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Drug Class Update with New Drug Evaluations: Topical Products for Inflammatory Skin Conditions

Date of Review: December 2022

Date of Last Review: June 2022 (Topical Products for Skin Inflammatory Skin Conditions)
September 2017 (Topical Anti-Psoriatics)

Dates of Literature Search: 01/01/2017 – 09/01/2022

Generic Name:
Roflumilast
Tapinarof

Brand Name (Manufacturer):
Zoryve™ (Arcutis Biotherapeutics)
Vtama® (Dermavant Sciences, Inc.)

Dossiers Received: yes

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

Plain Language Summary:

- Is there any new evidence for different topical medicines (treatments applied to the skin) for skin conditions including psoriasis, eczema (dry, itchy, red skin), and vitiligo (patchy loss of skin color) that would change the current policy of topical medicines for skin conditions?
- Psoriasis is a life-long condition that can cause red patches of thickened skin (plaques) and itching. The most commonly affected parts of the body are the elbows, knees, body, and scalp.
- One review looked to see if using topical pimecrolimus or tacrolimus caused cancer. People who apply pimecrolimus or tacrolimus may have a slightly increased risk of lymphoma. Lymphoma is a cancer of the lymphatic system, which is part of the body's germ-fighting defense system. This study did not find an overall increased risk cancer when these medicines are used
- The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) recommend several topical medicines to reduce irritation, redness, and itching in adults with psoriasis. These medicines include steroids like hydrocortisone, vitamin D products (calcipotriene, calcitriol), coal tar preparations, and vitamin A products (tazarotene).
- Topical medicines have not been studied very well in children and teenagers. The highest quality evidence is for a combination product containing calcipotriene and a steroid called betamethasone in people that are 12 years of age and older.
- This review also looked at the evidence for 2 new topical medicines, roflumilast and tapinarof, recently approved by the Food and Drug Administration (FDA) to treat psoriasis.
- Two 2-month studies showed that when roflumilast cream is applied to areas of the skin with psoriasis in people that were 2 years and older, the thickness of the skin improved and the redness decreased more than when people used a skin cream without medicine. People that used roflumilast cream did not experience very many side effects. The most common side effects were diarrhea and headache.

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- Two 3-month studies showed that tapinarof cream helped improved skin redness, itching and irritation from psoriasis in adults better than a skin cream without medicine. In these studies, some people developed itching and a rash where they put the tapinarof cream on their skin.
- Medicaid will pay for most generic topical steroid creams and ointments, calcipotriene, tazarotene, and an ointment that has both calcipotriene and a steroid called betamethasone.
- Providers must explain to the Oregon Health Authority why someone needs roflumilast or tapinarof cream before Medicaid will pay for it. This process is called prior authorization. Medicaid will pay for some older and less expensive topical medicines without prior authorization. Tapinarof and roflumilast have not been studied compared to older and less expensive agents to see if they work better.

Purpose for Class Update:
To review evidence for topical agents approved to treat inflammatory skin conditions published since the last literature scan and to evaluate place in therapy for 2 topical agents, roflumilast and tapinarof, recently FDA-approved for treatment of plaque psoriasis (PsO).

Research Questions:
1. Is there new evidence regarding the comparative safety and efficacy of topical agents to manage inflammatory skin conditions?
2. For adults and children with PsO, what is the safety and effectiveness of roflumilast 0.3% cream?
3. For adults with PsO, what is the safety and effectiveness of tapinarof 1% cream?
4. Are there patients based on demographics characteristics (i.e., age, race, ethnicity, gender), socioeconomic status, concomitant medications, severity of disease, or co-morbidities for which one topical agent is more effective or associated with fewer adverse events in treating inflammatory skin diseases?

Conclusions:
- Since the last review of topical agents for inflammatory skin diseases, one systematic review[1] and 2 guidelines[2,3] were published.
- A 2021 systematic review and meta-analysis investigated the association between topical calcineurin inhibitor use and risk of cancer including lymphoma, keratinocyte carcinoma and melanoma.[1] Compared with non-active comparators, moderate quality evidence from observational studies suggests there is no association between topical calcineurin inhibitor use and overall cancer risk (relative risk [RR], 1.03; 95% confidence interval [CI], 0.92 to 1.16).[1] However, moderate quality evidence suggests lymphoma risk is elevated with topical calcineurin inhibitor use when compared with both nonactive comparators (RR, 1.86; 95% CI, 1.39 to 2.49) and topical corticosteroids (RR, 1.35; 95% CI, 1.13 to 1.61).[1] In summary, these findings suggest an association between topical calcineurin inhibitor use and risk of lymphoma but without an increased risk of other cancers.[1]
- In July 2020, the American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) published recommendations for the treatment of adult psoriasis with topical therapy.[2] Moderate-to-high quality of evidence (QoE) supports a strong recommendation for the use of the following medications in managing psoriasis in adults:
    - Topical corticosteroids for up to 4 weeks the treatment of mild-to-severe psoriasis not involving intertriginous areas (high QoE).[2]
    - Topical vitamin D analogues (i.e., calcipotriene, calcitriol) for up to 52 weeks for the treatment of mild-to-moderate psoriasis (moderate-to-high QoE).[2]
    - Mild-to-high-potency topical corticosteroids in combination with tazarotene for 8 to 16 weeks for mild-to-moderate psoriasis (high QoE).[2]
    - Topical salicylic acid for 8 to 16 weeks for mild-to-moderate psoriasis (moderate-to-high QoE).[2]
    - Coal tar preparations for treatment of mild-to-moderate psoriasis (moderate-to-high QoE).[2]
- In November 2019, the AAD-NPF published recommendations for the treatment of psoriasis in pediatric patients.[3] Most of the available evidence for administering topical medications in children and adolescents ranges from low-to-moderate quality, resulting in recommendations based on inconsistent or

limited-quality evidence.[3] Combination products containing calcipotriene and betamethasone are FDA-approved for use in children ages 12 years and older with mild-to-moderate PsO for use on the body and scalp.[4] The evidence for use of this product in children and adolescents is considered moderate-to-high QoE by AAD-NPF.[3]

- There is insufficient evidence to base conclusions on the comparative safety and efficacy of topical agents for treatment of inflammatory skin conditions. specific to demographic characteristics, socioeconomic status, concomitant medications, severity of disease, or co-morbidities, for individuals with inflammatory skin disease.
- Roflumilast 0.3% cream, a selective inhibitor of phosphodiesterase type 4 (PDE-4), received FDA approval July 2022 for topical treatment of PsO, including intertriginous areas, in patients 12 years of age and older.[5] Two phase 3 multicenter, double-blind, vehicle-controlled RCTs, DERMIS-1 and DERMIS-2, supported the FDA-approval of topical roflumilast.[6] The primary endpoint was IGA success, defined as the percentage of patients who achieved IGA status of 0 or 1 and a 2 grade or greater improvement in IGA score from baseline at week 8.[6] In both studies, moderate-quality evidence showed a greater percentage of roflumilast-treated patients achieved IGA success at week 8 compared with vehicle-treated patients (DERMIS-1: 42.4% vs. 6.1%, respectively; difference, 39.6%; 95% CI 32.3 to 46.9; p<0.001 and DERMIS-2: 37.5% vs. 6.9%, respectively; difference, 28.9%; 95% CI 20.8% to 36.9%; p<0.001).[6] The number of pediatric patients assessed in these trials was small, making it difficult to draw firm conclusions regarding efficacy of roflumilast in this population.
- There were low rates of application-site adverse effects (AEs) with roflumilast 0.3% cream in phase 3 clinical trials.[5] The most frequently reported AEs included diarrhea, headache, insomnia, and nausea.[5]
- Tapinarof 1% cream, a novel aryl hydrocarbon receptor agonist, received FDA-approval for the topical treatment of PsO in adults May 2022.[7] Two identical, double-blind, multi-center, phase 3, vehicle-controlled, randomized clinical trials (PSOARING 1 and PSOARING 2) evaluated the safety and efficacy of tapinarof 1% cream in treating adults with mild-to-severe PsO.[8] The primary efficacy endpoint was Physician's Global Assessment (PGA) success, defined as a PGA score of 0 or 1 and a minimum 2-grade PGA score improvement from baseline at week 12.[8] Moderate-quality evidence showed the primary efficacy endpoint of a PGA success was achieved by a higher proportion of patients at week 12 in the tapinarof cream group versus the vehicle group in PSOARING 1 (35.4% versus 6.0%, respectively; difference 29.4%; RR 5.8; 95% CI 2.9 to 11.6; p<0.001) and PSOARING 2 (40.2% versus 6.3%, respectively; difference 33.9%; RR 6.1; 95% CI 3.3 to 11.4; p<0.001).[8]
- In clinical trials, folliculitis, contact dermatitis, and headache occurred more frequently in the tapinarof groups than in the vehicle groups.[7]
- Clinical trials of longer duration and with larger populations are needed to assess long-term safety and efficacy of roflumilast and tapinarof in patients with PsO. There is insufficient evidence to compare the safety and efficacy of roflumilast or tapinarof with other topical agents approved for treatment of PsO.
- The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents who are 20 years of age and younger enrolled in Medicaid.[9] The goal of this benefit is to ensure that children receive age-appropriate screening, preventive services, and treatment services that are medically necessary to correct or ameliorate any identified conditions.[9] Management of symptoms associated with inflammatory skin conditions when they impact the ability to grow, develop or participate in school falls under this benefit.
- In July 2022, ruxolitinib cream received an expanded FDA indication for topical treatment of nonsegmental vitiligo in patients aged 12 years and older.[10]

Recommendations:

- Add the medications listed in the "Topical Anti-Psoriatic" class to the "Topical Agents for Inflammatory Skin Conditions" class.
- Designate roflumilast and tapinarof as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Update clinical prior authorization (PA) criteria to remove PA for preferred products and accommodate individual review under EPSDT.
- Revise PA criteria for "Topical Agents for Inflammatory Skin Conditions" 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 or those having hand, foot, face, or mucous membrane involvement.

