evidence), combination TCS group 5 and tacrolimus (MD −10.22; 95% CrI −19.01 to −1.33; low-certainty evidence), delgocitinib (MD −9.98; 95% CrI −13.81 to −6.15; high-certainty evidence), ruxolitinib (MD −4.82; 95% CrI −5.65 to −4.00; high-certainty evidence), and crisaborole (MD −4.89; 95% CrI −8.69 to −1.08; high-certainty evidence).[2]
- Not effective: topical antibiotics (MD −1.48; 95% CrI −6.77 to 3.81; moderate certainty evidence) and prescription moisturizers (MD −1.94; 95% CrI −4.83 to 0.95; low certainty evidence).[2]

A total of 100 RCTs (n=19,685) evaluated itch severity.[2] The NMA results are presented as measured using a numeric rating scale (0-10, higher score indicates greater severity).[2] High-certainty evidence showed that high-dose tacrolimus (MD −2.27; 95% CrI −2.84 to −1.70), TCS group 2 (MD −3.39; 95% CrI −5.02 to −1.76), TCS group 3 (MD −2.37; 95% CrI −3.18 to −1.57), TCS group 4 (MD −2.62; 95% CrI −3.26 to −1.98), and TCS group 5 (MD −2.09; 95% CrI −2.54 to −1.64) were among the most effective interventions.[2] Other interventions were of lower effectiveness or certainty.[2]

A total of 15 RCTs (n=3,801) evaluated sleep disturbance.[2] Results are presented based on a 10-point numeric rating scale with higher score indicating greater sleep disturbance.[2] High-certainty evidence showed that pimecrolimus (MD −2.13; 95% CrI −3.15 to −1.01) was the most effective intervention.[2] No trials investigating tacrolimus, crisaborole, delgocitinib, or prescription moisturizers evaluated sleep disturbance.[2] Other interventions were of lower effectiveness.[2]

A total of 33 RCTs (n=8,170) evaluated eczema QoL using the DLQI (0-30, higher score indicates greater impairment to eczema QoL).[2] High-certainty evidence showed that delgocitinib (MD −7.41; 95% CrI −10.16 to −4.66) was the most effective intervention.[2] High-dose tacrolimus (MD −3.65; 95% CrI −5.59 to −1.83; high-certainty evidence), TCS group 4 (MD −5.96; 95% CrI −8.53 to −3.56; moderate-certainty evidence), and ruxolitinib (MD −4.82; 95% CrI −6.35 to −3.44; high-certainty evidence) were among those with intermediate superior effectiveness.[2] Other interventions were of lower effectiveness.[2]

A total of 44 RCTs (n=13,557) evaluated reduction of flares.[2] Moderate- or high-certainty evidence showed that tacrolimus (odds ratio [OR] 0.25; 95% CrI 0.10 to 0.54; risk difference: 70 fewer per 1000 patients; 95% CrI 85 to 41 fewer), pimecrolimus (OR 0.42; 95% CrI 0.29 to 0.57 risk difference: 53 fewer per 1000; 95% CrI 66 to 39 fewer), TCS group 5 (OR 0.12; 95% CrI 0.03 to 0.38; risk difference: 83 fewer per 1000; 95% CrI 92 to 57 fewer), and prescription moisturizers (OR 0.35; 95% CrI 0.13 to 0.94; risk difference: 60 fewer per 1000; 95% CrI 82 to 5 fewer) were among the most effective agents to decrease the number of patients experiencing flares.[2] Other interventions were of lower effectiveness or lower certainty.[2]

A total of 130 RCTs (n=32,200) evaluated adverse events.[2] There was high-certainty evidence that people prescribed TCS group 4 (OR 0.67; 95% CrI 0.44 to 0.99; risk difference: 76 fewer per 1000; 95% CrI 142 to 1 fewer) and TCS group 5 (OR 0.58; 95% CrI 0.46 to 0.73; risk difference: 102 fewer per 1000; 95% CrI 138 to 63 fewer) experienced the fewest adverse events.[2] JAK inhibitors (OR 0.83; 95% CrI 0.62 to 1.12; risk difference: 37 fewer per 1000; 95% CrI 93 fewer to 25 more),

pimecrolimus (OR 1.10; 95% CrI 0.93 to 1.31; risk difference: 21 more per 1000; 95% CrI 15 fewer to 59 more), and tacrolimus (OR 1.14; 95% CrI 0.92 to 1.42; risk difference: 29 more per 1000; 95% CrI 18 fewer to 79 more) were not different from control (moderate-certainty evidence).[2] All other interventions were of lower-certainty evidence.[2] Skin infections (bacterial, viral, or overall) as an adverse event were seldom reported and based on low- to very low–certainty evidence.[2]

A total of 115 RCTs (n=30,483) evaluated adverse events leading to discontinuation.[2] There was moderate-certainty evidence that TCS group 1 (OR 0.09; 95% CrI 0.02 to 0.33; risk difference: 25 fewer per 1000; 95% CrI 27 to 18 fewer) and the JAK inhibitors (OR 0.22; 95% CrI 0.10 to 0.47; risk difference: 21 fewer per 1000; 95% CrI 25 to 15 fewer) had the fewest number of patients experiencing adverse events leading to discontinuation.[2] Pimecrolimus (OR 0.61; 95% CrI 0.41 to 0.91; risk difference: 11 fewer per 1000 patients; 95% CrI 16 to 3 fewer), tacrolimus (OR 0.43; 95% CrI 0.30 to 0.62]; risk difference: 15 fewer per 1000; 95% CrI 19 to 10 fewer), and TCS group 5 (OR 0.32; 95% CrI 0.16 to 0.57; risk difference: 18 fewer per 1000; 95% CrI 23 to 12 fewer) were among those with intermediate effect in reducing the number of patients experiencing adverse events leading to discontinuation based on moderate or high-certainty evidence.[2] Other interventions were of lesser effect or lower-certainty evidence.[2]

In summary, for individuals with AD, pimecrolimus, tacrolimus, and moderate-potency TCS are among the most effective in improving and maintaining multiple AD outcomes.[2] Crisaborole was intermediately effective, but with uncertain harm due to low-quality evidence.[2] Topical antibiotics may be among the least effective agents for managing AD.[2] The TCS group 1 was among the best in improving AD severity; tacrolimus (high dose) and TCS groups 2 to 5 were among the best in improving itch severity; pimecrolimus was among the best in improving sleep disturbance; and delgocitinib was among the best in improving eczema-related QoL.[2]

Cancer Risk with Topical Calcineurin Inhibitors for Atopic Dermatitis

A 2023 systematic review and meta-analysis evaluated cancer associated with TCI administration (pimecrolimus and tacrolimus) as part of the 2022 AAAAI/ACAAI guidance update for AD.[3] Literature was searched through June 6, 2022 for RCTS and observational studies that addressed cancer risk in patients with AD using TCIs.[3] The authors identified 110 studies, including 52 RCTs and 60 observational trials, including 3.4 million patients followed for a mean of 11 months (range 0.7 to 120).[73] The absolute risk of any cancer with TCI exposure was not different from controls (absolute risk 4.70 per 1000 with TCI vs. 4.56 per 1000 without; OR 1.03; 95% CrI 0.94 to 1.11; moderate certainty).[3] For all age groups and using data from observational studies and RCTs, the use of pimecrolimus (OR 1.05; 95% CrI 0.94 to 1.15) or tacrolimus (OR 0.99; 95 % CrI 0.89 to 1.09) is likely to have had little to no association with cancer compared with no TCI exposure.[3] For pimecrolimus versus tacrolimus, the finding was similar (OR 0.95; 95% CrI 0.83 to 1.07).[3] Findings were similar in infants, children, and adults, and robust to trial sequential, subgroup, and sensitivity analyses.[3] The authors concluded that among individuals with AD, moderate-certainty evidence shows that TCIs do not increase the risk of cancer.[3]

After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses),[74-76] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force: Atopic Dermatitis Guidance
In 2022, a Joint Task Force comprised of AAAAI and ACAAI members updated 2012 guidance for management of AD in infants, children, and adults.[4] Although moisturization alone may achieve this goal in the mildest of patients, and can help improve AD severity and time-to-flare in those with more severe disease, almost all patients will require a prescription anti-inflammatory treatment including TCS, TCIs, or the topical PDE-4 inhibitor, crisaborole. Ruxolitinib, a topical JAK inhibitor, is not recommended by the task force panel.[4] The task force concluded that there insufficient evidence to assess whether topical ruxolitinib reduces AD flares due to imprecision and the short-term (4-8 weeks) nature of the available studies.[4] Overall, adverse events were similar between topical ruxolitinib and control groups in the short-term studies.[4] However, the direct data were too short and did not contain enough adults (at risk) to credibly estimate the effect on death, cancer, thrombosis, or serious infections observed with oral JAK inhibitors.[4]

The AAAAI/ACAAI recommendations focused on topical therapies are summarized below.

