# Roflumilast (ZORYVE) Cream in Plaque Psoriasis
# National Drug Monograph
# June 2023

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.*

## FDA Approval Information

### Description / Mechanism of Action

- Roflumilast is a phosphodiesterase-4 inhibitor previously approved for the oral treatment of adults with severe chronic obstructive pulmonary disease under the brand name DALIRESP (AstraZeneca).
- Roflumilast was approved in a cream formulation in July 2022.

### Indication Under Review in This Document

- Topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older.[1]

### Dosage Regimen and Dosage Form Under Review

- Roflumilast cream should be applied once daily to affected areas.
- Cream 0.3% (3 mg/g) in 60-g tubes.

## Efficacy Considerations

- No active-controlled trials have been performed.
- Two identically designed 8-week, phase 3, vehicle-controlled, randomized clinical trials (RCTs) showed efficacy of roflumilast cream in children and adults with mild to severe plaque psoriasis, including for intertriginous lesions.[2]
- A 24-week phase 3 open-label study and a 52-week phase 2 open-label study provided longer-term safety data.[7]
- A 4-week phase 1/2a study,[3] 4-week dose-ranging proof-of-concept RCT,[4] and a 12-week phase 2b dose-ranging RCT provided supportive evidence of efficacy, including for intertriginous areas[5] and itch-related sleep loss.[6]

### Phase 3 Randomized Clinical Trials

- Table 1 summarizes the methods of the phase 3 RCTs.

**Table 1 Methods of Major Clinical Trials**

| Topic | DERMIS-1 and DERMIS-2 |
|---|---|
| Study Design | 8-wk phase 3 MC DB RCT<br>2:1 randomization stratified by site, baseline IGA (2 vs ≥ 3), and intertriginous IGA score (< 2 vs ≥ 2) |

<table>
<tr><th>Topic</th><th>DERMIS-1 and DERMIS-2</th></tr>
<tr><td></td><td>Multiplicity controlled using a partitioned hierarchical procedure<br>US and CA</td></tr>
<tr><td>Major Entry Criteria</td><td>Inclusion Criteria<ul><li>Age ≥ 2 y</li><li>Clinical diagnosis of plaque psoriasis ≥ 6 mos</li><li>Stable disease for previous 4 wks</li><li>2% to 20% BSA involvement on face, extremities, trunk, and/or intertriginous areas, excluding scalp, palms, or soles</li><li>IGA ≥ 2</li><li>PASI ≥ 2</li></ul>Exclusion Criteria<ul><li>Nonplaque psoriasis</li><li>Planned excessive exposure to sunlight or artificial light</li></ul></td></tr>
<tr><td>Interventions</td><td>Applied once daily for 8 wks:<ul><li>Roflumilast cream 0.3%</li><li>Vehicle cream</li></ul>Treatment could be applied to affected palms and soles but these areas were not evaluated for efficacy.</td></tr>
<tr><td>Maintenance Phase or Long-term Extension</td><td>24-week open-label extension consisting of two cohorts: Cohort 1 included patients ≥ 2 years old from phases 1, 2 and 3 RCTs; and Cohort 2 included de novo patients 2–17 years old with affected BSA of 2%–25% excluding scalp, palms, and soles</td></tr>
<tr><td>Primary and Other Key Efficacy Measure(s)</td><td>All at Wk 8:<ul><li>Primary: Static IGA-0/1–2</li><li>Secondary: Intertriginous IGA-0/1–2, PASI-75, WI-NRS–4</li></ul></td></tr>
<tr><td>Baseline Patient Characteristics</td><td>Of 539 patients screened, 439 (81.4%) were enrolled.<br>A total of 18 patients were aged < 18 years.
<table>
<tr><th>Characteristic</th><th>DERMIS-1</th><th>DERMIS-2</th></tr>
<tr><td>Age, mean, y</td><td>48</td><td>47</td></tr>
<tr><td>Male, %</td><td>64</td><td>63</td></tr>
<tr><td>Race, White, %</td><td>81</td><td>83</td></tr>
<tr><td>Affected BSA, mean, %</td><td>6.8</td><td>7.4</td></tr>
<tr><td>IGA of</td><td></td><td></td></tr>
<tr><td>2 / Mild, %</td><td>15.4</td><td>16.5</td></tr>
<tr><td>3 / Moderate, %</td><td>76.0</td><td>76.8</td></tr>
<tr><td>4 / Severe, %</td><td>8.6</td><td>6.8</td></tr>
<tr><td>Intertriginous Involvement, %</td><td>22</td><td>20</td></tr>
</table></td></tr>
</table>