- Revise clinical PA criteria for "Topical Agents for Inflammatory Skin Conditions" to include roflumilast and tapinarof and limit 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 topical corticosteroids for at least 4 weeks
- After evaluation of costs in the executive session, make tazarotene gel nonpreferred.

Summary of Prior Reviews and Current Policy

- A literature scan for topical anti-psoriatic medications was presented to the Pharmacy and Therapeutics (P & T) Committee at the September 2017 meeting. At that time, coal tar products were designated as non-preferred products on the PDL.
- Topical agents for inflammatory skin conditions were recently reviewed by the P & T Committee at the June 2022 meeting as part of the OHSU Drug Effectiveness Review Project (DERP) summary on treatment of atopic dermatitis. A literature scan on management of vitiligo was also presented at the June 2022 P & T Committee meeting. First line, off-label, topical treatments for vitiligo are topical corticosteroids and topical calcineurin inhibitors. Clinical PA criteria for all drugs used to manage inflammatory skin conditions were updated to reflect 2022 Health Evidence Review Commission (HERC) guidance from Guideline Note 21, which was revised to include facial involvement in the severity assessment of skin conditions and severe vitiligo as a funded inflammatory skin condition.[11] The title for clinical PA criteria for "Topical Therapies for Atopic Dermatitis and Psoriasis" was revised to "Topical Agents for Inflammatory Skin Conditions" (**Appendix 4**). Topical ruxolitinib was added to the clinical PA criteria for "Topical Agents for Inflammatory Skin Conditions" and designated as non-preferred on the PDL.
- Calcipotriene, calcipotriene/betamethasone, and tazarotene are designated as preferred topical agents on the PDL and do not require PA authorization. Both of the drugs used to treat atopic dermatitis (pimecrolimus and tacrolimus) are preferred, but require PA to ensure appropriate utilization in FDA-approved populations. Non-preferred agents include anthralin, calcitriol, coal tar, crisaborole and ruxolitinib, which require PA to ensure appropriate utilization in inflammatory skin conditions funded by HERC.

Background:

Plaque psoriasis is a chronic, immune-mediated inflammatory disorder of the skin which affects about 3% of the United States (U.S.) adult population.[12] The onset generally occurs between 20 and 30 years of age.[12] Approximately 1% of children are affected by psoriasis, typically with onset during adolescence.[3] 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%.[12]

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), the duration of antipsoriatic treatments, endocrine factors, sunlight, alcohol, smoking, and stress.[13] Psoriasis is driven by multiple pathways of immune mediators, including tumor necrosis factor (TNF), interleukin (IL)-17 and IL-23 cytokines.[14] Plaque psoriasis is characterized by itchy, red, scaly, raised lesions on the skin, especially on the elbows, knees, scalp, and trunk, hands and feet.[15] Typically, PsO is classified as mild, moderate or severe. An estimated 20% of patients with PsO have moderate-to-severe disease, defined as greater than 10% of body surface area (BSA).[12] Mild disease involves less than 5% of BSA and has little to no impact on quality of life or function.[15] Mild PsO is not a funded condition per the HERC Guideline Note 21.[16] Per 2020 AAD-NPF guidance, first-line topical agents to treat mild-to-moderate PsO include: corticosteroids, vitamin D analogues (e.g., calcipotriene), retinoids (e.g., tazarotene) or salicylic acid.[2] The potency of topical corticosteroids varies depending on the drug and formulation.

Formulation considerations are presented in **Table 1**. **Table 2** summarizes the 7 different potency classifications (ranging from low to super-high potency) according to United States (U.S.) nomenclature.

Table 1. Topical Corticosteroid Formulation Considerations[17]

Ointment	Generally, most potent due to occlusive nature
	Most lubricating and greasy; limited use in intertriginous areas
	Least aesthetically appealing
Cream	Contain preservatives that can cause irritation or allergic reaction
	Can be used in intertriginous areas; may have a drying effect
	Most aesthetically appealing; quick absorption
Lotion	Contain alcohol which can cause irritation
	Can be used on scalp or hairy areas
	Typically cause a drying effect
Gel, Solution, Spray, Foam	Dry and absorb quickly
	Useful for exudative inflammation, scalp, or hairy areas
	Often contain alcohol or propylene glycol, which may cause irritation
	Most drying formulations

Table 2. Potency of topical corticosteroid preparations[17,18]

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

Phototherapy is an option for patients with moderate-to-severe PsO who have not responded to topical therapy.[19] Systemic non-biologic treatments are recommended for patients with moderate-to-severe PsO unresponsive to topical treatment or phototherapy and include methotrexate, cyclosporine, mycophenolate or azathioprine.[20] Targeted immune modulators including TNF-inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab), IL-12/23 antagonists (ustekinumab), IL-23 antagonists (guselkumab, risankizumab, tildrakizumab), or IL-17 antagonists (secukinumab, ixekizumab, brodalumab), may be added for patients with moderate-to-severe PsO not controlled by other therapies.[21]

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.[22,23] 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.[22] 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.[23] This tool is rarely used in clinical practice to assess psoriasis severity due to the substantial amount of time required to complete the scoring.[2] The PGA is a scoring system that assesses degree of erythema, induration, and scaling.[2] There are several different versions of the PGA, with most severity scores ranging from 0 to 4 or 0 to 5.[2] Higher scores indicate more severe disease. The PGA is also used in research, but not frequently used in clinical practice.[2] The IGA has also been used to measure the severity of PsO based on skin thickening and hyperpigmentation in clinical trials.[24] 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).[24] Response to therapy is indicated by a score of 0 or 1.[24]

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, and CADTH resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

Systematic Reviews:

Topical Calcineurin Inhibitor Use and Risk of Cancer

A 2021 systematic review and meta-analysis investigated the association between topical calcineurin inhibitor use and the risk of cancer including lymphoma, keratinocyte carcinoma and melanoma.[1] The review was based a 2006 box FDA warning indicating a potentially elevated risk of cancer with topical calcineurin inhibitors based on the findings of case reports (primarily of lymphomas and skin cancers), animal carcinogenicity studies, and studies on systemic tacrolimus use in organ transplant recipients.[25] The box warning was based on approximately 25 case reports, without systematic analysis supporting causation between topical calcineurin inhibitor use and malignant neoplasms.[1]

Literature was searched through August 21, 2020.[1] Observational studies investigating the association between treatment with tacrolimus and pimecrolimus and the development of cancer with nonactive or active comparators were included in the review.[1] Eight cohort studies and 3 case-control studies met inclusion criteria.[1] Six studies were conducted in the U.S., 3 studies were based in Europe (Denmark and United Kingdom), one study was conducted in Singapore, and one study included individuals from centers across North America and Europe.[1] Five studies included a nonactive comparator or untreated control group.[1] Two studies used expected or standardized incidence rates from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute as a comparator.[1] Four studies included an active comparator group treated with topical corticosteroids.[1]

A total of 408,366 participants were treated with topical calcineurin inhibitors in cohort studies, with a mean age of 17.1 years and a mean percentage of female participants of 55.1% and male participants of 44.9%.[1] Of these participants, 151,772 were treated with tacrolimus and 214,640 with pimecrolimus.[1] In the 5 studies with a nonactive comparator group, a total of 1,764,313 untreated controls were reported.[1] Of the 4 studies using a topical corticosteroid comparator, a total of 1,067,280 topical corticosteroid-treated participants were reported.[1] Mean follow-up time ranged from 1.5 to 10 years. [1] Duration of treatment with topical calcineurin inhibitors was not reported. Four cohort studies included a children-only group (n=93,120).[1] Quality of studies was assessed using the Newcastle-Ottawa scale for cohort and case-control studies.[26] One study was assigned 3 stars, indicating a high or unclear risk of bias, owing to insufficient description of study cohorts and self-report of malignant neoplasm; 6 studies were assigned 4 to 6 stars, indicating a moderate risk of bias; and 4 studies were assigned 7 to 9 stars, indicating a low risk of bias.[1]