- In patients with uncontrolled AD refractory to moisturization alone, addition of a TCS is recommended over no TCS (strong recommendation, high-certainty evidence).[4]
- In patients aged 3 months or older with uncontrolled AD refractory to moisturization alone, addition of a TCI (pimecrolimus, tacrolimus) is recommended over no added TCI (strong recommendation, high certainty evidence).[4]
- In patients with uncontrolled AD using mid-to high-potency topical treatments (tacrolimus, TCS US classes 1-5), applying the medication once per day over twice per day is suggested (conditional recommendation, moderate certainty evidence).[4]
- In patients with mild-moderate AD refractory to moisturization alone, adding topical crisaborole 2% ointment over usual care alone is suggested (conditional recommendation, high-certainty evidence).[4]
- In adolescent and adult patients with mild-moderate AD refractory to moisturization alone, the panel suggests against adding topical ruxolitinib over continued usual care alone (conditional recommendation, low-certainty evidence).[4]
- In patients with uncontrolled AD and no serious bacterial skin infection (i.e., without severe weeping, crusting, pustules, or painful skin or other signs of extensive infection or systemic illness), the panel suggests against adding topical antimicrobials to standard topical treatments (conditional recommendation, very low-certainty evidence).[4]
- In patients with AD and a relapsing course, proactive therapy with a TCI or mid-potency TCS (US classes 3-5) in areas that frequently flare is recommended over applying topical treatments only in reaction to flares (strong recommendation, moderate-certainty evidence).[4]

American Academy of Dermatology: Management of Atopic Dermatitis in Adults
The AAD guidance for AD management in adults was updated in 2023.[5,6] For most people with AD, emollients and prescription topical therapies are sufficient to achieve AD control.[5] Phototherapy or systemic therapies may be needed to improve disease control and QoL in people with severe or widespread AD, people with substantially impaired QoL and individuals whose AD is refractory to optimized topical therapy.[5] The use of TCS, TCI, crisaborole, and ruxolitinib for mild to severe AD are strongly recommended by AAD.[5] Two new recommendations for the use of tapinarof and roflumilast cream were also included in the update.

There are over 100 RCTs examining the efficacy of TCS in AD, and studies have shown TCS are effective in acute AD, chronic AD, pruritus due to AD, active disease, and prevention of relapses.[6] When choosing a steroid potency, it is important to consider the anatomical site (i.e., using lower potency agents on the

face, neck, genitals, and body folds).[6] While some dermatologists prefer high and very high potency steroids (at least initially) to control active disease, others use the lowest potency agent needed for the situation and increase potency if needed.[6] Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient.[6] Traditionally, TCS were stopped once AD signs and symptoms of an AD flare were controlled.[6] Maintenance in between AD flares with once to twice weekly use of TCS is another approach (available data indicate fewer and increased time between relapses with this strategy).[6] The incidence of adverse events with TCS is low.[6] Though TCS are associated with a variety of cutaneous side effects (i.e., purpura, telangiectasia, hypopigmentation, focal hypertrichosis, acneiform eruptions, and striae), skin atrophy is generally the most concerning for physicians and patients.[6] Risk factors for atrophy include higher potency TCS use, occlusion, use on thinner and intertriginous skin, older patient age, and long-term continuous use.[6]

Based on a review of studies of TCIs compared to vehicle, there is high certainty evidence to strongly recommend the use of tacrolimus 0.1% and 0.03% ointments to treat AD patients.[6] In AD patients with mild-to-moderate disease, there is high certainty evidence to strongly recommend pimecrolimus 1% cream.[6] Of note, recommendations were based heavily on consideration of change in clinical signs, as there are limited data on pruritus and quality of life outcomes for adults with AD.[6] The FDA labeling contains a box warning for elevated risk of cancer with TCIs, and several long-term safety studies suggest TCI may increase relative risk of lymphoma but no other cancers.[6] However, given the low absolute risk of lymphoma, cancer risk from TCIs is likely not clinically meaningful.[6]

Crisaborole 2% ointment is indicated in mild-to-moderate AD and used as an alternative to TCS and TCIs.[6] Crisaborole ointment had a small but significant improvement in dermatitis symptoms in 4 RCTs compared to vehicle.[6] Crisaborole has also improved pruritus in 3 studies.[6] Crisaborole appears to have a favorable safety profile (i.e., small percentage of patients with application burning, stinging, and/or pain) and discontinuation rate comparable to placebo.[6] The work group strongly recommends its use for mild-to-moderate AD, based on high certainty evidence.[6]

Topical ruxolitinib 1.5% cream is FDA-approved for short-term and noncontinuous chronic treatment of mild-to-moderate AD in patients 12 years of age and older.[6] The treatment area should not exceed 20% body surface area, and a maximum of 60 g should be applied per week; these stipulations are aimed at reducing systemic absorption, as black box warnings include serious infections, mortality, malignancies (e.g., lymphoma), major adverse cardiovascular events, and thrombosis.[6] Based on moderate certainty evidence, there are enough data to strongly recommend topical JAK inhibitors in AD.[6] However, this recommendation is based on short-term efficacy and safety data, and may require updating in the future as long-term safety data become available.[6]

Two phase 2 and two phase 3 randomized, double-blind, vehicle-controlled trials evaluated tapinarof 1% cream over 8 weeks.[5] The workgroup determined that the overall balance of benefits and potential harms favors using tapinarof cream for the management of AD.[5] Similar recommendations were made for roflumilast based on two phase 3 randomized, double-blind, vehicle-controlled trials that evaluated roflumilast 0.15% cream over 4 weeks.[5]

For management of AD in adults, the following therapies are recommended by AAD:

- TCS or tacrolimus 0.03% or 0.1% ointment (strong recommendation, high-certainty evidence).[6]
- Intermittent use of medium potency TCS as maintenance therapy (2 times/wk) to reduce disease flares and relapses (strong recommendation, high-certainty evidence).[6]
- For mild-to-moderate AD, pimecrolimus 1% cream, crisaborole ointment, or roflumilast 0.15% cream (strong recommendation, high-certainty evidence).[5,6]
- For mild-to-moderate AD, ruxolitinib cream (strong recommendation, moderate-certainty evidence).[6]
- For moderate-to-severe AD, tapinarof cream (strong recommendation, high-certainty evidence).[5]

Canada's Drug Agency: Delgocitinib for Chronic Hand Eczema

A draft of CDA's reimbursement recommendation for the use of delgocitinib in treating chronic hand eczema was published October 2025.[12] In Canadian clinical practice, treatment escalation for chronic hand eczema typically progresses from low- or mid-potency TCS to high-potency TCS, sometimes with the addition of TCIs, followed by phototherapy or systemic therapies such oral immunosuppressants (e.g., methotrexate, cyclosporine).[12] While delgocitinib has been directly compared with vehicle, there is no direct evidence available for its effectiveness and safety relative to other key comparators, creating uncertainty about its place in therapy.[12] The Canadian Drug Expert Committee (CDEC) emphasized that the definition of "inadequate response" to TCS remains unclear and may rely on clinical judgment.[12] Although TCIs may precede delgocitinib use, they should not be mandatory due to their lower efficacy compared to high-potency TCS.[12] Delgocitinib's topical formulation and favorable safety profile make it an option for patients seeking disease control before systemic treatments.[12] However, uncertainties persist regarding its long-term safety and efficacy beyond 36 weeks, and its role versus systemic agents (e.g., immunosuppressants, JAK inhibitors, dupilumab).[12]

The CDA recommends that delgocitinib be reimbursed for the treatment of moderate to severe chronic hand eczema in adults for whom TCS are inadequate or are not advisable, only if specific conditions are met:

- Treatment with delgocitinib should be initiated in adults (≥18 years) with moderate-to-severe chronic hand eczema as defined by an IGA-CHE score of 3-4 and who have had an adequate trial (with a documented refractory disease), were intolerant (with documented intolerance), or are ineligible for high-potency TCS.[12]
- Response should be assessed at 12 weeks for renewal of coverage.[12]
- Requests should be renewed if patients demonstrate either a ≥ 2-step improvement of IGA-CHE or a score of 0 to 1 (clear/almost clear).
- Delgocitinib should be prescribed by a practitioner experienced in the management of chronic hand eczema.[12]

Canada's Drug Agency: Ruxolitinib for Atopic Dermatitis

In May 2025, CDA recommended against reimbursement for ruxolitinib 1.5% cream in patients with mild-to-moderate AD.[7] Evidence from 2 clinical trials showed that ruxolitinib treatment improved the severity of AD compared with placebo in adult and adolescent patients with mild to moderate AD.[7] However, it is unclear if these patients were representative of the population expected to receive ruxolitinib including patients whose disease is not adequately controlled with TCS and/or TCI, or for whom such treatment(s) is not advisable.[7] Furthermore, there is insufficient evidence that directly compares ruxolitinib to currently available treatments for mild-to-moderate AD.[7]

