Tapinarof (VTAMA) Cream in Psoriasis
National Drug Monograph
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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

- Tapinarof (aka benvitimod, GSK2894512, or WBI-1001) is a natural stilbene drug that acts as an aryl hydrocarbon receptor (AHR) agonist.[1] The AHR is also known as the dioxin receptor. Tapinarof is the first drug in this class to be approved for the topical treatment of plaque psoriasis. Activation of the AhR pathway in multiple cells results in downregulation of interleukin-17A and interleukin-17F.[2] It also modulates the skin barrier proteins filaggrin and loricin and may have antioxidant effects.[2]
- Tapinarof is also being investigated for the treatment of atopic dermatitis.

Indication Under Review in This Document

- Topical treatment of plaque psoriasis in adults

Dosage Regimen and Dosage Form Under Review

- A thin layer of cream should be applied to affected areas once daily
- Cream, 1%

Efficacy Considerations

- Although tapinarof and benvitimod are the same active moieties, their formulations differ (benvitimod contains petrolatum) and their product development pathways and clinical trials are separate.[3] The benvitimod trial is reviewed in this monograph to provide supportive information of the potential comparative efficacy of tapinarof cream relative to an active control.
    - A 12-week, multicenter, active-controlled randomized clinical trial (RCT) conducted in China compared benvitimod cream 1% with calcipotriol ointment 0.005% or placebo twice daily in patients with mild to moderate plaque psoriasis.[4] This trial was conducted for regulatory approval in China.
    - No trial directly comparing tapinarof cream 1% with benvitimod cream 1% was found.
    - In a meta-analysis of "benvitimod" trials that included the active-controlled benvitimod trial,[4] the two tapinarof phase 3 trials (PSOARING 1 and PSOARING 2),[7] and a phase 2b tapinarof trial,[5] the risk ratio estimates for PASI-75 and PASI-90 responses were similar and 95% confidence intervals overlapped among the benvitimod trial and the three tapinarof trials.[6] These data suggested that the efficacy of benvitimod in PASI-75 and PASI-90 responses is similar to that of

tapinarof despite the difference in formulations. The interstudy heterogeneity among trials was moderate (I^2 = 43%) for PASI-75 and minimal (I^2 = 0%) for PASI-90.

- Two identically designed 12-week phase 3 vehicle-controlled RCTs conducted in North America, PSOARING 1 and PSOARING 2, supported the FDA approval of tapinarof in the treatment of adults with plaque psoriasis.[7]
- The 40-week open-label PSOARING 3 trial provided longer-term data (up to Week 52) on safety, tolerability, efficacy, remittive effects, and durability of response in adults with mild to severe plaque psoriasis who had participated in the two 12-week phase 3 RCTs.[8]
- A 12-week vehicle-controlled, phase 2 RCT[9] and a 12-week, dose-ranging, phase 2, vehicle-controlled RCT[5,10] provided evidence supporting the safety and efficacy of tapinarof in patients with psoriasis. The efficacy of twice daily application of 1% tapinarof cream was numerically better than once daily application; however, the authors suggested that it would be reasonable to consider a once-daily dosing regimen for patient convenience and perhaps improved adherence.
- A 30-day phase 2a maximal use, open-label observational study provided supportive data on the pharmacokinetics, safety, and efficacy in patients with extensive (≥ 20% BSA) plaque psoriasis.[11]

Randomized Clinical Trials

- Table 1 summarizes the methods of the major RCTs.