Compared with nonactive comparators, there was no association between topical calcineurin inhibitor use and any cancer overall (RR, 1.03; 95% CI, 0.92 to 1.16).[1] Lymphoma risk was elevated with topical calcineurin inhibitor use with both nonactive (RR, 1.86; 95% CI, 1.39 to 2.49) and topical corticosteroid comparators (RR, 1.35; 95% CI, 1.13 to 1.61).[1] No significant association was found between topical calcineurin inhibitor use and increased skin cancer (melanoma and keratinocyte carcinoma).[1] The association with lymphoma was stronger in studies with a nonactive comparator, as opposed to those that compared topical calcineurin inhibitor and topical corticosteroid use, indicating that some of the association is likely a result of confounding by indication.[1] Overall, these findings suggest an association between topical calcineurin inhibitor use and risk of lymphoma but with no increased risk of other cancers, including skin cancers.[1] Lymphoma is rare, with an annual worldwide incidence of 1.35 per 100,000 in children and 9.88 per 100,000 in adults.[27] The 35% increased relative risk found in this study for topical calcineurin inhibitor use compared with topical corticosteroids would, therefore, result in estimated numbers needed to harm for lymphoma of more than 200,000 in children and almost 30,000 in adults.[1]

There were several limitations of this systemic review. Some of the included studies were small with relatively short follow-up periods, which limits the ability to determine the risk of malignant neoplasm induction with long latency periods.[1] Lymphoma represents a heterogeneous group of diseases, which could bias the results toward the null if a true association exists for only one or some lymphoma subtypes.[1] Atopic dermatitis itself may be associated with increased risk of lymphoma and keratinocyte carcinoma.[1] In addition, there may be a severity gradient with worse skin disease (and associated increased systemic inflammation) associated with further increased risk of cancer.[1] Finally, given the observational design of the included studies, unmeasured confounding limits interpretation of association and causation.[1]

After review, 4 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses),[28] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[29-31]

New Guidelines:

High Quality Guidelines:

American Academy of Dermatology–National Psoriasis Foundation Guidelines for Treatment of Psoriasis with Topical Therapy

In July 2020, the AAD and NPF published recommendations for the treatment of adult psoriasis with topical therapy.[2] Topical medications are frequently used as adjunctive therapies for patients with psoriasis receiving phototherapy, systemic non-biologic, or targeted immune modulator (TIM) therapy.[2] This guideline evaluates the efficacy, effectiveness, and adverse effects of topical corticosteroids, vitamin D analogues, tazarotene, salicylic acid, anthralin, and coal tar. Clinical recommendations were developed by the guideline development committee after reviewing available evidence and ranked as "A" (based on consistent and good quality evidence), or "B" (based on inconsistent or limited-quality evidence) or "C" (based on consensus, opinion, or case studies).[2] For the purposes of this review, only recommendations warranting an "A" or "B" ranking are included in the summary.

Corticosteroids

Evidence on the efficacy of topical corticosteroids from RCTs varies due to the differences in study designs, patient populations, and end points, making it difficult to do an accurate statistical comparison of the majority of published studies.[2] In numerous RCTs, different potency topical corticosteroids were safe and effective at 2 to 4 weeks in the treatment of mild-to-severe PsO.[2] Choosing a corticosteroid with appropriate potency plus the appropriate vehicle should be based on the disease severity, disease location, patient preference, and the age of the patient.[2] Lower potency corticosteroids should be used on the face, intertriginous areas, and areas that are susceptible to steroid atrophy (e.g., forearms) and other adverse effects.[2] In adults, moderate- to high-potency corticosteroids are generally recommended as initial therapy.[2] Areas with thick, chronic plaques often require treatment with super-high potency corticosteroids.[2]

The most common local skin adverse effects of topical corticosteroid use include skin atrophy, striae, folliculitis, telangiectasia, and purpura.[2] The face and intertriginous areas, as well as chronically treated areas, are at greatest risk to develop these adverse effects.[2] Topical corticosteroids may exacerbate acne, rosacea, perioral dermatitis, and tinea infections and may occasionally cause contact dermatitis.[2] Risk of hypothalamic pituitary adrenal (HPA) axis suppression from the use of topical corticosteroids for extensive plaque or scalp psoriasis has been reported to be low.[2] Despite the safety data, caution is advised, because the greatest risk for systemic adverse effects occurs when super-high- or high-potency corticosteroids are used over a large surface (i.e., BSA greater than 20%) or under occlusion for a prolonged period (i.e., more than 4 weeks).[2] Clinicians should consider limiting the use of super-high-potency corticosteroids to no more than twice daily for up to 4 weeks, when possible.[2]

In rare cases, low fetal birth weight has been reported with prolonged potent topical corticosteroid use during pregnancy.[2] In addition, there is a single case report of a nursing mother who applied a potent topical corticosteroid on the nipple and the breastfeeding infant developed hypertension.[32] Therefore, the use of a high- or super-high potency corticosteroids in the nipple and the areola area should be avoided in nursing mothers.[2]

Recommendations:

- The use of moderate to super-high potency topical corticosteroids for up to 4 weeks is recommended for the treatment plaque psoriasis not involving intertriginous areas (strength of recommendation A; high QoE).[2]
- The use of mild to super-high potency topical corticosteroids for a minimum of 4 weeks is recommended as initial and maintenance treatment of scalp psoriasis (strength of recommendation A; high QoE).[2]

Vitamin D Analogues

The vitamin D analogues, calcitriol and calcipotriene, exert their effect in psoriasis by binding to vitamin D receptors, which inhibit keratinocyte proliferation and enhance keratinocyte differentiation.[2] Several studies have shown that 4-to-8 week treatment of calcipotriene and calcitriol is safe and efficacious for treating mild-to-moderate psoriasis.[2] The use of combination treatment with a vitamin D analogue and a potent topical corticosteroid from 3 to 52 weeks is more effective than either agent alone for the treatment of psoriasis.[2] Local adverse effects with vitamin D analogues can affect up to 35% of patients and include burning, pruritus, edema, peeling, dryness, and erythema.[2] With continued treatment, these adverse effects usually subside or disappear.[2] Systemic adverse effects due to topical vitamin D analogues include hypercalcemia and parathyroid hormone suppression.[2] These effects are quite rare unless more than 30% of BSA is treated, the recommended dose is exceeded, or the patient has an underlying renal disease or impaired calcium metabolism.[2]

Recommendations:

- The long-term use of topical vitamin D analogues (i.e., up to 52 weeks), is recommended for the treatment of mild-to-moderate psoriasis (strength of recommendation A; moderate-to-high QoE).[2]
- Use of calcipotriene foam and calcipotriene plus betamethasone dipropionate gel is recommended for 4-12 weeks for the treatment of mild to moderate scalp psoriasis (strength of recommendation A; high QoE).[2]
- Topical calcipotriene combined with hydrocortisone for 8 weeks can be used for the treatment of facial psoriasis (strength of recommendation B; moderate-to-high QoE).[2]
- Use of combination treatments with vitamin D analogues and potent class topical corticosteroids up to 52 weeks is recommended for the treatment of psoriasis (strength of recommendation A; moderate-to-high QoE).[2]

Tazarotene

Tazarotene is a topical retinoid that exerts its therapeutic effects by acting on keratinocyte differentiation and proliferation and by downregulating the expression of proinflammatory genes.[2] The use of topical tazarotene for 8 to 12 weeks is recommended for the treatment of mild-to-moderate psoriasis.[2] Adverse effects with tazarotene include erythema, burning, and pruritus and are more prominent at higher concentrations.[2] Adverse effects can be reduced by using a cream formulation or lower concentration formulation, combining tazarotene with moisturizers, applying it on alternate days, or short-contact (i.e., 30 to 60 minutes) treatment, and combining it with topical corticosteroids.[2] The use of a medium- or high-potency topical corticosteroid in combination with tazarotene for 8 to 16 weeks is recommended for the treatment of mild-to-moderate psoriasis.[2] Tazarotene should not be used in pregnant women.[33] No human data are available on excretion in human milk.[33]

Recommendations:

- Topical tazarotene can be used for the treatment of mild-to-moderate psoriasis (strength of recommendation B; low-to-high QoE).[2]
- The use of mid- or high-potency topical corticosteroid in combination with tazarotene for 8-16 weeks is more effective than monotherapy with tazarotene and is recommended for the treatment of mild-to-moderate psoriasis (strength of recommendation A; high QoE).[2]
- The use of topical corticosteroids along with tazarotene is recommended to decrease the duration of treatment as well as increase the length of remission (strength of recommendation A; high QoE).[2]