Canada's Drug Agency: Roflumilast for Plaque Psoriasis

In September 2023, the CDA issued a reimbursement recommendation for the use of roflumilast 0.3% cream in treatment of PsO for patients aged 12 years and older.[8] Evidence from 2 phase 3 RCTs demonstrated that roflumilast improved severity of psoriasis over 8 weeks, including in intertriginous areas, and reduced the severity of itch compared to treatment with vehicle.[8] Roflumilast may provide an alternative, nonsteroidal topical treatment option for patients living with PsO, including psoriasis in the intertriginous area.[8]

CDA Recommendations:

- Roflumilast should only be covered to treat patients who have a clinical diagnosis of PsO with an IGA score of at least 2 (mild) and an area of PsO appropriate for topical treatment covering a body surface area of 2% to 20% (inclusive).[8]
- Roflumilast should be discontinued if a response has not been demonstrated by 8 weeks. A response to treatment is defined as at least a 2-grade improvement from baseline in IGA score or an IGA score of "clear" or "almost clear" (0 or 1).[8]

Canada's Drug Agency: Ruxolitinib for Vitiligo

In August 2025, the CDA recommended against reimbursement of topical ruxolitinib for NSV.[9] Evidence from 2 phase 3 RCTs demonstrated that about 30% of patients using ruxolitinib saw significant improvement in facial repigmentation, compared to around 8% to 11% using a placebo.[9] More patients also reported that their vitiligo became less noticeable or no longer noticeable compared to those who received placebo.[9] However, the impact of vitiligo on daily life varies, and the treatment did not lead to meaningful improvements in overall HRQoL.[9] The studies only compared ruxolitinib to a placebo; therefore, there is no data on how it performs against other commonly used treatments.[9] The Canadian Drug Expert Committee (CDEC) recognized that vitiligo can seriously affect people's lives, especially those with darker skin tones, who may face stigma, loss of identity, and low self-esteem.[9] Most trial participants had lighter skin tones, and the treatment did not improve their HRQoL. These limitations make it difficult to know how effective ruxolitinib would be for those most affected by vitiligo.[9]

After review, 2 guidelines were excluded due to poor quality.[77,78]

New Indications and New Formulations:

- A new formulation of roflumilast 0.05% cream received FDA-approval in October 2025. This product is indicated for topical treatment of mild-to-moderate AD in pediatric patients aged 2 to 5 years of age.[17]

- In September 2025, ruxolitinib cream received expanded FDA-approved for topical short-term and noncontinuous chronic treatment of mild-to-moderate AD in non-immunocompromised patients at least 2 years of age.[16] The prescribing information recommends adults not use more one 60 gram tube per week in adults and in children no more than one 60 gram tube per 2 weeks.[16] Ruxolitinib cream should not be applied to more than 20% of body surface area (BSA).[16] Prior to this approval, topical ruxolitinib was FDA-approved for NSV in patients at least 12 years of age.[16] Ruxolitinib cream has a box warning for risk of serious infections, all-cause mortality, and major cardiovascular events based on studies of oral JAK inhibitors.[16] Malignancies and thromboembolic events have been reported with topical ruxolitinib and are also included in the box warning.[16]

  Two double-blind, vehicle controlled RCTs (n=1249) evaluated ruxolitinib in patients at least 12 years of age with AD (TRuE-AD1 and TRuE-AD2) over 8 weeks.[16] Patients enrolled in these studies had an affected BSA of 3 to 20%, and an IGA score of 2 (mild) to 3 (moderate) on a severity scale of 0 to 4.[16] The primary efficacy endpoint was the proportion of subjects at week 8 achieving IGA treatment success defined as a score of 0 (clear) or 1 (almost clear) with ≥ 2 grade improvement from baseline.[16] In TRuE-AD1, 53.8% of ruxolitinib-treated patients achieved IGA treatment success compared with 15.1% of placebo-treated patients (difference 38.9%; 95% CI 30.3 to 47.4).[16] In TruE-AD2, similar results were observed with ruxolitinib versus placebo (51.3% vs. 7.6%; difference 44.1%; 95% CI 36.2 to 52).[16] A third RCT, TruE-AD3, conducted in pediatric patients 2 to 11 years of age (n=330) showed more IGA treatment success with ruxolitinib than placebo at week 8 (56.5% vs. 10.8%; 95% CI 34.7 to 56.8%).[16]

  Adverse reactions occurred in TRuE-AD1 and TRuE-AD2 infrequently (less than 1%) in the ruxolitinib group and none were reported in the vehicle group. [16] In TRuE-AD3, the most frequently adverse effects associated with ruxolitinib included upper respiratory tract infections, application site reactions, pyrexia, and decrease in white blood cell counts.[16]

- In May 2025, roflumilast 0.3% topical foam received an expanded indication for treatment of PsO in patients at least 12 years of age.[18] Prior to this expanded indication, roflumilast 0.3% foam was FDA-approved for the treatment of seborrheic dermatitis in patients at least 9 years of age.[18] Two randomized, double-blind, vehicle-controlled trials (ARRECTOR [NCT05028582] and Trial 204 [NCT04128007]) enrolled a total of 736 adult and pediatric subjects 12 years of age and older with mild to severe PsO of the scalp and body.[18] In each trial, subjects were randomized 2:1 to receive roflumilast foam, 0.3%, or vehicle foam

applied once daily for 8 weeks.[18] The combined trial population was 55% female, 85% White, 5% Black, 6% Asian, and 4% other races.[18] The median age was 47 years (range 12 to 87 years).[18]
In both trials, Scalp Investigator Global Assessment (S-IGA) treatment success, a primary endpoint in ARRECTOR and Trial 204, and Body Investigator Global Assessment (B-IGA) treatment success, a primary endpoint in ARRECTOR, were defined as a score of "Clear" (0) or "Almost Clear" (1), plus a 2-grade improvement from baseline.[18] In both trials, roflumilast foam was superior to vehicle foam at Week 8 at achieving S-IGA and B-IGA success as presented in **Table 5**. The most frequently reported adverse events with roflumilast foam were headache, diarrhea, nausea, and nasopharyngitis.[18]

Table 5. Treatment Success at Week 8 with Roflumilast Foam versus Vehicle Foam in Patients with Plaque Psoriasis Trials[18]

	ARRECTOR Trial		**Trial 204**	
	Roflumilast 0.3% Foam (n=281)	Vehicle Foam (n=151)	Roflumilast 0.3% Foam (n=200)	Vehicle Foam (n=104)
Percent of Patients with S-IGA Success (Clear or Almost Clear)	66.4%	27.8%	56.7%	11.0%
Difference (95% CI)	37.1% (27.1 to 47.1)		47.7% (37.9 to 57.5)	
Percent of Patients with B-IGA Success (Clear or Almost Clear)	45.5%	20.1%	39.0%	7.4%
Difference (95% CI)	24.8% (15.0 to 34.6)		32.4 (23.3 to 41.6)	
Abbreviations: B-IGA = Body Investigator Global Assessment; CI = Confidence Interval; S-IGA = Scalp Investigator Global Assessment				

- Roflumilast 0.15% cream was FDA-approved in July 2024 for the treatment of mild-to-moderate AD in people at least 6 years of age.[17] Prior to this approval, roflumilast 0.3% cream was FDA-approved for PsO in patients at least 6 years of age.[17] Two double-blind, vehicle-controlled RCTs (n=1337) evaluated the efficacy of once daily roflumilast 0.15% cream in patients with mild-to-moderate AD over 4 weeks (INTEGUMENT-1 and INTEGUMENT-2).[17] The primary endpoint was the proportion of subjects who achieved IGA-AD treatment success, defined as a score of 0 (clear) or 1 (almost clear) at Week 4.[17] More patients in both trials achieved IGA-AD treatment success with roflumilast compared to vehicle cream (INTEGUMENT-1: 32% vs. 15.2%; difference 17.4%; 95% CI 11.09 to 23.75 and INTEGUMENT-2: 28.9% vs. 12.0%; difference 16.5%; 95% CI 10.61 to 22.42).[17] The most frequently reported adverse effects with roflumilast in these 4-week RCTs included headache, nausea, application site pain, diarrhea, and vomiting.[17]

- Tapinarof cream received an expanded FDA-approved indication for AD in people at least 2 years of age in December 2024.[19] Prior to this approval, tapinarof was FDA-approved for PsO in adults.[19] Two multicenter, double-blind, vehicle-controlled trials (n=813) evaluated the safety and efficacy of tapinarof cream over 8 weeks in patients with AD (ADORING 1 and ADORING 2).[19] Eighty percent of enrolled patients were 2 to 17 years of age. Baseline disease severity was graded using the 5-point IGA-AD. The majority of subjects had "Moderate" disease (87%), while 13% had "Severe" disease at baseline.[19] The primary efficacy endpoint in both studies was the proportion of subjects who achieved treatment success, defined as a IGA-AD score of 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline.[19] At 8 weeks, more tapinarof-treated patients achieved IGA-AD treatment success compared with vehicle-treated patients (ADORING 1: 45% vs. 14%; difference 32%; 95% CI 23 to 40 and ADORING 2: 46% vs. 18%; difference 29%; 95% CI 19 to 38).[19] Adverse

effects reported with tapinarof over 8 weeks included respiratory tract infection, folliculitis, headache, asthma, vomiting, ear infection, pain in extremity and abdominal pain.[19]

New FDA Safety Alerts: No new FDA safety alerts were identified for this class of drugs.