Table 1 Methods of the Major RCTs of Tapinarof or Benvitimod

Topic	Benvitimod ACT	PSOARING 1 PSOARING 2
Study Design	12-week multicenter, double-blind, active- and vehicle-controlled RCT in China Superiority (vs vehicle) and noninferiority (vs calcipotriol; margin 15% points in 95% CI) Full analysis set with last observation carried forward for missing data	12-week Phase 3 multicenter, double-blind, vehicle-controlled RCT in US and CA Stratified by baseline PGA of 2, 3, or 4 (range 0 to 4) Patients with mild or severe disease were limited to ~10% of the total study population; ≥ 80% of patients would have moderate disease. ITT analysis with imputation for missing data Multiplicity was controlled with a fixed sequence method
Major Entry Criteria	Adults 18–65 years old Mild to moderate plaque psoriasis BSA < 10% sPGA ≥ 2 (scale, 0–5) Exclusions: Plaque psoriasis of face, scalp, groin, genitals, palms, or soles; systemic biologics, phototherapy or photochemical therapy, systemic psoriasis drugs, topical psoriasis drugs (except desonide or hydrocortisone to face or groin)	Adults 18–75 years old Chronic plaque psoriasis, stable for ≥ 6 mos BSA 3%–20% excluding scalp, palms, fingernails, toenails, and soles PGA of 2 / mild, 3 / moderate, or 4 / severe Notable Exclusions: Non-plaque variant psoriasis; any sign of infection of psoriatic lesions; UV light therapy within previous 4 weeks Excluded Concomitant Therapies: Biologics, other systemic therapies, other topical psoriasis medications; live vaccine within previous 2 weeks
Interventions	Applied twice daily to lesions except those on the face, scalp, groin, or genital area.: • Benvitimod cream 1% (tapinarof drug moiety in petrolatum-containing vehicle) • Calcipotriol ointment 0.005% • Vehicle of benvitimod cream Concomitant Medications: See Exclusions.	Applied in a thin layer once daily on new and cleared lesions (including on face and intertriginous areas): • Tapinarof cream 1% (without petrolatum) • Vehicle cream Treatment could be applied to sensitive areas (e.g., genitals, face, intertriginous areas). Application to fingernails, toenails, palms, soles, and scalp lesions was allowed but not required, and assessment were excluded from efficacy analyses.

Topic	Benvitimod ACT	PSOARING 1	PSOARING 2
Maintenance Phase or Long-term Extension	Long-term extension: Patients with sPGA-0/1 without recurrence by Week 20 after the vehicle-controlled trial were followed for up to 52 weeks. Those with recurrence were retreated with tapinarof until sPGA-0/1 was achieved or until Week 52.	Long-term extension PSOARING 3 trial: 40 weeks of open-label treatment with tapinarof cream 1% QD and 4 weeks of follow-up. Patients with PGA ≥ 1 received tapinarof until PGA was 0. Patients with PGA = 0 discontinued tapinarof and were monitored for remittive effect. Patients with PGA ≥ 2 were restarted on tapinarof and treated until PGA was 0.	
Primary and Other Key Efficacy Measures	PASI-75 and sPGA-0/1 at Week 12 Secondary: PASI-50, PASI-90 at Week 12	PGA Response, defined as PGA of 0 (clear) or 1 (almost clear) and a decrease from baseline of ≥ 2 points at Week 12 Secondary: PASI-75, PASI-90, PP-NRS-4 response, CFB in DLQI	
Baseline Patient Characteristics			
N-screened	732	674	692
N-randomized	686 (94%)	510 (76%)	515 (74%)
Age, yr	41	49	50
Male	62%	56%	57%
White	0%	85%	84%
Duration of PsO	8.6 yr	> 10 yr: 54%	> 10 yr: 57%
PGA score	3.1	2 / mild: 12%	2 / mild: 8%
		3 / moderate: 79%	3 / moderate: 84%
		4 / severe: 9%	4 / severe: 8%
Affected BSA	5.4%	7.9%	7.5%

Sources: 4,7,8
ACT, Active-controlled trial; **BSA**, Body surface area; **CFB**, Change from baseline; **DLQI**, Dermatology Life Quality Index; **PGA**, Physicans Global Assessment

Results

Benvitimod Active-controlled Trial

- Efficacy data are summarized in Table 2 and Table 3.