Salicylic Acid

Salicylic acid is used as a topical keratolytic agent in the treatment of psoriasis.[2] Its mechanism of action is believed to involve the reduction of the binding between keratinocytes; it minimizes scaling and softens psoriatic plaques.[2] Topical salicylic acid for 8 to 16 weeks is recommended for the treatment of mild- to-moderate psoriasis.[2] Salicylic acid is effective for the treatment of psoriasis, alone or combined with other topical therapies, including corticosteroids and topical

immunomodulators.[2] Systemic absorption and increased risk for salicylate toxicity are higher in patients with renal disease and patients with hepatic disease when treating large body surface areas (i.e., greater than 20%); therefore, its use should be avoided or used with caution in these groups.[2] Topical salicylic acid should not be applied before ultraviolet B (UVB) phototherapy because it reduces the efficacy of phototherapy.[2] There are inadequate human data available for the use of salicylic acid during pregnancy or lactation.[2]

Recommendations:

- Topical salicylic acid can be used for 8 to 16 weeks for the treatment of mild-to-moderate psoriasis (strength of recommendation B; moderate-to-high QoE).[2]
- The combination of salicylic acid with topical corticosteroids can be used for the treatment of moderate-to-severe psoriasis with BSA less than or equal to 20% (strength of recommendation B; high QoE).[2]

Anthralin

Anthralin is a polycyclic aromatic hydrocarbon derivative.[2] The exact mechanism of action of anthralin is not fully understood, although it is thought to be mediated by preventing T-lymphocyte activation and promoting keratinocyte differentiation.[2] Topical anthralin is effective in the treatment of psoriasis.[2] The recommended treatment for mild-to-moderate psoriasis is 8 to 12 weeks of topical anthralin starting at 0.1% concentration, with increasing concentration over time as tolerated.[2] Short contact (i.e., up to 2 hours per once-daily application) anthralin therapy is recommended to limit adverse effects.[2] Adverse effects include perilesional erythema, burning, and mild-to-severe staining of the skin.[2] These are improved by using the short-contact application method (i.e., up to 2 hours). Application to the face or other highly visible areas should be avoided.[2] There is no evidence of any topical or systemic toxicities related to prolonged anthralin use.[2] No data are available on human milk excretion.[2]

Recommendation:

- Topical anthralin for 8-12 weeks can be used for the treatment of mild-to-moderate psoriasis. Short contact (up to 2 hours per day) anthralin is recommended to limit adverse side effects (strength of recommendation B; low-to-high QoE).[2]

Coal Tar

Coal tar has been used for the treatment of psoriasis for more than a century.[2] The polyaromatic hydrocarbons bind to the aryl hydrocarbon receptor, and tar is known to decrease keratinocyte proliferation by suppressing DNA synthesis.[2] It also suppresses inflammation and may affect immunologic function.[2] Coal tar preparations are recommended for the treatment of mild-to-moderate psoriasis.[2] Coal tar products can stain clothes, and tar odor is present in most preparations, thus reducing patient adherence.[2] The risks of coal tar application include local irritation, folliculitis, contact dermatitis, and phototoxicity.[2] Therapy is associated with possible carcinogenicity, but risk remains unproven.[2] Dermatologic studies on topical preparations have not revealed an increased risk, but animal and occupational studies document carcinogenicity with prolonged exposures over many years.[2] A retrospective analysis of human use of coal tar preparations during pregnancy has not shown any adverse effects on the fetus, although in animal studies, large doses have been observed to increase the risk of cleft palates, small lungs, and perinatal mortality.[34] Thus, it may be advisable to avoid the use of coal tar preparations during pregnancy and lactation.[2]

Recommendation:

- Coal tar preparations are recommended for the treatment of mild-to-moderate psoriasis (strength of recommendation A; moderate-to-high QoE).[2]

<u>American Academy of Dermatology–National Psoriasis Foundation Guidelines for Treatment of Psoriasis in Pediatric Patients</u>

In November 2019, the AAD and NPF published recommendations for the treatment of psoriasis in pediatric patients.[3] The guidance addresses the use of topical agents, systemic nonbiologic agents, and TIMs in children and adolescents. For the purposes of this class update, recommendations and strength of evidence for just the topical treatments are summarized.

Corticosteroids

Topical steroid use for psoriasis in children is technically an off-label treatment (due to lack of clinical trials in this population) but is frequently practiced and widely considered for localized disease.[3] The adverse effect profile for topical corticosteroids in children is analogous to that in adults, particularly relating to burning and stinging at the application site.[3] Younger patients 0 through 6 years of age, especially infants are vulnerable to HPA axis suppression given their high BSA-to-volume ratio compared with older children and adults.[3] High-potency or super-high-potency topical corticosteroids should be used with caution, and patients should be followed closely by a dermatologist to ensure proper use and to monitor for overuse and adverse effects.[3]

Recommendation:

- Topical corticosteroids are recommended for the treatment of pediatric psoriasis as an off-label therapy (strength of recommendation B; moderate QoE).

Vitamin D Analogues

An important advantage of the vitamin D analogues, especially for pediatric use, is their corticosteroid-sparing function.[3] Treatment with vitamin D analogues is safe, effective, and relatively well tolerated in children of all ages.[3] Several small case series and clinical trials of low to good quality have been performed in children.[3] Vitamin D analogue preparations can cause local irritation and are often avoided on the face, genitals, and intertriginous skin.[3] Irritation is often improved or ameliorated with the concomitant application of an emollient.[3] Caution must be taken regarding quantities used, given the theoretical risk of hypercalcemia and vitamin D deficiency associated with systemic absorption, although no specific data or recommendations exist on maximum use in children.[3]

Recommendations:

- Calcipotriene is recommended as a treatment option for childhood PsO (strength of recommendation B; moderate QoE).[3]
- Because of the theoretical risk of increased calcium absorption and systemic effects of hypercalcemia, calcipotriene applied to large body surface areas is not recommended (strength of recommendation B; low QoE).[3]
- Monitoring of vitamin D metabolites may be considered during calcipotriene therapy when applied to a large body surface area (strength of recommendation B; moderate-to-high QoE).[3]

Combination Topical Therapy

Combination products containing calcipotriene and betamethasone are FDA-approved for use in children ages 12 years and older with mild-to-moderate PsO for use on the body and scalp.[4] Transitioning from combination therapy to topical vitamin D monotherapy upon disease improvement may be beneficial to decrease topical steroid use.[3] Combination calcipotriene and betamethasone may result in adverse effects (such as striae and HPA axis suppression) due largely to the steroid component.[3]

Recommendations:

- The combination of calcipotriene/betamethasone dipropionate ointment applied once daily for up to 4 weeks at a time is recommended as a safe and effective treatment for children ages 12 years and older with mild-to-moderate PsO (strength of recommendation B; moderate-to-high QoE).[3]
- The combination of calcipotriene/betamethasone dipropionate suspension applied once daily for up to 8 weeks at a time is recommended as a safe and effective treatment for children ages 12 years and older with mild-to-moderate plaque psoriasis of the scalp (strength of recommendation B; moderate QoE).[3]

Anthralin

Anthralin is FDA-approved for use in children and adolescents aged 12 years and older with scalp psoriasis.[35] Anthralin has many adverse effects, including burning, stinging, pruritus, and perilesional erythema.[3] Staining often results upon application and removal, affecting the skin, clothing, and tub/shower.[3] As such, anthralin application is usually limited by poor tolerability and cosmetic concerns and is rarely used on the face and intertriginous areas.[3]

Recommendation:

- Long-term use (12 weeks or longer) of topical anthralin is recommended for the treatment of mild-to-moderate psoriasis. Short-contact anthralin protocols are recommended to limit adverse effects (strength of recommendation B; moderate QoE).[3]

Tazarotene and Coal Tar

Tazarotene cream is only FDA-approved for the treatment of stable PsO of less than 20% BSA in adults.[35] The safety and efficacy of tazarotene gel have not been established in pediatric patients with psoriasis under the age of 12 years.[33] Coal tar is commonly used in combination with phototherapy (Goeckerman treatment) for psoriasis.[3] There is no current literature studying coal tar in pediatric psoriasis as monotherapy.[3]

New Formulations or Indications:

December 2018: The combination product of calcipotriene and betamethasone dipropionate (ENSTILAR, TACLONEX) received expanded FDA-approval for topical treatment of PsO in patients aged 12 years and older.[4] The combination product is available as an ointment, foam, and topical suspension which can be applied to the scalp or body. Prior to this approval, these products were approved for topical treatment of psoriasis vulgaris in adults aged 18 years and older.

November 2019: Calcipotriene (SORILUX) topical foam received expanded FDA-approval for use in patients aged 4 years and older.[36] Prior to this approval, calcipotriene was approved for topical treatment of PsO of the scalp and body in patients 12 years and older.

July 2020: Calcitriol (VECTICAL) topical ointment received expanded FDA-approval for use in patients 2 years and older.[37] Prior to this approval, calcitriol was approved for topical treatment of mild-to-moderate PsO in adults 18 years and older.

August 2020: Halobetasol (ULTRAVATE) topical lotion received expanded FDA-approval for use in patients aged 12 years and older.[38] Prior to this approval, halobetasol was approved for topical treatment of PsO in adults 18 years and older.
May 2021: Halobetasol (LEXETTE) topical foam received expanded FDA-approval for use in patients aged 12 years and older.[39] Prior to this approval, halobetasol was approved for topical treatment of PsO in adults 18 years and older.