Randomized Controlled Trials:
A total of 36 citations were manually reviewed from the initial literature search. After further review, 36 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Delgocitinib (ANZUPGO)
See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 4**.

Clinical Efficacy:
Delgocitinib is a JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) inhibitor available as 2% topical cream in the United States.[10] The medication received FDA-approval in July 2025 for moderate-to-severe chronic hand eczema in adults who have had inadequate response to, or for whom TCS therapies are not advisable.[10] FDA-approval was supported by 2 double-blind, placebo-controlled, multi-center phase 3 RCTs, DELTA 1 and DELTA 2, in adults with moderate-to-severe chronic hand eczema (**Table 6)**.[11] Adults enrolled in the trial were randomly assigned 2:1 to twice-daily delgocitinib cream or placebo.[11] The trials were conducted in Europe and Canada. The primary endpoint of each trial was IGA-CHE treatment success, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) at week 16 with a 2-step or greater improvement from baseline.[11]

DELTA 1 enrolled 487 patients (181 male and 306 female) while DELTA 2 enrolled 473 patients (161 male and 321 female) with an IGA-CHE score of 3 or 4 and inadequate response or contraindication to the use of TCS or for whom TCS were documented to be medically inadvisable as assessed by the investigator.[11] The mean age of enrolled patients was 44 years, 64% were female, 90% were White, 4% were Asian, and 1% were Black.[10] The primary classifications of chronic hand eczema by subtype were atopic hand eczema (35.9%), hyperkeratotic eczema (21.5%), irritant contact dermatitis (19.6%), allergic contact dermatitis (13.9%), vesicular hand eczema (9.1%), and contact urticaria/protein contact dermatitis (0.1%).[10] The use of hand emollients was permitted in both trials; however, patients were instructed to avoid using emollients on the affected area 2 hours before and after application of the study drug.[11] If medically necessary, rescue treatment for chronic hand eczema (i.e., treatment initiated to control intolerable chronic hand eczema symptoms during the treatment and follow-up periods) was prescribed to patients at the investigator's discretion. Once rescue treatment was initiated, patients had to stop trial treatment immediately and were not allowed to restart it.[11] At week 16, a greater proportion of patients using delgocitinib had IGA-CHE treatment success compared to vehicle cream (19.7% vs. 9.9%; difference, 9.8%; 95% CI 3.6 to 16.1; $p<0.0055$ in DELTA 1 and 29.1% vs. 6.9%; difference, 22.2%; 95% CI 15.8 to 28.5; $p<0.0001$ in DELTA 2).[11]

Key secondary endpoints included reduction of Hand Eczema Symptoms Diary (HESD) overall score, reduction of HESD itch score, and reduction of HESD pain score as measured by a change in weekly averaged patient-reported diary scores of at least 4 points from baseline at week 16 and at least 75% improvement in Hand Eczema Severity Index (HECSI) score from baseline (HECSI-75) at week 16.[11] At baseline, mean HESD itch and pain scores were 7.1 and 6.7, respectively.[10] Delgocitinib was superior to placebo for all key secondary endpoints (**Table 4)**. Both trials were conducted over a relatively short time frame (16 weeks) and included a mostly White patient population.

Eligible patients (n=801) were followed over 36 weeks in an open-label, long-term extension trial.[79] Overall, 82.9% (664/801) completed DELTA 3, and 17.1% (137/801) of the patients discontinued trial treatment.[79] The most common reasons for trial discontinuation were lack of efficacy (6.9% [55/137]) and patient withdrawal from the trial (6.5% [52/137]).[79] Rescue treatment was used by 29 (3.6%) patients.[79] Among patients previously treated with delgocitinib cream 20 mg/g who had achieved IGA-CHE 0/1 at DELTA 3 baseline (i.e., parent trial responders in DELTA 1 or DELTA 2 at week 16), the proportion who maintained IGA-CHE 0/1 response without treatment was 40.6% at week 4 and 28.3% at week 8.[79]

Clinical Safety:
Most adverse events were mild to moderate and not considered related to trial treatment.[11] In both trials, the most frequently reported adverse events occurred in less than 1% of people treated with delgocitinib and included application site pain, paresthesia, pruritis, erythema, and bacterial skin infections.[11] The proportion of patients reporting adverse events leading to discontinuation of trial treatment was lower in delgocitinib treatment groups (2 [1%] in DELTA 1 and 1 [<1%] in DELTA 2) compared with their corresponding cream vehicle groups (6 [4%] in DELTA 1 and 5 [3%] in DELTA 2).[11] In both trials, few serious adverse events were reported (≤2% of patients), and all were determined to be unrelated to trial drug by both trial investigator and sponsor; none led to any safety concerns.[11] In the open-label extension trial, eczema herpeticum was observed in one patient and herpes zoster was observed in 2 patients treated with delgocitinib.[10] In this trial delgocitinib was well-tolerated with most frequent adverse events being COVID-19 (17%), nasopharyngitis (16%), and upper respiratory tract infection (4%).[79]

The manufacturer recommends completing any necessary immunizations, including herpes zoster vaccinations, prior to initiating delgocitinib therapy.[11] Use with other JAK inhibitors or potent immunosuppressants is not recommended.[11] It is not known if topical delgocitinib is associated with adverse reactions (i.e., cardiovascular events, deep venous thrombosis, malignancies) that have been observed with oral JAK inhibitors.[11] At this time, delgocitinib does not carry the boxed warning of oral JAK inhibitors for the risk of serious infections, mortality, malignancy, cardiovascular events, and thrombosis.
Look-alike / Sound-alike Error Risk Potential: No issues identified in Micromedex

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Hand eczema symptoms (reduced redness, itching, pain, cracking, flaking, dryness)
2) Quality of life or functional improvement
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) treatment success, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement on the 5-point scale at week 16.