**IGA-0/1–2**, Investigator Global Assessment of 0/Clear or 1/Almost Clear plus ≥ 2-grade improvement from baseline (scale 0–4); **PASI-75**, ≥ 75% improvement in Psoriasis Area and Severity Index; **WI-NRS–4**, Worst Itch Numerical Rating Scale improvement of ≥ 4 points from a baseline of ≥ 4 (scale: 0 / No Itch to 10 / Worst Imaginable Itch; minimum clinically important change of 4 points)

**Results**

- The FDA did not consider PASI endpoints to be clinically meaningful for mild psoriasis and recommended their removal from the analyses.[7]
- The published article of DERMIS-1 and DERMIS-2 reported primary efficacy results using the per-protocol population (completers at Week 8).[2]

- In DERMIS-1, static IGA-0/1–2 was achieved at Week 8 in 42.4% (108/255) and 6.1% (8/132) in the roflumilast cream and vehicle cream groups, respectively (difference, 39.6% [95% CI 32.3%–46.9%]; NNT 2.8 [95% CI 2.3–3.4]).
- The corresponding results in DERMIS-2, were 37.5% (99/264) vs 6.9% (9/131), respectively (difference, 28.8% [20.8%–36.9%]; NNT 3.3 [2.6–4.3]).

- Selected efficacy data from FDA intent-to-treat (ITT) analyses are summarized in Table 2 and Table 3.

**Table 2 FDA ITT efficacy results at Week 8**

| Outcome | Study | Roflumilast Cream | Vehicle Cream | Relative Risk (95% CI) | Difference (95% CI) |
|---|---|---|---|---|---|
| Primary Outcome | | | | | |
| sIGA-0/1–2, n/N (%) | DERMIS-1 | 119/286 (41.5) | 9/153 (5.8) | **7.1 (3.70, 13.53)** | **39.7 (32.4, 47.0)** |
| | DERMIS-2 | 106/290 (36.7) | 11/152 (7.1) | **5.1 (2.80, 9.10)** | **29.5 (21.5, 37.6)** |
| | Pooled | 225/576 (39.1) | 20/305 (6.6) | **6.0 (3.85, 9.21)** | **32.5 (27.6, 37.4)** |
| Selected Secondary Outcomes | | | | | |
| I-IGA-0/1–2, n/N (%) | DERMIS-1 | 45/63 (71.5) | 4/32 (13.8) | **5.7 (2.23, 14.48)** | **63.6 (43.7, 83.4)** |
| | DERMIS-2 | 36/53 (67.5) | 5/31 (17.4) | **4.2 (1.85, 9.60)** | **52.7 (30.9, 74.5)** |
| | Pooled | 81/116 (69.8) | 9/63 (14.3) | **4.9 (2.64, 9.06)** | **55.5 (43.5, 67.6)** |
| WI-NRS–4, n/N (%) | DERMIS-1 | 145/218 (66.7) | 30/115 (25.7) | **2.6 (1.85, 3.52)** | **41.1 (30.0, 52.3)** |
| | DERMIS-2 | 157/229 (68.6) | 39/116 (33.3) | **2.0 (1.56, 2.67)** | **30.3 (18.1, 42.5)** |
| | Pooled | 302/447 (67.6) | 69/231 (29.9) | **2.3 (1.84, 2.78)** | **37.7 (30.4, 45.0)** |

Source: FDA Multi-discipline Review[7]
**Bold blue text** indicates statistically significant difference.
**CFB**, Change from baseline; **I-IGA-0/1–2**, Intertriginous Investigator Global Assessment of 0 / Clear or 1 / Almost Clear and ≥2-point reduction from baseline; **ITT**, Intent-to-treat; **sIGA-0/1–2**, Static Investigator Global Assessment of 0 / Clear or 1 / Almost Clear and ≥2-point reduction from baseline; **WI-NRS–4**, ≥ 4-point reduction from baseline on the Worst Itch Numerical Rating Scale

**Table 3 Absolute Effects at Week 8 (Pooled Data)**

| Outcome Measure | AAE, per 1000 pts (95% CI) | NNT (95% CI) | Q |
|---|---|---|---|
| sIGA-0/1–2 | 400 (187, 538) more | 4 (3, 4) | H |
| I-IGA-0/1–2 | 555 (435, 676) more | 2 (2, 3) | M[α] |
| WI-NRS–4 | 388 (251, 532) more | 3 (3, 4) | H |

**AAE**, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low)
[α] Downgraded for imprecision (wide CIs, optimal information size not met).