July 2022: Ruxolitinib (OPZELURA) cream received an expanded FDA indication for topical treatment of nonsegmental vitiligo in patients aged 12 years and older.[10] The initial approval of ruxolitinib cream in 2021 was for the short-term and non-continuous treatment of mild-to-moderate atopic dermatitis in non-immunocompromised patients aged 12 years and older.[10] The expanded approval was based on 2 RCTs, TRuE-V1 and TRuE-V2, conducted in 674 adults and pediatric patients 12 years of age and older with nonsegmental vitiligo.[10] Ruxolitinib was administered twice daily for 24 weeks and compared with an inert vehicle.[10] Lesions were assessed using the total body Vitiligo Area Scoring Index (T-VASI) or the facial Vitiligo Area Scoring Index (F-VASI).[10] The primary efficacy endpoint was the proportion of subjects achieving at 75% improvement in the F-VASI at week 24.[10] In TRuE-V1, 30% of patients receiving ruxolitinib achieved F-VASI-75 compared with 7.5% of placebo-treated patients (difference = 22.5%; 95% CI 14.2% to 30.8%).[10] Similar results in 75% achievement of F-VASI-75 were observed in TRuE-V2 with ruxolitinib versus vehicle (30% vs. 12.9%, respectively; difference=16.9%; 95% CI 7.8% to 26.0%).[10]

New FDA Safety Alerts: No new safety alerts were identified.

Randomized Controlled Trials:
A total of 67 citations were manually reviewed from the initial literature search. After further review, 67 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: Roflumilast Topical Cream
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.

Clinical Efficacy:
Roflumilast (ZORYVE) 0.3% cream received FDA approval July 2022 for topical treatment of PsO, including intertriginous areas, in patients 12 years of age and older.[5] Roflumilast is a selective inhibitor PDE-4.[5] Overexpression of PDE-4 appears to contribute to the pathogenesis of psoriasis.[40] The inhibition of PDE-4 increases cyclic adenosine monophosphate (cAMP) levels, leading to a downregulation of immune modulators involved in psoriasis pathophysiology such as TNF, interferon, IL-17 and IL-23.[40]

Two phase 3 multicenter, double-blind, vehicle-controlled RCTs, DERMIS-1 and DERMIS-2, supported the FDA-approval of topical roflumilast.[6] The 2 studies were conducted in patients aged 2 years and older with an affected BSA of 2 to 20% (excluding scalp, palms or soles) with mild-to-severe PsO.[6] The median age was 47 years, the majority of subjects were male (64%) and White (82%).[6] At baseline, 16% of subjects had an IGA score of 2 (mild), 76% had an IGA score of 3 (moderate), and 8% had an IGA score of 4 (severe).[6] Patients were randomized 2:1 to roflumilast 0.3% cream or vehicle applied to skin once a day for 8 weeks.[6] The primary efficacy outcome was Investigator's Global Assessment (IGA) success at week 8.[6] This was defined as an IGA status of clear or almost clear (assessed on a 5-point scale of plaque thickening, scaling, and erythema; a score of 0 indicates clear, 1 almost clear, and 4 severe) and a 2-grade or greater improvement from baseline.[6] Secondary outcomes, included IGA score of clear, 75% reduction in Psoriasis Area and Severity Index (PASI) score, and Worst Itch Numeric Rating Scale score of 4 or higher at baseline and with a 4-point reduction (WI-NRS success) at week 8 (scale: 0 [no itch] to 10 [worst imaginable itch]; minimum clinically important difference, 4 points).[6]
In both studies, a greater percentage of roflumilast-treated patients achieved IGA success at week 8 compared with vehicle-treated patients (DERMIS-1: 42.4% vs. 6.1%, respectively; difference = 39.6%; 95% CI 32.3 to 46.9; p<0.001 and DERMIS-2: 37.5% vs. 6.9%, respectively; difference = 28.9%; 95% CI 20.8% to 36.9%; p<0.001).[6] At 8-week follow-up, compared with vehicle, roflumilast improved IGA clear status (DERMIS-1: 63.5% vs. 10.3%; difference, 58.1%; 95% CI, 39.3 to 76.9; p<0.001 and DERMIS-2: 57.4% vs. 7.4%; difference, 52.2%; 95% CI, 32.1 to 72.2; p<0.001).[6] At 8-week follow-up, compared with vehicle, roflumilast increased the proportion of patients who achieved a 75% reduction from baseline in PASI score (DERMIS-1: 41.6% vs. 7.6%; difference, 36.1% ; 95% CI, 28.5 to 43.8; p<0.001 and DERMIS-2: 39.0% vs. 5.3%; difference, 32.4%; 95% CI, 24.9 to 39.8; p<0.001).[6] Among patients with WI-NRS scores of 4 or higher at baseline, compared with vehicle, roflumilast improved the proportion of patients achieving at least a 4-point WI-NRS reduction.[6] At week 8, percentages of patients with at least a 4-point WI-NRS reduction were 67.5% versus 26.8% for DERMIS-1 (difference, 42.6%; 95% CI, 31.3 to 53.8; p<0.001) and 69.4% versus 35.6% for DERMIS-2 (difference, 30.2%; 95% CI, 18.2 to 42.2; p<0.001).[6] Of the 4 patients 2 to 11 years of age who participated in either trial, 1 (33.3%) of the 3 roflumilast-treated patients achieved IGA success at week 8; the 1 vehicle-treated patient did not achieve IGA success at week 8.[6] Of the 14 patients 12 to 17 years of age who participated in either trial, 2 (25.0%) of the 8 roflumilast-treated and 1 (16.7%) of the 6 vehicle-treated patients achieved IGA success at week 8.[6] Additional phase 3 study details are presented in **Table 3.**

This study has several limitations. First, the lack of an active comparator treatment group makes the comparative efficacy of topical roflumilast with other active treatments uncertain.[6] Second, the trials did not assess the efficacy of roflumilast beyond 8-week follow-up.[6] Third, the proportion of children and adolescents enrolled in the studies was very small. Further research is needed to assess efficacy compared with other active treatments and to assess longer-term efficacy and safety.[6]

Clinical Safety:

In clinical trials, low rates of application-site AEs were observed with roflumilast.[5] The most frequently reported AEs were diarrhea, headache, insomnia, and nausea.[5] Rates of AEs with roflumilast compared with vehicle are described in **Table 1**. Because metabolism of roflumilast is primarily via hepatic enzymes, it is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C).[5] Medications that inhibit CYP3A4 or CYP1A2 (e.g., erythromycin, ketoconazole, fluvoxamine, cimetidine) should be cautiously co-administered with roflumilast, as they may increase systemic exposure of roflumilast and result in increased AEs.[5] There are no RCTS of topical roflumilast in pregnant or lactating women.[5]

Table 1. Adverse Effects Reported in Clinical Trials with Roflumilast Cream 0.3% Versus Vehicle Cream[5]

Adverse Effect	Roflumilast Cream (n=576) n (%)	Vehicle Cream (n=305) n (%)
Diarrhea	18 (3.1)	0 (0.0)
Headache	14 (2.4)	3 (1.0)
Insomnia	8 (1.4)	2 (0.7)
Nausea	7 (1.2)	1 (0.3)
Application Site Pain	6 (1.0)	1 (0.3)
Upper Respiratory Tract Infection	6 (1.0)	1 (0.3)
Urinary Tract Infection	6 (1.0)	2 (0.7)

Look-alike / Sound-alike Error Risk Potential: No issues identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptom improvement
2) Quality of life
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Percentage of patients with achievement of IGA score of clear (0) or almost clear (1) at 8 weeks

Table 2. Pharmacology and Pharmacokinetic Properties.[5,17]

Parameter	
Mechanism of Action	Phosphodiesterase-4 inhibitor
Oral Bioavailability	Not Applicable
Distribution and Protein Binding	Volume of distribution: 2.9 Liters/kilogram; 99% protein bound
Elimination	Total body clearance:9.6 Liters/hour
Half-Life	4.6 days
Metabolism	Extensively metabolized via CYP1A2 and CYP3A4 hepatic enzymes