Table 6. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints (assessed at 16 weeks)	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Bissonnette, R., et al[11] DELTA 1 and DELTA 2 DB, PC, Phase 3 RCT	1. Delgocitinib 2% cream applied twice daily over 16 weeks 2. Cream vehicle applied twice daily over 16 weeks	Demographics: **DELTA 1** -Mean Age: 44 yo -Female: 63% -Race: White: 88% Black: < 1% Asian: 4% Geographic Region: Europe: 80% North America: 20% -Baseline IGA-CHE score: Moderate (3 points): 67% Severe (4 points): 33% **DELTA 2** Mean Age: 44 yo -Female: 66% -Race: White: 93% Black: < 1% Asian: 3% -Geographic Region: Europe: 80% North America: 20% -Baseline IGA-CHE score: Moderate (3 points): 76% Severe (4 points): 24% Key Inclusion Criteria: -Adults ≥ 18 yo -Diagnosis of CHE that had persisted for > 3 mos or returned 2 or more times in the previous 12 mos -IGA-CHE score of 3 (moderate) to 4 points (severe) at baseline -HESD itch score ≥ 4 points at baseline -Documentation of inadequate response to	**DELTA 1** ITT: 1. 325 2. 162 PP: 1. 305 2. 141 Attrition: 1. 20 (6%) 2. 21 (13%) **DELTA 2** ITT: 1. 314 2. 159 PP: 1. 291 2. 122 Attrition: 1. 23 (7%) 2. 37 (23%)	**DELTA 1** Primary Endpoint: People with IGA-CHE score of 0/1 1. 64 (19.7%) 2. 16 (9.9%) Difference: 9.8% 95% CI 3.6 to 16.1; P<0.0055 Secondary Endpoints: People with ≥ 4 points reduction in HESD score* 1. 146 (47.2%) 2. 38 (24.4%) Difference: 22.8% 95% CI 14.0 to 31.7; P<0.0001 People with ≥ 4 points reduction in HESD itch score* 1. 152 (47.1%) 2. 37 (23%) Difference: 24.1% 95% CI 15.5 to 32.6; P<0.0001 People with ≥ 4 points reduction in HESD pain score* 1. 143 (49.1%) 2. 41 (27.5%) Difference: 21.7% 95% CI 12.4 to 30.9; P<0.0001 People with 75% improvement in HECSI score 1. 160 (49.2%) 2. 38 (23.5%) Difference: 25.7% 95% CI 17.2 to 34.3; P<0.0001 **DELTA 2** Primary Endpoint: People with IGA-CHE score of 0/1 1. 91 (29.1%) 2. 11 (6.9%)	9.8/ 11 22.8 /5 24.1 /5 21.7 /5 25.7 /4	**DELTA 1** Adverse Events 1. 147 (45%) 2. 82 (51%) RD = -5.4 95% CI -14.7 to 4.0 Adverse Events Leading to Discontinuation 1. 2 (1%) 2. 6 (4%) RD = -3.1 95% CI -7.3 to -0.5 Serious Adverse Events 1. 6 (2%) 2. 3 (2%) RD = 0 95% CI -3.6 to 2.4 **DELTA 2** Adverse Events 1. 143 (46%) 2. 71 (45%) RD = 1.0 95% CI -8.4 to 10.4 Adverse Events Leading to Discontinuation 1. 1 (<1%) 2. 5 (3%) RD = -2.8 95% CI -5.5 to 4.6 Serious Adverse Events 1. 5 (2%)	NS 3.1/3 3 NS NS NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 to delgocitinib or cream vehicle via interactive response technology system and stratified by baseline CHE severity (moderate vs. severe) and region (Europe vs. North America). Baseline characteristics were comparable between active treatment and cream vehicle arms. Performance Bias: Low. Active drug and placebo vehicle were identical in appearance and scent. Patient and investigators blinded to treatment arms. Protocol standardized across all trial sites. Detection Bias: Unclear. Primary outcome (IGA-CHE) was conducted by investigators. Secondary outcomes were primarily patient reported in a daily diary, which may be affected by recall bias and subjective assessment of improvement. Attrition Bias: High. Higher percentage of vehicle-treated patients withdrew from both studies due to lack of efficacy and adverse events. Missing data imputed as non-response. Reporting Bias: Low. Protocol available online. All pre-specified outcomes reported as outlined in the protocol. Other Bias: High. Manufacturer had a role in trial design, data collection, data analysis, data interpretation, writing of the report and trial funding. **Applicability**: Patient: More females enrolled in the study, which is typical for CHE. Most participants were White, which limits applicability to a more diverse population. All patients had inadequate response to TCS prior to enrollment (potency not reported). Intervention: Strength and dosing of delgocitinib cream determined in Phase 2 RCTs. Comparator: Placebo cream is appropriate, although comparison to TCS or TCI would provide more meaningful outcomes. Outcomes: Primary outcome was the IGA-CHE, which was approved by the FDA as an effective

		TCS within 1 yr prior to study enrollment <u>Key Exclusion Criteria</u>: -Concurrent skin disease on the hands including significant infection -Active psoriasis on any part of the body -Active atopic dermatitis requiring medical treatment in regions other than the hands and feet -Previous treatment with systemic therapy or topical JAK-I		Difference: 22.2% 95% CI 15.8 to 28.5; P<0.0001 <u>Secondary Endpoints</u>: People with ≥ 4 points reduction in HESD score* 1. 137 (44.5%) 2. 32 (20.9%) Difference: 23.7% 95% CI 15.1 to 32.3; P<0.0001 People with ≥ 4 points reduction in HESD itch score* 1. 146 (47.2%) 2. 31 (19.9%) Difference: 27.4% 95% CI 19.0 to 35.8; P<0.0001 People with ≥ 4 points reduction in HESD pain score* 1. 143 (48.6%) 2. 32 (22.7%) Difference: 26.0% 95% CI 17.0 to 35.1; P<0.0001 People with 75% improvement in HECSI score 1. 155 (49.5%) 2. 29 (18.2%) Difference: 31.3% 95% CI 23.1 to 39.5; P<0.0001 *11-point scale	22.2 /5 23.7 /5 27.4 /4 26/4 31.3 /4	2. 3 (2%) RD = -0.3 95% CI -3.9 to 2.1		assessment tool. Trial was conducted over a relatively short period, 16 weeks. <u>Setting</u>: **DELTA 1**: 53 sites in 6 countries -Canada: 20% France: 17% -Germany: 28% Italy: 9% -Poland: 22% United Kingdom: 5% **DELTA 2**: 50 sites in 7 countries: -Belgium: 5% Canada: 20% -Denmark: 5% Germany: 28% -Netherlands: 5% Poland: 22% -Spain: 14%
<u>Abbreviations</u>: ARR = absolute risk reduction; CHE = chronic hand eczema; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; HESD = Hand Eczema Symptom Diary; HECSI = Hand Eczema Severity Index; IGA-CHE = Investigator's Global Assessment of Chronic Hand Eczema; ITT = intention to treat; JAK-I = Janus kinase inhibitor; mos= months; N = number of subjects; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial; RD = risk difference; TCS = topical corticosteroids; yo = years old								

NEW DRUG EVALUATION: Sirolimus (HYFTOR)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 6**.

Sirolimus 0.2% gel is indicated as topical treatment for facial angiofibromas associated with TSC in adults and pediatric patients aged 6 years and older.[15] The mechanism of action of sirolimus in the treatment of angiofibroma associated with TSC is unknown.[15] The gel is applied twice daily to the areas of the face with angiofibromas.[15] The maximum daily dosage for patients 6 to 11 years of age is 600 mg (2 cm), while patients at least 12 years of age have a maximum daily dosage of 800 mg (2.5 cm).[15]

Clinical Efficacy:

A phase 3, double-blind, placebo-controlled, randomized trial was conducted in 62 patients at least 3 years of age with angiofibromas due to TSC.[13] This trial is described in detail below in **Table 8**. The trial was conducted at 9 centers in Japan.[13] Patients were eligible for this study if they had a diagnosis of TSC with 3 or more facial angiofibromas that were 2 or more mm in diameter.[13] Patients were excluded if they had received treatment with a local or systemic mTOR inhibitor within the preceding 12 months or had undergone laser or surgical treatment within the preceding 6 months.[13] Enrolled participants were randomized 1:1 to receive sirolimus 0.2% gel or placebo gel , each applied topically twice daily for 12 weeks.[13] Dosing was modified based upon age (400 mg, 600 mg, and 800 mg for patients younger than 6 years, 6 to 11 years, and older than 11 years, respectively).[13] Concurrent use of the following medications was not permitted: any mTOR inhibitors, topical tacrolimus, topical steroids, topical antibiotics, topical vitamin D3, adapalene, benzoyl peroxide, ibuprofen piconol, resorcinol, and zinc-salicylic acid.[13] Laser therapy and surgery of the site of topical application were also not permitted.[13]

Patients underwent a 12-week treatment plan with lesion assessment every 4 weeks and the final evaluation at a 4-week follow-up after completing treatment.[13] At each visit, patients were medically examined and their facial lesions were photographed with the same digital camera at all sites.[13] A color chart with a scale was used to calibrate the color tones and clarity of all photographs taken and to measure the size of skin lesions.[13] The primary end point was composite improvement in the combined size and color of angiofibromas as documented in photographs obtained at week 12 of treatment.[13] Three blinded dermatologists assessed the changes using a 6-category scale with the following categories: markedly improved, improved, slightly improved, unchanged, slightly aggravated, and aggravated.[13] It is not clear how this scale was developed and validated.[14] The proportion of patients with angiofibroma improvement after 12 weeks was 60% in the sirolimus group compared to 0% in the placebo group ($p<0.001$).[13] Secondary endpoints included changes from baseline in the Dermatology Life Quality Index (DLQI) and Children's DLQI (CDLQI) based upon the patient's age; neither outcome achieved statistical significance compared to placebo.[13] An additional secondary outcomes was the in person investigator assessment of improvement in size and color of the fibroangioma lesions. The proportion of patients assessed in person by the investigator (instead of by photograph) as "improved" or "markedly improved" at Week 12 was 23% for sirolimus-treated patients compared to 6% of vehicle-treated patients, which did not reach statistical significance.[14] Because the study was not powered to detect differences in secondary outcomes it is unclear if these secondary endpoint results are related to a type 2 error (finding no difference when one actually exists).