- Other secondary efficacy results:
  - PASI-75 at 8 weeks was achieved in a significantly higher percentage of patients in the roflumilast group than the vehicle group in DERMIS-1 (41.6% vs 7.6%, respectively; difference 36.1 [95% CI 28.5, 43.8]) and DERMIS-2 (39.0% vs 5.3%, respectively; difference 32.4% [24.9, 39.8]).[2]
  - Roflumilast cream was also better than vehicle cream in PASI-90 response at 8 weeks: 22.4% vs 2.3%, respectively, in DERMIS-1 and 17.0% vs. 2.3%, respectively, in DERMIS-2.
- Subgroup Analyses
  - Not reported.

**Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial**

- Onset of effects (earliest significant treatment difference in both trials): **Week 2** based on PASI-50 response; **Week 4** based on sIGA-0/1–2 success rate and WI-NRS–4, PASI-75, and PASI-90 response rates; and **Week 6** based on I-IGA-0/1–2 rate.[2]
- Duration of an adequate therapeutic trial: **≥ 8 weeks** based on sIGA-0/1–2 success.[2]

**Durability of Response**

- Data not reported beyond 8 weeks.

## Safety Considerations

### Safety Profile from US Prescribing Information

- **Boxed Warnings**: None
- **Contraindications**: Moderate to severe liver impairment (Child-Pugh B or C). (This contraindication is based on studies using oral roflumilast. No hepatic impairment studies were done with topical roflumilast. According to an FDA reviewer, "actual clinical use would most likely not produce any increased risk" for topical roflumilast.[7])
- **Other Warnings / Precautions**: None
- **Common Adverse Events (≥ 1%)**: Diarrhea, headache, insomnia, application site pain, upper respiratory tract infections, urinary tract infections

### Safety Results from Clinical Trials

- **Deaths and Serious Adverse Events**: No deaths were reported. A total of 0.4% (2/576) of patients on roflumilast cream and 0.7% (2/305) on vehicle cream experienced serious adverse events.
- **Discontinuations Due to Adverse Events**: 1.0% (6/576) vs. 1.3% (4/305) in the roflumilast vs vehicle groups, respectively.

### Drug Interactions

- No drug interaction studies were done with roflumilast cream.
- Potential drug interactions with CYP3A4 inhibitors, dual CYP3A4 and CYP1A2 inhibitors, and oral contraceptives containing gestodene and ethinyl estradiol, all of which can increase systemic exposure to roflumilast, are based on drug interaction studies performed with oral roflumilast.[7] The potential risks vs benefits of these drug interactions should be considered when roflumilast cream is used.

### Evidence Gaps

- Health-related Quality of Life: Evaluated but results not reported / published
- Functional ability / Disability
- Patient Satisfaction

### Network Meta-analyses

- No network meta-analyses that included roflumilast cream were found.

### Other Considerations

- **Pharmacokinetics**. Bioavailability of roflumilast after topical administration of 0.3% cream is 1.5%.[8] Skin concentrations of roflumilast after topical application of 0.15% and 0.5% cream for 28 days are 126- and 61.8-folder higher than in plasma, much higher than expected with oral administration. Metabolism to roflumilast N-oxide does not occur to a relevant degree in the skin.

## Other Therapeutic Options

- Topical medications may be used for treatment of mild / limited plaque psoriasis or as adjuncts to systemic therapies for moderate to severe psoriasis.
- Topical corticosteroids are the first-line agents but can cause unacceptable adverse effects such as skin atrophy or folliculitis when overused or used long-term. Nonsteroidal topical medications are used as steroid-sparing agents to reduce the risk of topical corticosteroid complications. Vitamin D agonists can be considered the preferred topical steroid-sparing agents for plaque psoriasis.
- Alternative nonsteroidal topical treatments for plaque psoriasis are summarized in Table 4.