Table 3. 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. Lebwohl MG, et al[6] DERMIS-1 Phase 3, DB, PG, MC, RCT	1. Roflumilast 0.3% cream applied once a day 2. Vehicle cream applied once a day Duration: 8 wks	Demographics: 1. Mean age: 47 yo 2. Male: 64% 3. Race - White: 81% Black: 3% Asian: 7% Other: 3% 4. Median psoriasis-affected BSA: 4.6% (range 2 to 20%) 5. Mean PASI score: 3.5 6. Mild PsO: 15% Moderate PsO: 75% Severe PsO: 9% Key Inclusion Criteria: -2 yo and older -PsO for > 6 mos in adults and 3 mos in children -IGA ≥ 2 -PASI ≥ 2 -PsO BSA of 2 to 20% Key Exclusion Criteria: -Above normal exposure to sun or tanning beds - Diagnosis of guttate psoriasis or pustular psoriasis - Currently taking cytochrome P450 inducers or inhibitors or oral roflumilast or other PDE-4 inhibitors	ITT: 1. 286 2. 153 Attrition: 1. 31 (11%) 2. 20 (13%)	Primary Endpoint: Proportion of patients with IGA success at week 8 (IGA score of 0 or 1 and ≥ 2-grade improvement in IGA from baseline). 1. 42.4% (n=108) 2. 6.1% (n=8) Difference: 39.6%, 95% CI 32.3 to 46.9; p<0.001 Secondary Endpoints: 1. Proportion of patients achieving IGA clear status (score = 0) at week 8 1. 63.5% 2. 10.3% Difference: 58.1% 95% CI 39.3 to 76.9; p<0.001 2. Proportion of patients achieving PASI-75 at week 8 1. 41.6% 2. 7.6% Difference: 36.1% 95% CI 28.5 to 43.8; p<0.001 3. Proportion of patients with a ≥ 4 point reduction in WI-NRS at week 8 1. 67.5% 2. 26.8% Difference: 42.6% 95% CI 31.3 to 53.8; p<0.001	39.6%/ 3 58.1%/ 2 36.1%/ 3 42.6%/ 3	AEs: 1. 25.2% (n=72) 2. 23.5% (n=36) SAEs: 1. 0.7% (n=2) 2. 0.7% (n=1) AE leading to withdrawal: 1. 3.5% (n=10) 2. 0 p-value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 2:1 via computer-generated list. Patients stratified by study site, baseline IGA (IGA=2 vs. IGA≥3) and intertriginous area involvement. Baseline characteristics balanced among groups. Performance Bias: Low. Active drug similar in appearance to inert vehicle cream. Detection Bias: Unclear. Patients and investigators blinded to treatment allocation. Method of blinding not described. Unblinding may have occurred with local reactions to active drug or non-response to inert vehicle. Attrition Bias: High. More attrition in placebo arm due to withdrawal, loss to follow-up, or an AE. Missing data imputed, but method not described. Reporting Bias: Low. Protocol available on-line and all pre-specified outcomes were reported. Other Bias: Unclear. Manufacturer compiled and analyzed data, funded the study. **Applicability**: Patient: Study population was mostly adult, white males with moderate PsO which limits applicability to other races and patients with severe PsO. Small percentage of children and adolescents also enrolled in the trial. Intervention: Dosing used in this trial was proven efficacious in phase 2 trials. Comparator: Placebo comparator appropriate for safety and efficacy comparison. Outcomes: IGA is a validated measure to assess efficacy of new drugs used to treat PsO. Setting: 40 sites in the US and Canada

2. Lebwohl MG, et al[6] DERMIS-2 Phase 3, DB, PG, MC, RCT	1. Roflumilast 0.3% cream applied once a day 2. Vehicle cream applied once a day Duration: 8 wks	Demographics: 1. Mean age: 47 yo 2. Male: 63% 3. Race - White: 82% Black: 5% Asian: 6% Other: 3% 4. Median psoriasis-affected BSA: 4.9% (range 2 to 20%) 5. Mean baseline PASI score: 3.3 6. Mild PsO: 16% Moderate PsO: 76% Severe PsO: 6.7% Key Inclusion Criteria: see DERMIS-1 Key Exclusion Criteria: see DERMIS-1	ITT: 1. 290 2. 152 Attrition: 1. 26 (9%) 2. 21 (14%)	Primary Endpoint: Proportion of patients with IGA success at week 8 (IGA score of 0 or 1 and ≥ 2-grade improvement in IGA from baseline). 1. 37.5% (n=99) 2. 6.9% (n=9) Difference: 28.8%, 95% CI 20.8 to 36.9 p<0.001 Secondary Endpoints: 1.Proportion of patients achieving IGA clear status (score = 0) at week 8 1. 57.4% 2. 7.4% Difference: 52.2% 95% CI 32.1 to 72.2 P<0.001 2.Proportion of patients achieving PASI-75 at week 8 1. 39.0% 2. 5.3% Difference: 32.4% 95% CI 24.9 to 39.8 P<0.001 3. Proportion of patients with a WI-NRS score reduction of at least 4 points at week 8 1. 69.4% 2. 26.8% Difference: 30.2% 95% CI 18.2 to 42.2 P<0.001	28.8/4 52.2%/2 32.4%/4 30.2%/4	AEs: 1. 25.9% (n=75) 2. 18.4% (n=28) SAEs: 1. 0 2. 0.7% (n=1) AE leading to withdrawal: 1. 0.3% (n=1) 2. 1.3% (n=2) p-value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: see DERMIS-1 Performance Bias: see DERMIS-1 Detection Bias: see DERMIS-1 Attrition Bias: see DERMIS-1 Reporting Bias: see DERMIS-1 Other Bias: see DERMIS-1 **Applicability**: Patient: see DERMIS-1 Intervention: see DERMIS-1 Comparator: see DERMIS-1 Outcomes: see DERMIS-1 Setting: 39 sites in the US and Canada

Abbreviations: AE = adverse event: RR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DB = double blind; IGA = Investigator's Global Assessment; ITT = intention to treat; MC = multi-center; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PDE = phosphodiesterase; PG = parallel group; PSAI = Psoriasis Area and Severity Index; PsO = plaque psoriasis; SAE = serious adverse event; US = United States; WI-NRS = Worst Itch Numeric Rating Scale; wks = weeks; yo = years old

NEW DRUG EVALUATION: Tapinarof Topical Cream

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.

Clinical Efficacy:

Tapinarof 1% cream, an aryl hydrocarbon receptor agonist, received FDA-approval for the topical treatment of PsO in adults May 2022.[7] The aryl hydrocarbon receptor is a ligand-dependent transcription factor expressed in keratinocytes, which is increased in patients with psoriasis.[40] Aryl hydrocarbon receptor signaling regulates the terminal differentiation of T helper (Th) type-17 and Th-22 lymphocytes, which ultimately decreases pro-inflammatory interleukin cytokines.[40] In summary, tapinarof is a novel anti-inflammatory agent. Tapinarof cream is currently being studied for use in atopic dermatitis and in pediatric patients with psoriasis.

Two identical, double-blind, multi-center, phase 3, RCTs, PSOARING 1 and PSOARING 2, evaluated the safety and efficacy of tapinarof 1% cream in treating adults with psoriasis.[8] These RCTs were conducted over 12 weeks in 1,025 adults with mild-to-severe PsO and an affected BSA of 3% to 20%. Patients were randomized 2:1 to once-daily application of tapinarof 1% cream or inert vehicle cream to any lesions.[8] Study participants ranged in age from 18 to 75 years, with an overall median age of 51 years.[7] The majority of participants were White (85%) and male (57%); and 85% were non-Hispanic or Latino.[7] Most of the adults enrolled in the RCTs (82%) had moderate PsO (baseline PGA score of 3).[7] The primary efficacy endpoint was PGA response, defined as a PGA score of clear (0) or almost clear (1) with at least a two-grade reduction from baseline in PGA at week 12.[8] Secondary endpoints included proportion of subjects achieving PASI-75, PASI-90, PGA score of 0 or 1, and change in percent of BSA affected at week 12.[8]

The primary efficacy endpoint of a PGA response was achieved by a higher proportion of patients in the tapinarof cream group versus the vehicle group in PSOARING 1 (35.4% vs. 6.0%, respectively; difference 29.4%; RR 5.8; 95% CI 2.9 to 11.6; p<0.001) and PSOARING 2 (40.2% vs. 6.3%, respectively; difference 33.9%; RR 6.1; 95% CI 3.3 to 11.4; p<0.001).[8] Secondary endpoints also improved in more patients treated with tapinarof cream compared with vehicle cream. PASI-75 response at Week 12 was achieved by a higher proportion of patients in the tapinarof cream group than the vehicle group in PSOARING 1 (36.1% vs. 10.2%, difference 25.9%; RR 2.8; 95% CI 1.7 to 4.5; p<0.001) and PSOARING 2 (47.6% vs. 6.9%, difference 40.7%; RR 6.5; 95% CI 3.7 to 11.5; p<0.001).[8] A PGA score of 0 (clear) or 1 (almost clear) at Week 12 was achieved by a higher proportion of patients in the tapinarof cream group than the vehicle group in PSOARING 1 (37.8% vs. 9.9%; difference 27.9%; RR 2.7; 95% CI 1.6 to 4.4; p<0.001) and PSOARING 2 (43.6% vs. 8.1%, difference 35.5%; RR 4.6; 95% CI 2.7 to 7.6; p<0.001).[8] A PASI-90 response at Week 12 was achieved by a higher proportion of patients in the tapinarof group than the vehicle group in PSOARING 1 (18.8% vs. 1.6%, difference 17.2%; RR 8.5; 95% CI 26 to 28.4; p<0.001) and PSOARING 2 (20.9% vs. 2.5%, difference 18.4, RR 7.2; 95% CI 2.9 to 18.4; p<0.001).[8] Finally, a greater mean improvement in percent BSA affected at Week 12 was observed in the tapinarof cream group compared with the vehicle group in PSOARING 1 (-3.5% vs. -0.2%, difference -3.3; 95% CI -4.4 to -2.1; p<0.001) and PSOARING 2 (-4.2% vs. 0.1%, difference -4.3; 95% CI -5.2 to -3.5; p<0.001).[8] Additional study details are presented in **Table 5**.