Trial Limitations

The FDA identified several issues with primary outcome used in this trial. The photographic technique was not standardized in terms of lighting, background, distance from the camera to the subject, or subject position.[14] Investigators, as well as personnel who performed the editing of photographs, were blinded only to the treatment arm, and not to whether photographs were taken before or after treatment.[14] In addition, the reliability of the scale used to document

angiofibroma improvement was not confirmed prior to its use in the study.[14] The final assessment score could be modified based upon consensus discussions of the blinded assessors. The rationale for conducting the consensus discussions was not provided by the investigators. The need to discuss and change the scores of several assessments during the trial raises concerns related to accuracy and inter-rater reliability of the rating instrument.[14] The FDA reviewers concluded that composite improvement scale was not appropriate to support regulatory decision making based on its design and lack of sufficient supportive evidence of content validity (e.g., evidence of clinician's understanding of the categories, descriptors, threshold, etc.).[14] A key limitation of the scale was that it assesses changes in angiofibromas relative to baseline, instead of assessing absolute angiofibroma severity.[14] Because of these issues, the FDA based its approval on the secondary endpoint, the investigator's in person assessment of composite changes in angiofibromas.[14]

Clinical Safety:

A summary of adverse events reported during the 12-week trial of sirolimus compared to placebo vehicle is presented in **Table 7**. In a 104-week, open-label safety trial, the most common adverse reactions associated with sirolimus application were application site irritation (31%), dry skin (28%), acne (20%), pruritus (9%), eye irritation (9%), erythema (7%), acneiform dermatitis (6%), contact dermatitis (5%), solar dermatitis (1%), and photosensitivity reaction (1%).[15] Adverse reactions occurred with similar frequency in adult and pediatric subjects 6 years of age and older.[15] Systemic exposure of drugs that are both substrates and inhibitors of CYP3A could be increased with coadministration with sirolimus.[15] Concomitant use of sirolimus with inhibitors of CYP3A4 has the potential to increase the systemic exposure of sirolimus and increases the risk of sirolimus adverse reactions.[15] Live vaccines should not be administered while using topical sirolimus, as the vaccines may be less effective.[15] Sirolimus is systemically absorbed after topical administration and may result in fetal exposure.[15] Effective contraceptive methods are recommended for females of reproductive potential during treatment and for 12 weeks after completing sirolimus therapy.[15]

Table 7. Adverse Reactions Reported in Sirolimus Trial Compared to Placebo Vehicle Through Week 12[15]

Adverse Event	Sirolimus (n = 30)	Vehicle (n = 32)
Dry Skin and Asteatosis	12 (40%)	4 (13%)
Application Site Irritation	11 (37%)	9 (28%)
Pruritis	5 (17%)	4 (13%)
Acne	2 (7%)	0
Acneiform Dermatitis	1 (3%)	0
Ocular Hyperemia	1 (3%)	0
Skin Hemorrhage	1 (3%)	0
Skin Irritation	1 (3%)	0

Look-alike / Sound-alike Error Risk Potential: Rapamune or Rapaflo

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Decreased size of facial angiofibromas
2) Decreased redness of facial angiofibromas

Primary Study Endpoint:
1) Composite assessment of improvement in size and redness of fibroangiomas

3) Improved quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Table 8. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Wataya-Kaneda, et al[13] Phase 3 MC, DB, PC, RCT	1. Sirolimus 0.2% gel applied topically twice daily for 12 weeks. Dosing determined by age. 2. Placebo applied twice daily for 12 weeks	Demographics: -Adults: n=35 -Pediatrics: n=27 -Male: 57% (n=17) in group 1 and 34% (n=11) in group 2 -Mean age: 22.5 yrs (range 6 -53 yrs) -Mean baseline total DLQI/CDLQI score: 1.8 (total score = 30) Key Inclusion Criteria: -Male and females aged 3 years or older -Diagnosis of TSC -Three or more facial angiofibromas ≥ 2 mm in diameter with redness in each -Inability to photograph lesions -Local or systemic treatment with mTOR inhibitor within previous 12 months -Not eligible for surgery or laser therapy or did not want these therapies	ITT: 1. 30 2. 32 Attrition: 1. 0 2. 0	Primary Endpoint Percent of patients with "marked improvement" and "improvement" in composite assessment (size and redness) of angiofibroma observed *in photographs* after 12 weeks of treatment using 6-point scale. 1. n=18 (60%) 2. n=0 95% CI, 41 to 77 P<0.001 Secondary Endpoints Percent of patients with composite angiofibroma improvement based on *in-person assessment* at week 12 ("marked improvement" and "improvement"). 1. n=7 (23%) 2. n=2 (6%) NS* Mean change in DLQI at week 12 1. -0.2 2. -0.5 Difference = -0.3 NS* Mean change in CDLQI at week 12 1. 2.9 2. 2.3 Difference = 0.6	60%/2 NA NA NA	Any Adverse Event 1. n=27 (90%) 2. n=22 (69%) Dry Skin 1. n=11 (37%) 2. n=4 (13%) Application Site Irritation 1. n=11 (37%) 2. n=9 (28%) Pruritus 1. n=7 (23%) 2. n=4 (13%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 using 4 block permutation by an independent statistician. Stratified by age (3-18 yrs and > 18 yrs). More males enrolled in the active comparator group, otherwise baseline demographics were similar. Performance Bias: Low. Sirolimus gel and placebo were identical in appearance. Patients and investigators blinded to treatment allocation. Detection Bias: High. Independent review committee of 3 dermatologists assessed the photographs using a 6-point scale (markedly improved, improved, slightly improved, unchanged, slightly aggravated, aggravated). Scale was not validated prior to use in the RCT. Committee could confer if assessments differed and modify their assessment based on consensus of the 3 reviewers. Attrition Bias: Low. No patients withdrew from the study. Photographic results of one placebo-treated patients were deemed unassessable as the pictures were unfocused. Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Study was sponsored by manufacturer. Conflict of interest declarations for investigators was not provided. **Applicability**: Patient: Conducted in Japan, applicability to Oregon Medicaid patients is unclear. Intervention: Phase 2 RCTs evaluated doses of 0.05%, 0.1% and 0.2% gel with largest benefit compared to placebo in patients randomized to the 0.2% dose.

		Key Exclusion Criteria: -Skin lesions that were ulcerated or had erosions -Poorly controlled dyslipidemia -Local or systemic treatment with an mTOR inhibitor (sirolimus, everolimus) within previous 12 months -Laser therapy or surgery within previous 6 months		NS* *p-value and CIs not reported				Comparator: No currently approved drugs for this condition. Placebo is an appropriate comparator. Outcomes: Instrument used to assess angiofibroma improvement was not validated prior to its use in this RCT. Setting: Conducted at 9 sites in Japan
Abbreviations: CI = confidence interval; CDLQI = Children's Dermatology Life Quality Index; DB = double-blind; DLQI = Dermatology Life Quality Index; ITT = intention to treat; MC = multi-center; mITT = modified intention to treat; mm = millimeters; mTOR = mammalian target of rapamycin; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial; TSC = tuberous sclerosis complex; yrs = years								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
calcipotriene	CALCIPOTRIENE	TOPICAL	CREAM (G)	Y
pimecrolimus	ELIDEL	TOPICAL	CREAM (G)	Y
pimecrolimus	PIMECROLIMUS	TOPICAL	CREAM (G)	Y
tazarotene	TAZAROTENE	TOPICAL	CREAM (G)	Y
calcipotriene/betamethasone	CALCIPOTRIENE-BETAMETHASONE	TOPICAL	OINT. (G)	Y
tacrolimus	TACROLIMUS	TOPICAL	OINT. (G)	Y
anthralin	ANTHRALIN	TOPICAL	CREAM (G)	N
ruxolitinib phosphate	OPZELURA	TOPICAL	CREAM (G)	N
tapinarof	VTAMA	TOPICAL	CREAM (G)	N
roflumilast	ZORYVE	TOPICAL	CREAM (G)	N
calcipotriene	CALCIPOTRIENE	TOPICAL	FOAM	N
calcipotriene/betamethasone	ENSTILAR	TOPICAL	FOAM	N
calcipotriene	SORILUX	TOPICAL	FOAM	N
roflumilast	ZORYVE	TOPICAL	FOAM	N
tazarotene	TAZAROTENE	TOPICAL	GEL (GRAM)	N
halobetasol propion/tazarotene	DUOBRII	TOPICAL	LOTION	N
calcipotriene	CALCIPOTRIENE	TOPICAL	OINT. (G)	N
calcitriol	CALCITRIOL	TOPICAL	OINT. (G)	N
crisaborole	EUCRISA	TOPICAL	OINT. (G)	N
calcitriol	VECTICAL	TOPICAL	OINT. (G)	N
calcipotriene/betamethasone	CALCIPOTRIENE-BETAMETHASONE	TOPICAL	SUSPENSION	N
calcipotriene/betamethasone	TACLONEX	TOPICAL	SUSPENSION	N
tazarotene	FABIOR	TOPICAL	FOAM	N
tazarotene	TAZAROTENE	TOPICAL	FOAM	N
tazarotene	ARAZLO	TOPICAL	LOTION	N
coal tar	DHS TAR	TOPICAL	SHAMPOO	N
coal tar	DHS TAR GEL	TOPICAL	SHAMPOO	N
coal tar	THERA-GEL	TOPICAL	SHAMPOO	N
coal tar	T-PLUS	TOPICAL	SHAMPOO	N
delgocitinib	ANZUPGO	TOPICAL	CREAM (G)	
sirolimus	HYFTOR	TOPICAL.	GEL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to August 19, 2025>