Table 2 Week-12 Efficacy results from the active-controlled clinical trial

				Benvitimod vs Calcipotriol	
Outcome*	Benvitimod Cream	Calcipotriol Ointment	Vehicle Cream	Relative Risk (95% CI)	Difference (95% CI)
Primary Outcomes					
PASI-75, n/N (%)	173/344 (50.4)	65/169 (38.5)	24/173 (13.9)	**1.3 (1.05, 1.63)**	**11.9 (2.73, 20.65)**
sPGA-0/1, n/N (%)	228/344 (66.3)	107/169 (63.9)	58/173 (33.5)	1.0 (0.91, 1.20)	2.4 (–6.18, 11.28)
Selected Secondary Outcome					
PASI-90, n/N (%)	112/344 (32.6)	35/169 (20.1)	6/173 (3.5)	**1.6 (1.13, 2.19)**	**12.5 (4.31, 19.90)**

Bold blue text indicates statistically significant difference.
PASI-75 or -90, Psoriasis Area and Severity Index improvement by ≥ 75% or ≥ 90% from baseline; **sPGA-0/1**, Static physician's global Assessment of 0/Clear or 1/Almost Clear.

Table 3 Absolute Effects for Achieving Selected Outcomes With Benvitimod Cream vs Calcipotriol Ointment at Week 12

Outcome Measure	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
PASI-75	115 (19, 242) more	9 (5, 37)	VL[α]
PASI-90	124 (27, 246) more	9 (5, 28)	VL[α]

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (VL = Very low)

[α] Triple downgraded for risk of bias (randomization and allocation methods not mentioned, and blinding was likely compromised by the use of cream for benvitimod vs ointment for calcipotriol), inconsistency (between PASI responses and sPGA), indirectness (benvitimod vs tapinarof cream, potential differences in effects from the use of different, and Chinese vs North American study population), and imprecision (wide CIs).

- Benvitimod cream was superior to calcipotriol ointment, showing small but statistically significant greater improvements in PASI-75 and PASI-90 responses.

Tapinarof PSOARING 1 and PSOARING 2 Phase 3 Trials

- The percentages of missing data across outcome measures in both 12-week trials ranged from 15.7% to 22.9%.[7] To handle the missing data, the efficacy outcome measures were calculated using 100 multiple imputations generated from the intent-to-treat population data and therefore could not be expressed as numerators and denominators.
- The results of PSOARING 1 and PSOARING 2 are summarized in Table 4.

Table 4 Week-12 Efficacy results from PSOARING 1 and PSOARING 2

Outcome*	Study	Tapinarof	Vehicle	Relative Risk (95% CI)	Difference
Primary Outcome					
PGA-0/1–2, mean % (N randomized)	PSOARING 1	35.4 (340)	6.0 (170)	**5.8 (2.9, 11.6)**	**29 (23, 36)**
	PSOARING 2	40.2 (343)	6.3 (172)	**6.1 (3.3, 11.4)**	**34 (27, 41)**
Selected Secondary Outcomes					
PASI-75, mean % (N randomized)	PSOARING 1	36.1 (340)	10.2 (170)	**2.8 (1.7, 4.5)**	**26 (19, 33)**
	PSOARING 2	47.6 (343)	6.9 (172)	**6.5 (3.7, 11.5)**	**41 (34, 47)**
PASI-90, mean % (N randomized)	PSOARING 1	18.8 (340)	1.6 (170)	**8.5 (2.6, 28.4)**	**17 (13, 22)**
	PSOARING 2	20.9 (343)	2.5 (172)	**7.2 (2.9, 18.4)**	**18 (13, 23)**
PPNRS-4, mean % (N with data)	PSOARING 1	60.7 (255)	43.2 (134)	**1.4 (1.1, 1.7)**	18 (NR)
	PSOARING 2	56.9 (264)	29.6 (137)	**1.8 (1.4, 2.4)**	27 (NR
CFB in DLQI (N randomized)	PSOARING 1	–4.6 (340)	–2.8 (170)	—	**–1.8 (–2.6, –1.0)**
	PSOARING 2	–4.4 (343)	–1.1 (172)	—	**–3.3 (–4.2, –2.4)**