Approximately 15 to 20% of end-point data were missing, and multiple imputation was used to adjust for missing data as prespecified in the statistical analysis plan in providing estimates of many of the trial end points.[8] Larger and longer trials are needed to evaluate the efficacy and safety of tapinarof cream as compared with existing treatments for psoriasis.[8]

Results from an open-label, extension trial (PSOARING 3) from patients who completed PSOARING 1 or PSOARING 2 (n=763) are available.[41] This trial assessed the safety, efficacy, durability of response, and tolerability of tapinarof 1% cream applied once daily after 40 weeks of treatment.[41] The treatment phase was followed by 4 weeks of off-treatment assessment.[41] The primary efficacy endpoint was the proportion of patients who achieved complete disease clearance (PGA = 0).[41] Of the eligible enrolled patients, 40.9% of them achieved complete disease clearance (PGA = 0).[41] Mean duration of off-therapy remittive effect for patients achieving PGA = 0 was 130.1 days.[41] No new safety signals were observed.[41] Most frequent adverse events were folliculitis (22.7%), contact dermatitis (5.5%), and upper respiratory tract infection (4.7%).[41] Trial discontinuation rates due to folliculitis or contact dermatitis were low (1.2% and 1.4%), respectively.[41] Of the 763 patients enrolled, 69.6% (n=531) completed the trial.[41] Attrition was approximately 30% and primarily due to withdrawal of consent (10%), loss to follow-up (8%), and adverse events (6%).[41] Trial limitations include the open-label design, high attrition rate, and lack of a control group.[41] As is possible with all extension trials, patients who opted to enroll might represent a self-selected, enriched population, with improved response and tolerability to treatment.[41]

Clinical Safety:

In clinical trials, folliculitis, contact dermatitis, and headache occurred more frequently in the tapinarof groups than in the vehicle groups.[7] No SAEs were observed with tapinarof administration.[8] AEs that occurred in at least 1% of individuals treated with tapinarof cream compared to the inert vehicle are presented in **Table 4**. There is insufficient data regarding the safety of tapinarof administration in pregnancy and lacatation.[7] Although tapinarof is extensively metabolized by the liver, no significant drug interactions were observed during clinical trials.[7]

Table 4. Adverse Reactions Observed in Clinical Trials With Tapinarof Cream Versus Vehicle Cream[7]

Adverse Effect	Tapinarof 1% Cream n = 683 n (%)	Vehicle Cream n= 342 n (%)
Folliculitis	140 (20)	3 (1)
Nasopharyngitis	73 (11)	31 (9)
Contact Dermatitis	45 (7)	2 (1)
Headache	26 (4)	5 (1)
Pruritus	20 (3)	2 (1)
Influenza	14 (2)	2 (1)

Look-alike / Sound-alike Error Risk Potential: No issues identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptom improvement
2) Quality of life
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

2) PGA response (score of 0 or 1 with $\geq$2 point decrease from baseline) at week 12

Table 5. Pharmacology and Pharmacokinetic Properties.[7]

Parameter	
Mechanism of Action	Aryl hydrocarbon receptor agonist
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Volume of distribution not reported due to limited systemic absorption after topical administration; plasma protein binding: approximately 99%
Elimination	Not reported
Half-Life	Not reported
Metabolism	Extensive hepatic metabolism

Table 6. 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. Lebwohl M, et al.[8] PSOARING-1 Phase 3, DB, MC, PC, RCT	1. Tapinarof 1% applied cream once a day 2. Vehicle cream applied once a day Duration: 12 wks	Demographics: 1. Mean age: 49 yo 2. Male: 56% 3. Race White: 84% Black: 5% Asian: 4% Other: 4% 4. Mild PsO: 11% Moderate PsO: 79% Severe PsO: 8% 5. Mean baseline PASI: 8.9 Key Inclusion Criteria: -Adults aged 18-75 yo with chronic PsO and stable disease for 6 mos prior to study enrollment -BSA between 3 and 20%, excluding scalp, palms, nails, and soles -PGA score of 2, 3, or 4 (mild, moderate, severe PsO) Key Exclusion Criteria: -Psoriasis other than the plaque variant	ITT: 1.340 2.170 Attrition: 1. 71 (20.9%) 2. 40 (23.5%)	Primary Endpoint: Proportion with PGA response (score of 0-1 & 2-point change from baseline) at week 12 1. 35.4% 2. 6% Difference: 29.4% RR 5.8; 95% CI 2.9 to 11.5; p<0.001 Secondary Endpoints: 1. Proportion with PASI-75 at week 12 1. 36.1% 2. 10.2% Difference: 25.9% RR 2.8; 95% CI 1.7 to 4.5; p<0.001 2. Proportion with PASI-90 at week 12 1. 18.8% 2. 1.6% Difference: 17.2% RR 8.5; 95% CI 2.6 to 28.4; p<0.001 3. Percentage of subjects with a PGA score of 0 or 1 at week 12 1. 37.8% 2. 9.9% Difference: 27.9% RR 2.7; 95% CI 1.6 to 4.4; p<0.001	29.4%/4 25.9%/4 17.2%/6 27.9%/4	AEs 1. 171 (50.3%) 2. 38 (22.4%) SAEs: 1. 0 2. 0 AE leading to withdrawal: 1. 19 (5.6%) 2. 0 p-value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 to tapinarof: vehicle. Subjects randomized using a pseudo-random number generator and stratified according to PsO severity. Baseline characteristics balanced between groups. Performance Bias: Low. Vehicle cream and tapinarof cream were identical in excipients, amount (30 gm) and color. Detection Bias: Unclear. Investigator, study center staff, and subjects blinded to treatment assignment. Method of blinding not described. Non-response to inert vehicle or local AEs with active drug may have resulted in unblinding. Attrition Bias: High. High attrition rates in both arms. Missing data imputed using multiple imputation. Reporting Bias: Low. Protocol available online and all prespecified outcomes were reported. Other Bias: Unclear. Manufacturer designed the trials, provided medication and placebo, analyzed the data and funded writing assistance. **Applicability**: Patient: Small study population, mostly white males with stable, moderate PsO limits applicability to other races and patients with severe PsO or those experiencing flares.

		-Prolonged exposure to ultraviolet light within 4 wks of study enrollment -Hepatic disease -Use of biologic agents, systemic immunomodulators or glucocorticoids		4. Mean change from baseline to week 12 in percent of BSA affected 1. -3.5% 2. -0.2% Difference: -3.3% 95% CI -4.4 to -2.1; p<0.001	NA			Intervention: Phase 2b dose finding trials indicated efficacy with tapinarof 1% daily. Comparator: Placebo comparator appropriate for safety and efficacy comparison. Comparison with a topical corticosteroid would provide more meaningful evaluation. Outcomes: PGA and PASI-75 are validated measures to assess efficacy of new drugs used to treat PsO. Setting: 48 centers in the US (n=40) and Canada (n=8)
2. Lebwohl M, et al.[8] PSOARING-2 Phase 3, DB, MC, PC, RCT	1. Tapinarof 1% applied cream once a day 2. Vehicle cream applied once a day Duration: 12 wks	Demographics: 1. Mean age: 50 yo 2. Male: 57% 3. Race White: 84% Black: 3.5% Asian: 9% Other: 2% 4. Mild PsO: 8% Moderate PsO: 84% Severe PsO: 7% 5. Mean baseline PASI: 9.1 Key Inclusion Criteria: see PSOARING-1 Key Exclusion Criteria: see PSOARING-1	ITT: 1.343 2.172 Attrition: 1.61 (17.8%) 2.30 (17.4%)	Primary Endpoint: Proportion of subjects with PGA response (score of 0 or 1- and 2-point improvement from baseline) at week 12 1. 40.2% 2. 6.3% Difference: 33.9% RR: 6.1; 95% CI 3.3 to 11.4; p<0.001 Secondary Endpoints: 1. Proportion of subjects achieving PASI-75 at week 12 1. 47.6% 2. 6.9% Difference: 40.7% RR 6.5; 95% CI 3.7 to 11.5; p<0.001 2. Proportion of subjects achieving PASI-90 at week 12 1. 20.9% 2. 2.5% Difference: 18.4% RR 7.2; 95% CI 2.9 to 18.4; p<0.001 3. Percentage of subjects with a PGA score of 0 or 1 at week 12 1. 43.6% 2. 8.1% Difference: 35.5% RR 4.6; 95% CI 2.7 to 7.6; p<0.001 4. Mean change from baseline to week 12 in percentage of BSA affected 1. -4.2% 2. 0.1% Difference: -4.3% 95% CI -5.2 to -3.5; p<0.001	33.9%/3 40.7%/3 18.4%/5 35.5%/3 NA	AEs 1. 187 (54.5%) 2. 45 (26.2%) SAEs: 1. 0 2. 0 AE leading to withdrawal: 1. 20 (5.8%) 2. 1 (0.6) p-value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: see PSOARING-1 Performance Bias: see PSOARING-1 Detection Bias: see PSOARING-1 Attrition Bias: see PSOARING-1 Reporting Bias: see PSOARING-1 Other Bias: see PSOARING-1 **Applicability**: Patient: see PSOARING-1 Intervention: see PSOARING-1 Comparator: see PSOARING-1 Outcomes: see PSOARING-1 Setting: 49 centers in the US (n=41) and Canada (n=80)