**Table 4 Topical Nonsteroidal Treatments for Plaque Psoriasis**

| Topical Product | On VANF | CFU Place in Therapy | FDA Place in Therapy for PsO | Guideline Place in Therapy | Safety Considerations | Other Considerations |
|---|---|---|---|---|---|---|
| **PDE4 Inhibitor** | | | | | | |
| Roflumilast cream 0.3% | TBD | TBD | 1st line, mild–severe including for intertriginous areas in pts ≥ 12 years of age | Not available | Contraindicated in moderate to severe liver impairment (Child-Pugh B or C).<br>Most common AEs: Diarrhea, headache.<br>Low rates of AEs (not more than 3.1% for any AE).<br>Based on oral roflumilast studies: Potential DDIs with CYP3A4 and CYP1A2 inhibitors, gestodene, and ethinyl estradiol.[1]<br>Limited long-term experience. | No active-controlled trials<br>Large PGA-0/1–2 treatment effect for intertriginous areas.[7]<br>Unknown safety and efficacy of co-use with other topical, systemic, or UV light therapies<br>Unknown TCS sparing effects |
| **Aryl Hydrocarbon Receptor Agonist** | | | | | | |
| Tapinarof cream 1% | TBD | TBD | 1st line, mild–severe PsO<br>*(Note: Studied but not specifically labelled for application to facial or intertriginous areas.)* | Not available | Folliculitis, contact dermatitis, headache<br>No CYP450 or transporter DDIs.<br>Limited long-term experience. | Unknown safety and efficacy of co-use with other topical, systemic, or UV light therapies<br>Unknown TCS sparing effects |

| Topical Product | On VANF | CFU Place in Therapy | FDA Place in Therapy for PsO | Guideline Place in Therapy | Safety Considerations | Other Considerations |
|---|---|---|---|---|---|---|
| **Vitamin D Analogs** | | | | | | |
| Calcipotriene (CCP) cream 0.005%<br>AKA calcipotriol | Yes | NA | 1st line, mild–severe, body and scalp | Alternative or adjunct to TCS<br>Long-term therapy of mild–moderate PsO<br>CCP + class II or III TCS for PsO<br>CCP + HC for facial PsO | Skin irritation; photosensitizing; otherwise minimal adverse effects.<br>Max 100 g/wk and max 30% BSA treated may minimize systemic adverse effects (hypercalcemia, parathyroid hormone suppression) | At least as effective as potent TCSs.<br>Co-use of CCP with TCS is more effective than either agent alone.<br>TCS and UVB sparing<br>Available as TCS combination product. |
| Calcitriol (CCT) oint 3 mcg/g | Yes | NA | 1st line, mild–moderate PsO | Alternative or adjunct to TCS<br>Long-term therapy of mild–moderate PsO | Less irritating than calcipotriene on sensitive skin areas.<br>Hypercalcemia | Similar in efficacy to CCP or BDP oint 0.05%.<br>TCS and UVB sparing |
| **Calcineurin Inhibitors** | | | | | | • |
| Tacrolimus oint 0.03%, 0.1% | Yes | NA | Off-label | For face and other sensitive skin areas | Burning, pruritus<br>No definite causal relationship with lymphoma and skin cancer | May be less effective than TCSs.<br>TCS sparing |
| Pimecrolimus cream 1% | No | NA | Off-label | For face and other sensitive skin areas | See tacrolimus. | Less effective than BMV 0.1%.<br>TCS sparing<br>Efficacy may require use of occlusion. |
| **Retinoid** | | | | | | |
| Tazarotene cream 0.05%, 0.1% | No | NA | 1st line, for stable PsO involving up to 20% BSA | For mild–moderate PsO, particularly palmoplantar and nail psoriasis | Skin irritation, stinging, desquamation; photosensitizing; avoid use in pregnancy | Co-use with TCS is more effective than tazarotene alone, reduces TCS-induced skin atrophy, and reduces tazarotene-induced irritation.<br>Co-use with UVB is better than UVB alone.<br>Similar in efficacy to fluocinonide cream and CCP.<br>Available as TCS combination product. |

| Topical Product | On VANF | CFU Place in Therapy | FDA Place in Therapy for PsO | Guideline Place in Therapy | Safety Considerations | Other Considerations |
|---|---|---|---|---|---|---|
| **Other** | | | | | | |
| Coal tar / LCD, available in multiple formulations and concentrations | Yes | NA | — FDA-designated Category I (safe and effective) OTC drug product for dandruff, seborrhea, and psoriasis. | Recommended for mild–moderate psoriasis (SOR: A; LOE: I–II)[9] Goeckerman therapy (coal tar + phototherapy) is recommended for treatment of psoriasis (SOR: B; LOE: II–III)[9] 15% LCD solution is more effective than calcipotriene; 6% coal tar + 3% salicylic ointment is less effective than calcipotriene; 5% crude coal tar ointment is similar in efficacy to tazarotene.[9] | **CI:** Active or inflamed psoriasis, erythrodermic and generalized pustular psoriasis; hypersensitivity; photosensitivity; local irritation; folliculitis; acne vulgaris.[10] **WP:** Avoid sunlight for ≥ 24 h; avoid application to acutely inflamed skin **AEs**: Folliculitis, phototoxicity, generalized pustular psoriasis; skin ulcers; herpes **Carcinogenicity**: Controversial; tumorigenic in animal studies but not in clinical studies. | Known for long-lasting remission and effectiveness in treating scalp, palmoplantar, and intertriginous psoriasis. May be effective when other treatments have failed. Generally safe but messy, staining, and malodorous, which tend to reduce patient adherence. A stain-free lecithinized formulation, a liposomal formulation, foam vehicles, and emulsion formulations may improve cosmetic acceptance. |