Sources: 7, 12

CFB, Change from baseline; **DLQI**, Dermatology Life Quality Index (minimal clinically important difference = 4); **PGA-0/1–2**, Physician's Global Assessment rating of 0 / Clear or 1 / Almost Clear and a decrease of at least 2 points; **PASI-75 or -90**, Psoriasis Area and Severity Index improvement by ≥ 75% or ≥ 90% from baseline; **PPNRS-4**, Peak Pruritus Numerical Rating Scale improvement by ≥ 4 points

* All outcome measures cannot be reported as a numerator and denominator because they represent the means of proportions on the basis of 100 imputed data sets.

- Tapinarof cream was significantly better than vehicle in the primary outcome measure, PGA response, and all secondary outcomes (PASI-75, PGA-0/1, change in percent of affected BSA, and PASI-90).
- Tapinarof cream was numerically better than vehicle in patient-reported outcomes (PP-NRS score, PP-NRS-4 response, DLQI total score, and psoriasis symptom diary score.
- Subgroup Analyses: None reported.

- The rates of loss to follow-up were similar between the tapinarof and vehicle groups in PSOARING 1 (6.2% vs 8.8%) and unbalanced in PSOARING 2 (6.1% vs 2.3%, respectively). The GRADE quality of evidence was moderate (downgraded for imprecision due to wide confidence intervals).

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest apparent difference between tapinarof cream and vehicle) seemed to occur by **Week 4** based on the PGA response rates in both PSOARING 1 (14.0% vs 1.3%, respectively) and PSOARING 2 (13.7% vs 3.1%, respectively).[7]
- In the long-term extension of the active-controlled trial, the peak PASI-75 response in patients retreated for recurrence was **not reached after 24 weeks**. Based on PGA-0/1 response, the duration of an adequate trial was about **20 weeks**.
- The duration of an adequate therapeutic trial seems to be **20 weeks** based on the peak or near-peak PGA-0/1 response rate, percentage BSA affected, and PASI scores over time in patients who switched from vehicle-to-tapinarof upon entry to the long-term extension PSOARING 3 trial.[8]

Durability of Response and Duration of Remittive Effects

- In the long-term extension of the active-controlled trial, 49% (29/59) of patients maintained resolution of psoriasis lesions until Week 52, with a median recurrence time of 36 weeks.[4]
- In PSOARING 3, tapinarof showed durability of effects for up to 1 year without tachyphylaxis.
    - The mean duration of remittive effects off therapy was 130.1 days (about 4 months) in patients who achieved PGA = 0 at least once during long-term treatment (40.9% of 763 enrolled patients).

Safety Considerations

Safety Profile from US Prescribing Information

- **Boxed Warnings**: None
- **Contraindications**: None
- **Other Warnings / Precautions**: None
- **Common Adverse Events (≥ 10%)**: Folliculitis, nasopharyngitis
- **Adverse Events of Interest**: Folliculitis, contact dermatitis, headache
- **Pregnancy**: Insufficient data in humans. No significant adverse effects in animal reproduction studies.
- **Lactation**: Insufficient data in humans. Animal data suggest tapinarof will be present in human milk. Weigh risks vs benefits.
- **Geriatric Use**: No overall differences in efficacy, safety, or tolerability were seen between elderly and younger patients in clinical trials.