Abbreviations: AE = adverse event: RR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DB = double blind; IGA = Investigator's Global Assessment; ITT = intention to treat; MC = multi-center; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PDE = phosphodiesterase; PG = parallel group; PP = per protocol; PSAI = Psoriasis Area and Severity Index; PsO = plaque psoriasis; RR = relative rate; SAE = serious adverse event; US = United States; wks = weeks; yo = years old

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Appendix 1: Current Preferred Drug List

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

Generic	Brand	Route	Form	PDL
calcipotriene	CALCIPOTRIENE	TOPICAL	CREAM (G)	Y
calcipotriene	DOVONEX	TOPICAL	CREAM (G)	Y
tazarotene	TAZAROTENE	TOPICAL	CREAM (G)	Y
tazarotene	TAZORAC	TOPICAL	CREAM (G)	Y
tazarotene	TAZORAC	TOPICAL	GEL (GRAM)	Y
calcipotriene/betamethasone	CALCIPOTRIENE-BETAMETHASONE DP	TOPICAL	OINT. (G)	Y
calcipotriene/betamethasone	TACLONEX	TOPICAL	OINT. (G)	Y
calcipotriene	CALCIPOTRIENE	TOPICAL	SOLUTION	Y
anthralin	ANTHRALIN	TOPICAL	CREAM (G)	N
tapinarof	VTAMA	TOPICAL	CREAM (G)	N
calcipotriene	CALCIPOTRIENE	TOPICAL	FOAM	N
calcipotriene/betamethasone	ENSTILAR	TOPICAL	FOAM	N
coal tar	PSORIATAR	TOPICAL	FOAM	N
calcipotriene	SORILUX	TOPICAL	FOAM	N
halobetasol propion/tazarotene	DUOBRII	TOPICAL	LOTION	N
calcipotriene	CALCIPOTRIENE	TOPICAL	OINT. (G)	N
calcitriol	CALCITRIOL	TOPICAL	OINT. (G)	N
calcitriol	VECTICAL	TOPICAL	OINT. (G)	N
calcipotriene/betamethasone	CALCIPOTRIENE-BETAMETHASONE	TOPICAL	SUSPENSION	N
calcipotriene/betamethasone	TACLONEX	TOPICAL	SUSPENSION	N
coal tar	ANTI-DANDRUFF	TOPICAL	SHAMPOO	N
coal tar	DHS TAR	TOPICAL	SHAMPOO	N
coal tar	DHS TAR GEL	TOPICAL	SHAMPOO	N
coal tar	IONIL T	TOPICAL	SHAMPOO	N
coal tar	POLYTAR	TOPICAL	SHAMPOO	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to August Week 4 2022; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations September 01, 2022

1	exp Psoriasis/	31016
2	exp Dermatitis, Atopic/	17675
3	tapinarof.mp.	59
4	exp Tacrolimus/	15377
5	pimecrolimus.mp.	904
6	Administration, Topical/	27072
7	Anti-Inflammatory Agents, Non-Steroidal/	60734
8	crisaborole.mp.	135
9	ruxolitinib.mp.	1913
10	roflumilast.mp.	664
11	Calcitriol/	8617
12	tazarotene.mp.	598
13	Betamethasone/ or Calcitriol/	11382
14	Anthralin/	287
15	Coal Tar/	486
16	3 or 4 or 5 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	91232
17	6 and 16	2911
18	exp Skin Diseases/	734309
19	1 or 2 or 18	734309
20	17 and 19	1615
21	limit 20 to (English language and humans and yr="2017 -Current")	231
22	limit 21 to (clinical trial, all or comparative study or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	67

Appendix 3: Prescribing Information Highlights

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

ZORYVE™ (roflumilast) cream, for topical use
Initial U.S. Approval: 2011

----------INDICATIONS AND USAGE----------
ZORYVE is a phosphodiesterase 4 inhibitor indicated for topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Apply once daily to affected areas. (2)
- For topical use only. (2)
- Not for ophthalmic, oral, or intravaginal use. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Cream, 0.3%: 3 mg of roflumilast per gram in 60-gram tubes. (3)

----------CONTRAINDICATIONS----------
- Moderate to severe liver impairment (Child-Pugh B or C). (4)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (reported in ≥1% of patients) are diarrhea, headache, insomnia, application site pain, upper respiratory tract infections, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Arcutis Biotherapeutics, Inc. at 1-844-692-6729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Coadministration of roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. (7.1)
- Coadministration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit. (7.2)

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

Revised: 7/2022

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VTAMA (tapinarof) cream, for topical use
Initial U.S. Approval: 2022

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

VTAMA cream, 1% is an aryl hydrocarbon receptor agonist indicated for the topical treatment of plaque psoriasis in adults. (1)

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

- Apply a thin layer of VTAMA cream to affected areas once daily. (2)
- VTAMA cream is not for oral, ophthalmic, or intravaginal use. (2)

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

Cream, 1% (3)

Each gram of VTAMA cream contains 10 mg of tapinarof. (3)

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

None. (4)

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

Most common adverse reactions (incidence ≥ 1%) in subjects treated with VTAMA cream were folliculitis, nasopharyngitis, contact dermatitis, headache, pruritus, and influenza. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dermavant Sciences, Inc. at 1-8DERMAVANT or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 05/2022

Topical Agents for Inflammatory Skin Disease

Goal(s):

- Restrict dermatological drugs only for funded OHP diagnoses for adults. Treatments are funded on the OHP for severe inflammatory skin diseases including: psoriasis, atopic dermatitis, lichen planus, Darier disease, pityriasis rubra pilaris, discoid lupus and vitiligo. Treatments for mild or moderate psoriasis, mild or moderate atopic dermatitis, seborrheic dermatitis, keratoderma and other hypertrophic and atrophic conditions of skin are not funded.
- 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 atopic dermatitis, psoriasis, and vitiligo 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

Generic Drug Name	Brand Name	Minimum Age	Indication (severity)
Crisaborole 2% ointment	EUCRISA	3 months	Atopic Dermatitis (Mild-to-Moderate)
Pimecrolimus 1% cream	ELIDEL	2 years	Atopic Dermatitis (Mild-to-Moderate)
Ruxolitinib 1.5% cream	OPZELURA	12 years	Atopic Dermatitis (Mild-to-Moderate) Nonsegmental Vitiligo
Tacrolimus 0.03% ointment	PROTOPIC	2 years	Atopic Dermatitis (Moderate-to-Severe)
Tacrolimus 0.1% ointment	PROTOPIC	16 years	Atopic Dermatitis (Moderate-to-Severe)
Roflumilast 0.3% cream	ZORYVE	12 years	Plaque Psoriasis

Tapinarof 1% cream	VTAMA	18 years	Plaque Psoriasis
Calcipotriene cream, solution, and ointment Calcipotriene foam	DOVONEX SORILUX	18 years 4 years	Plaque Psoriasis
Tazarotene cream and gel	TAZORAC	12 years	Plaque Psoriasis
Calcipotriene/Betamethasone ointment, suspension, and foam Calcipotriene/Betamethasone cream	TACLONEX ENSTILAR WYNZORA	12 years 18 years	Plaque Psoriasis
Anthralin Shampoo Anthralin Cream	ZITHRANOL	12 years 18 years	Plaque Psoriasis
Halobetasol propionate/Tazarotene Lotion	DUOBRII	18 years	Plaque Psoriasis
Calcitriol ointment	VECTICAL	2 years	Plaque Psoriasis

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

Atopic Dermatitis (AD)	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 treatment of severe inflammatory 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 #3	**No: For age ≥ 21 years:** Pass to RPh; deny, not funded by the OHP For age < 21 years: Go to #3
3. Is the diagnosis plaque psoriasis, atopic dermatitis or nonsegmental vitiligo?	**Yes:** Go to #4	**No:** Go to #8

Approval Criteria		
4. 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 #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the requested product preferred?	**Yes**: Go to #6	**No**: Go to #7
6. For patients 20 years of age or younger, 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)??	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical necessity
7. Does the patient have a documented contraindication, intolerance or failed trials of at least 2 preferred first line agents (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
8. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP. *	**If funded, and clinic provides supporting literature:** Approve for 1 year.	**If not funded:** Go to # **9**

Approval Criteria		
9. Is the request for an FDA approved indication?	**Yes**: Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *12/22 (DM); 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: *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*

**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.*