1	tapinarof.mp.	182
2	exp Tacrolimus/	18681
3	pimecrolimus.mp.	1080
4	Administration, Topical/	41802
5	Anti-Inflammatory Agents, Non-Steroidal/	74426
6	crisaborole.mp.	268
7	ruxolitinib.mp.	3589
8	roflumilast.mp.	996
9	Calcitriol/	15100
10	tazarotene.mp.	735
11	Betamethasone/ or Calcitriol/	21249
12	Anthralin/	948
13	Coal Tar/	2370
14	delgocitinib.mp.	115
15	calcipotriene.mp.	1294
16	crisaborole.mp.	268
17	Sirolimus/	21760
18	1 or 2 or 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 or 16 or 17	180988
19	exp Psoriasis/th [Therapy]	5154
20	exp Dermatitis, Atopic/th [Therapy]	2809
21	exp Eczema/th [Therapy]	1148
22	exp Vitiligo/th [Therapy]	1127
23	19 or 20 or 21 or 22	9869
24	18 and 23	802
25	limit 24 to (english language and humans and yr="2022 -Current")	36

Appendix 3: Prescribing Information Highlights

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

ANZUPGO® (delgocitinib) cream, for topical use
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
ANZUPGO is a Janus kinase (JAK) inhibitor indicated for the topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable. (1)

Limitations of Use: Use of ANZUPGO in combination with other JAK inhibitors or potent immunosuppressants is not recommended. (1)

----------DOSAGE AND ADMINISTRATION----------
- See the full prescribing information for recommended immunizations prior to treatment. (2.1)
- Do not use more than 30 grams per 2 weeks or 60 grams per month.
- Apply twice daily to skin of the affected areas only on the hands and wrists. (2.2)
- For topical use only. Not for oral, ophthalmic, or intravaginal use. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Cream: Each gram of ANZUPGO cream contains 20 mg of delgocitinib. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Serious Infections: ANZUPGO may increase the risk of infection. Eczema herpeticum was observed in a subject treated topically with ANZUPGO. Avoid use of ANZUPGO in patients with an active or serious infection. If a serious infection develops, discontinue ANZUPGO until the infection resolves. (5.1)
- Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell carcinoma have been reported in subjects treated with ANZUPGO. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer. (5.2)
- Immunizations: Avoid vaccination with live vaccines immediately prior to, during, and immediately after ANZUPGO treatment. (5.3)
- Potential Risks Related to JAK Inhibition: It is not known whether ANZUPGO may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer) were observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in rheumatoid arthritis (RA) patients. ANZUPGO is not approved for use in RA. Treatment with oral and topical JAK inhibitors has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. (5.4)

----------ADVERSE REACTIONS----------
Adverse reactions that were reported in ≤ 1% of subjects were application site pain, paresthesia, pruritus, erythema, and bacterial skin infections including finger cellulitis, paronychia, other skin infections, leukopenia, and neutropenia. (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: 7/2025

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HYFTOR® (sirolimus topical gel)
Initial U.S. Approval: 1999

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

HYFTOR is an mTOR inhibitor immunosuppressant indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older. (1)

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

- Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to HYFTOR initiation. (2)
- Apply to the skin of the face affected with angiofibroma twice daily. (2)
- The maximum daily dosage is:
  - 600 mg (2 cm) for patients 6 to 11 years of age. (2)
  - 800 mg (2.5 cm) for patients 12 years of age and older. (2)
- Do not use with occlusive dressings. (2)
- For topical use only. Not for oral, ophthalmic, or intravaginal use. (2)

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

Topical gel, 0.2%: 2 mg of sirolimus per gram. (3)

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

History of hypersensitivity to sirolimus or any other component of HYFTOR. (4)

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

- *Hypersensitivity Reactions*: Oral sirolimus has been associated with hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis. Discontinue HYFTOR immediately if symptoms of hypersensitivity occur. (5.1)
- *Serious Infection*: Serious infections, including opportunistic infections and latent viral infections, such as progressive multifocal leukoencephalopathy, have been reported with oral sirolimus. Discontinue HYFTOR immediately if symptoms of infection occur. (5.2)
- *Malignancy*: Oral sirolimus has been associated with malignancy, including lymphoma and skin cancer. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using HYFTOR. (5.3)
- *Hyperlipidemia*: Oral sirolimus has been associated with increased serum cholesterol and triglycerides requiring treatment. Monitor for hyperlipidemia during treatment. (5.4)
- *Interstitial Lung Disease (ILD)/Non-infectious Pneumonitis*: Oral sirolimus has been associated with ILD, sometimes fatal. Discontinue HYFTOR if ILD symptoms occur. (5.5)
- *Immunizations:* During treatment with HYFTOR, vaccinations may be less effective. Avoid use of live vaccines during treatment with HYFTOR. (5.6)
- *Embryo-Fetal Toxicity*: Based on animal studies, HYFTOR can cause fetal harm. Use of effective contraception is recommended for females of reproductive potential prior to and throughout treatment, and for 12 weeks after final dose of HYFTOR. (5.7, 8.1, 8.3)
- *Male Infertility*: Oral sirolimus has been associated with azoospermia and oligospermia. Advise males that HYFTOR may impair fertility. (5.8, 8.3, 13.1)

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

Most common adverse reactions (≥1%) are dry skin, application site irritation, pruritus, acne, acneiform dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Nobelpharma America, LLC at 1 (877) 375-0825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- *CYP3A4 Inhibitors:* During concomitant use of HYFTOR with CYP3A4 inhibitors, monitor for adverse reactions of HYFTOR. (7.1)
- *Substrates and Inhibitors of CYP3A*: During concomitant use of HYFTOR with drugs that are both substrates and inhibitors of CYP3A, monitor for adverse reactions of the CYP3A substrate and inhibitor. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Breastfeeding not recommended. (8.2)

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

101-101-02
Revised: 5/2025

Appendix 4. Delgocitinib Pharmacology and Pharmacokinetic Properties.[10]

Parameter	
Mechanism of Action	Janus kinase inhibitor
Bioavailability	Maximum plasma concentration was 1.53 nanograms/milliliter
Distribution and Protein Binding	Protein binding: 22-29%; Volume of distribution not reported
Elimination	75% of total dose after oral administration was found unchanged in the urine
Half-Life	21 hours
Metabolism	Metabolized primarily through CYP3A enzyme pathway. Drug interaction studies with delgocitinib have not been conducted.

Appendix 5: Key Inclusion Criteria for Delgocitinib Trial

Population	Adults with moderate to severe chronic hand eczema
Intervention	Delgocitinib topical cream
Comparator	Placebo
Outcomes	Improvement in eczema symptoms to clear or almost clear
Timing	16 weeks
Setting	Outpatient

Appendix 6. Sirolimus Pharmacology and Pharmacokinetic Properties.[15]

Parameter	
Mechanism of Action	Inhibits activation of the mammalian target of rapamycin (mTOR). Exact mechanism of action in the treatment of angiofibromas is unknown.
Bioavailability	Not applicable
Distribution and Protein Binding	No evidence of sirolimus systemic accumulation after topical application
Elimination	Studies have not been conducted on metabolism of topical sirolimus
Half-Life	Studies have not been conducted on metabolism of topical sirolimus
Metabolism	Studies have not been conducted on metabolism of topical sirolimus

Appendix 7: Key Inclusion Criteria for Sirolimus Trial

Population	Adults and children aged 3 years and older
Intervention	Sirolimus 0.2% gel applied twice daily in doses based upon age
Comparator	Placebo
Outcomes	Improvements in size and redness of facial angiofibromas
Timing	12 weeks
Setting	Outpatient

Appendix 8: Prior Authorization Criteria

Topical Agents for Inflammatory Skin Disease

Goal(s):

- Restrict dermatological drugs only for funded OHP diagnoses. Treatments are funded on the OHP for severe forms of certain 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.
- Allow case-by-case review for members covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program.