Safety Results from Active-Controlled Clinical Trial and Long-term Extension

- **Deaths and Serious Adverse Events**: Serious adverse events were reported in 1.2% of patients in each treatment group.
- **Discontinuations Due to Adverse Events (DAEs)**: Numerically more DAEs occurred on benvitimod cream than on calcipotriol or vehicle: 8.4% (29/344) vs 2.9% (5/169) vs 2.3% (4/173), respectively. The relative risk (RR; 95% CI) of DAE with benvitimod vs calcipotriol was 2.8 (1.12, 7.23) and the number needed to harm (NNH, 95% CI) was 19 (10, 110).
- **Skin and Subcutaneous Adverse Events**. The rate of skin adverse events with tapinarof was more than twice those of calcipotriol and vehicle: 48.3% (166/344) vs 20.7% (35/169) vs 20.8% (36/173), respectively. The RR (95% CI) for tapinarof vs calcipotriol was 2.3 (1.70, 3.19) and the NNH (95% CI) was 3.6 (2.76, 5.30).

- **Infectious Adverse Events**. Tapinarof was associated with a numerically lower rate of infectious adverse events than calcipotriol: 6.7% (23/344) vs 8.3% (14/169). The rate on vehicle was 2.9% (5/173).
- **Most Common Adverse Events**. Pruritus, contact dermatitis, folliculitis. Pruritus was more common on tapinarof than calcipotriol or placebo: 21.2% (73/344) vs 10.1% (17/169) vs 12.1% (21/173), respectively.
- **Adverse Events During Long-term Extension**: Drug-related adverse events occurred in 16.7% (5) patients and were mostly transient and mild.

Safety Results from PSOARING 1–3 Trials

- **Deaths and Serious Adverse Events**: Grade 4 (life-threatening) adverse events occurred in 0.6% (2/340) vs 0% of tapinarof vs vehicle patients, respectively, in PSOARING 1. The corresponding results in PSOARING 2 were 0.3% (1/343) vs 0%, respectively.[7]
- **DAEs**: Rates of DAEs for tapinarof vs vehicle, respectively, were 5.6% (19/340) vs 0% in PSOARING 1 and 5.8% (20/343) vs 0.6% (1/172) in PSOARING 2.
    - The rates of DAEs for specific adverse events on tapinarof in PSOARING 1 and PSOARING 2, respectively, were 1.8% and 0.9% for folliculitis; 1.5% and 2.0% for contact dermatitis, and 0.3% and 0.6% for headache.
- **Irritation**. In the 40-week PSOARING 3 trial, > 90% of patients had an irritation score of 0 (no irritation) at all visits.[8] Investigator-assessed irritation scores were low (mean < 0.5 on a scale of 0 to 4) for tapinarof and vehicle across all sensitive skin areas (face and intertriginous).[13]
- **Burning / Stinging and Itching**. A total of 86% to 92% of patients reported no, slight, or mild burning / stinging and itching over the 40-week PSOARING 3 trial.[8]

Evidence Gaps

- Functional Ability / Disability
- Patient Satisfaction

Network Meta-analyses

- No network meta-analyses that included tapinarof were found.

Other Considerations

- **Absorption**. No accumulation was observed with repeated topical application. The mean ± SD C_{max} was 0.90 ± 1.4 ng/mL on Day 1 and 0.12 ± 0.15 ng/mL on Day 29. AUC_{0-last} was 4.1 ± 6.3 ng.h/mL and 0.61 ± 0.65 ng/h/mL, respectively. Plasma concentrations of tapinarof were below detectable limits (< 50 pg/mL) in 68% of samples.

Other Therapeutic Options

- Topical medications for psoriasis may be used as sole therapy for treatment of mild / limited plaque psoriasis (affecting < 3% BSA) or as adjunctive therapy for moderate to severe psoriasis.
- Topical corticosteroids are the mainstay of psoriasis therapy. Vitamin D agonists can be considered the preferred topical steroid-sparing agents.
- Alternative nonsteroidal topical treatments for plaque psoriasis are summarized in Table 5.