Sources: 9, 11, 12, 13, 14

To be comparable with the cream formulation of roflumilast, cream formulations of alternative topical agents are listed unless the product is available only in a non-cream vehicle, in which case the available non-cream vehicle is shown.

**AE**, Adverse event; **BDP**, Betamethasone dipropionate; **BMV**, Betamethasone valerate; **CCP**, Calcipotriene; **CCT**, Calcitriol; **CFU**, Criteria for Use; **CI**, Contraindications; **HC**, Hydrocortisone; **LCD**, Liquor carbonis distillate; **LOE**, Level of evidence; **NA**, Not applicable; **Oint**, Ointment; **PsO**, Plaque psoriasis; **SOR**, Strength of recommendation; **TCS**, Topical corticosteroid; **TVDA**, Topical vitamin D analogue; **UVB**, Ultraviolet-B phototherapy; **WP**, Warnings and Precautions

## Projected Place in Therapy

- **Epidemiology and Prevalence of Plaque Psoriasis**. Psoriasis is a relatively common chronic inflammatory skin disease. Its worldwide prevalence in adults has been estimated to be 0.5% to 11.4%, with prevalence increasing with older age. Estimates of its incidence range from 0.09% to 11.43%.[15] A Canadian study estimated that 50% of patients with plaque psoriasis had mild disease (< 3% BSA involved), 78% had mild to moderate disease (< 10% BSA), and only 2% had disease affecting > 50% BSA.[16] In a UK study, the incidences of mild (≤ 2 % BSA), moderate (3%–10% BSA), and severe (> 10% BSA) psoriasis were estimated to be 51.8%, 35.8%, and 12.4%, respectively.[17]
- **Potential Place in Therapy Based on the Evidence**. Although no head-to-head trials were available, moderate- to high-quality evidence from two vehicle-controlled trials supports the use of roflumilast cream in patients with mild–severe (mainly moderate) chronic plaque psoriasis affecting 2% to 20% of BSA including intertriginous areas. Efficacy and safety of application to the scalp, palms, and soles are unknown. Overall, roflumilast cream produces potentially large benefits in lesion clearance especially in

intertriginous areas and small to moderate antipruritic effects. These benefits are likely to be clinically meaningful but there is some uncertainty; dermatologic health-related qualify of life was not reported and functional ability was apparently not evaluated. Although systemic absorption of topically applied roflumilast is low, the use of roflumilast cream is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C) and requires assessment of risk-benefits of potential drug interactions with CYP3A4 and CYP1A2 inhibitors, gestodene, and ethinyl estradiol. In contrast to tapinarof cream (the other recently approved topical nonsteroidal antipsoriatic), roflumilast cream lacks data on the durability of its effects but seems to have a more favorable safety and tolerability profile, with no labeled warnings or precautions, no increased risk of discontinuation due to adverse events, and no identified risks of contact dermatitis and folliculitis.

- **Potential Place in Therapy in VHA**. Topical roflumilast may be used in patients with plaque psoriasis who have an inadequate response or intolerance to either (1) ≥ 2 classes of topical antipsoriatics (e.g., topical corticosteroids, vitamin D analogs, calcineurin inhibitors, retinoids (tazarotene), or coal tar), unless the therapy is medically inadvisable; OR (2) 1 class of topical antipsoriatic and 1 class of systemic antipsoriatic (e.g., phototherapy, methotrexate, or biologic) unless medically inadvisable, not available, or not feasible. Issues for consideration include the unknown safety and efficacy of concomitant use of other topical, systemic, or ultraviolet light therapies, the unknown topical corticosteroid sparing effects of roflumilast cream, and its limited long-term safety data and real-world experience.

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