Length of Authorization:

- From 6 to 12 months

Requires PA:

- Non-preferred topical medications for inflammatory skin conditions.
- All topical medications approved for treatment of inflammatory skin conditions for adults 21 years and older.
- This PA does not apply to oral or injectable 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 and Evidence-Supported Indications for Topical Drugs Approved for Inflammatory Skin Conditions

Generic Drug Name	Brand Name	Minimum Age	Indication (severity)

Anthralin Shampoo Anthralin Cream	ZITHRANOL	12 years 18 years	Plaque Psoriasis
Calcipotriene cream, solution, and ointment Calcipotriene foam	DOVONEX SORILUX	18 years 4 years	Plaque Psoriasis
Calcipotriene/Betamethasone ointment, suspension, foam Calcipotriene/Betamethasone cream	TACLONEX ENSTILAR WYNZORA	12 years 18 years	Plaque Psoriasis
Calcitriol ointment	VECTICAL	2 years	Plaque Psoriasis
Crisaborole 2% ointment	EUCRISA	3 months	Atopic Dermatitis (Mild-to-Moderate)
Delgocitinib 2% cream	ANZUPGO	18 years	Chronic Hand Eczema (Moderate-to-Severe)
Halobetasol propionate/Tazarotene Lotion	DUOBRII	18 years	Plaque Psoriasis
Pimecrolimus 1% cream	ELIDEL	2 years	Atopic Dermatitis (Mild-to-Moderate)
Roflumilast 0.05% cream Roflumilast 0.15% cream Roflumilast 0.3% cream Roflumilast 0.3% foam Roflumilast 0.3% foam	ZORYVE	2-5 years 6 years 6 years 9 years 12 years	Atopic Dermatitis (Mild-to-Moderate) Atopic Dermatitis (Mild-to-Moderate) Plaque Psoriasis Seborrheic Dermatitis Plaque Psoriasis
Ruxolitinib 1.5% cream	OPZELURA	2 years 12 years	Atopic Dermatitis (Mild-to-Moderate) Nonsegmental Vitiligo
Sirolimus 0.2% gel	HYFTOR	6 years	Facial Angiofibromas Associated with Tuberous Sclerosis Complex (TSC)
Tacrolimus 0.03% ointment	PROTOPIC	2 years	Atopic Dermatitis (Moderate-to-Severe)
Tacrolimus 0.1% ointment	PROTOPIC	18 years	Atopic Dermatitis (Moderate-to-Severe)
Tapinarof 1% cream	VTAMA	2 years 18 years	Atopic Dermatitis Plaque Psoriasis
Tazarotene cream and gel	TAZORAC	12 years	Plaque Psoriasis

Table 2. Topical First-Line Treatment Options Based on Disease Severity

Atopic Dermatitis (AD) or Eczema	• Mild to Moderate AD: Low-, Medium-, or High-Potency Corticosteroids* for 2-4 weeks or Calcineurin Inhibitors (pimecrolimus, tacrolimus) • Severe AD: High to Super-High Potency Corticosteroids for 2 weeks or Tacrolimus
Plaque Psoriasis (PsO)	• Mild to Moderate PsO: Moderate- to High-Potency Corticosteroids* for 4 weeks, Calcineurin Inhibitors (pimecrolimus, tacrolimus) for 8 weeks, Vitamin D Analogues (calcitriol, calcipotriene) for 4 weeks, or Tazarotene for 8 weeks[1] • Severe PsO: High to Super-High Potency Corticosteroids for 4 weeks[1]
Nonsegmental Vitiligo	• Mild to Severe Vitiligo: Moderate- to High-Potency Corticosteroids* for 2 months or Calcineurin Inhibitors (pimecrolimus, tacrolimus) for 3 months[2]
Note: *Strength of corticosteroid determined by patient age, site of inflammation, and severity of the condition	

Table 3. Potency Of Topical Corticosteroid Preparations Using U.S. Classification[3]

Potency Group	Corticosteroid	Strength	Formulation
Lowest Potency (Group 7)	Hydrocortisone Base and Hydrocortisone Acetate	0.5%, 1.0%, 2.0%	cream, ointment, gel, lotion, solution

Low Potency (Group 6)	Alcometasone dipropionate	0.05%	cream, ointment
	Betamethasone valerate	0.05%	lotion
	Desonide	0.05%	cream
	Fluocinolone acetonide	0.01%	cream, oil, shampoo, solution
	Triamcinolone acetonide	0.1%	cream
Medium-Low Potency (Group 5)	Betamethasone dipropionate	0.05%	lotion
	Betamethasone valerate	0.1%	cream
	Betamethasone valerate	0.01%	cream, lotion
	Desonide	0.05%	lotion, ointment
	Fluocinolone acetonide	0.025%	cream
	Flurandrenolide	0.05%	cream
	Fluticasone propionate	0.05%	cream
	Hydrocortisone butyrate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Prednicarbate	0.1%	cream
	Triamcinolone acetonide	0.1%	lotion
Medium Potency (Group 4)	Betamethasone valerate	0.12%	foam
	Desoximetasone	0.05%	cream
	Fluocinolone acetonide	0.025%	ointment
	Fluocinolone acetonide	0.2%	cream
	Flurandrenolide	0.05%	ointment
	Halcinonide	0.025%	cream
	Hydrocortisone probutate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Mometasone furoate	0.1%	cream, lotion, solution
	Prednicarbate	0.1%	ointment
Medium-High Potency (Group 3)	Amcinonide	0.1%	cream, lotion
	Betamethasone valerate	0.1%	ointment
	Diflorasone diacetate	0.05%	cream
	Fluocinonide	0.05%	cream
	Fluticasone propionate	0.005%	ointment
	Halcinonide	0.1%	ointment, solution
	Triamcinolone acetonide	0.5%	cream
	Triamcinolone acetonide	0.1%	ointment
High Potency (Group 2)	Amcinonide	0.1%	ointment
	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	cream, lotion
	Betamethasone dipropionate, unaugmented (Diprosone®)	0.05%	cream, ointment
	Desoximetasone	0.25%	cream, ointment, spray
	Desoximetasone	0.05%	gel
	Diflorasone diacetate	0.05%	ointment

	Fluocinonide	0.05%	cream, gel, ointment, solution
	Halcinonide	0.1%	cream
	Mometasone furoate	0.1%	ointment
	Triamcinolone acetonide	0.5%	ointment
Super-High Potency (Group 1)	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	gel, ointment
	Clobetasol propionate	0.05%	cream, foam, gel, lotion, ointment, shampoo, spray
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.1%	cream
	Flurandrenolide	4 mcg/cm^2	tape
	Halobetasol propionate	0.05%	cream, ointment

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for treatment of severe skin disease? Severe disease is defined as:[4] • 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 #6	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #4
4. Is there documentation of disease severity based on DLQI (or other validated scale) AND body surface area (BSA) involvement?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)? Examples include quality of life scores indicating moderate disease (DLQI ≥ 6)	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity
6. Does the patient meet the age requirements per the FDA label? Note: minimum ages for commonly prescribed drugs are listed in **Table 1**	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the diagnosis plaque psoriasis, atopic dermatitis, chronic hand eczema, or nonsegmental vitiligo?	**Yes:** Go to #8	**No:** Go to #10
8. Is the requested product preferred?	**Yes**: Approve for 6 months	**No**: Go to #9
9. Does the patient have a documented contraindication, intolerance or failed trials of at least 1 topical corticosteroid and 1 additional non-steroidal preferred agent (Table 2)?	**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
10. Is the diagnosis facial angiofibroma associated with tuberous sclerosis complex?	**Yes:** Go to #11	**No:** Go to #16

Approval Criteria		
11. Is there documentation of functional impairment, ulceration, recurrent bleeding, infection, or pain related to the facial angiofibromas?	**Yes**: Go to #12	**No:** Pass to RPh. Deny; medical necessity
12. Is the medication prescribed by a dermatologist, neurologist, or in consultation with another provider with expertise in managing tuberous sclerosis complex (TSC) and its complications?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the patient of childbearing potential?	**Yes:** Go to #14	**No:** Approve for 12 weeks
14. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15
15. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant and has the patient been advised to use effective contraception during therapy and for 12 weeks after stopping treatment?	**Yes:** Approve for 12 weeks	**No:** Pass to RPh. Deny; medical appropriateness
16. Is the request for an FDA approved indication and age OR is supporting literature provided?	**Yes**: Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew therapy for plaque psoriasis, atopic dermatitis, chronic hand eczema, or nonsegmental vitiligo ?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved after treatment with topical 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) or Children's Dermatology Life Quality Index (CDLQI from when treatment started OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score or attainment of clear or almost clear skin?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request to renew therapy for treatment of facial angiofibroma due to TSC?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is there provider documentation of response to therapy (improvement in size and redness of skin lesions)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

**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. *Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. J Am Acad Dermatol. 2021;84(2):432-470.*
2. *Eleftheriadou, V., Atkar, R., Batchelor, J., McDonald, B., etal., British Association of Dermatologists guidelines for the management of people with vitiligo 2021*. Br J Dermatol, 186: 18-29. https://doi.org/10.1111/bjd.20596*
3. *Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed October 6, 2022.*
4. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx. Accessed March 1, 2022.*

P&T/DUR Review: 12/25 (DM); 12/22; 6/22; 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: 1/1/26, 2/1/23; 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