Table 5 Nonsteroidal Topical Medications 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
Aryl Hydrocarbon Receptor Agonist						
Tapinarof cream 1%	TBD	TBD	1st line, mild–severe PsO *(Note: Studied but not specifically labelled for application to facial or intertriginous areas.)*	Not available	Folliculitis, contact dermatitis, headache No CYP450 or transporter DDIs. Limited long-term experience.	Unknown safety and efficacy of co-use with other topical, systemic, or UV light therapies Unknown TCS sparing effects
PDE4 Inhibitor						
Roflumilast cream 0.3%	TBD	TBD	1st line, mild–severe PsO including for intertriginous areas in pts ≥ 12 years of age	Not available	Contraindicated in moderate to severe liver impairment (Child-Pugh B or C). Most common AEs: Diarrhea, headache. Low rates of AEs (not more than 3.1% for any AE). Based on oral roflumilast studies: Potential DDIs with CYP3A4 and CYP1A2 inhibitors, gestodene, and ethinyl estradiol.[14] Limited long-term experience.	No active-controlled trials Large PGA-0/1–2 treatment effect for intertriginous areas.[14] Unknown safety and efficacy of co-use with other topical, systemic, or UV light therapies Unknown TCS sparing effects
Vitamin D Analogs						
Calcipotriene (CCP) cream 0.005% AKA calcipotriol	Yes		1st line, mild–severe, body and scalp	Alternative or adjunct to TCS Long-term therapy of mild–moderate PsO CCP + class II or III TCS for PsO CCP + HC for facial PsO	Skin irritation; photosensitizing; otherwise minimal adverse effects. 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. Co-use of CCP with TCS is more effective than either agent alone. TCS and UVB sparing Available as TCS combination product.
Calcitriol (CCT) oint 3 mcg/g	Yes		1st line, mild–moderate PsO	Alternative or adjunct to TCS Long-term therapy of mild–moderate PsO	Less irritating than calcipotriene on sensitive skin areas. Hypercalcemia	Similar in efficacy to CCP or BDP oint 0.05%. TCS and UVB sparing

Topical Product	On VANF	CFU Place in Therapy	FDA Place in Therapy for PsO	Guideline Place in Therapy	Safety Considerations	Other Considerations
Calcineurin Inhibitors						•
Tacrolimus oint 0.03%, 0.1%	Yes	NA	Off-label	For face and other sensitive skin areas	Burning, pruritus No definite causal relationship with lymphoma and skin cancer	May be less effective than TCSs. TCS sparing
Pimecrolimus cream 1%	No	NA	Off-label	For face and other sensitive skin areas	See tacrolimus.	Less effective than BMV 0.1%. TCS sparing 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. Co-use with UVB is better than UVB alone. Similar in efficacy to fluocinonide cream and CCP. 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)[15] Goeckerman therapy (coal tar + phototherapy) is recommended for treatment of psoriasis (SOR: B; LOE: II–III)[15] 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.[15]	**CI:** Active or inflamed psoriasis, erythrodermic and generalized pustular psoriasis; hypersensitivity; photosensitivity; local irritation; folliculitis; acne vulgaris.[16] **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: 15, 17, 18, 19, 20
To be comparable with the cream formulation of tapinarof, 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.
BDP, Betamethasone dipropionate; **BMV**, Betamethasone valerate; **CCP**, Calcipotriene; **CCT**, Calcitriol; **CFU**, Criteria for Use; **HC**, Hydrocortisone; **NA**, Not applicable; **Oint**, Ointment; **PsO**, Plaque psoriasis; **TCS**, Topical corticosteroid; **TVDA**, Topical vitamin D analogue; **UVB**, Ultraviolet-B phototherapy

Projected Place in Therapy

- **Epidemiology and Prevalence of Plaque Psoriasis**. Psoriasis is a relatively common disorder with an estimated worldwide prevalence in adults ranging from 0.5% to 11.4% and incidence of 0.09% to 11.43%.[21] Prevalence increases with advancing age. In a Canadian study using expert elicitation methods to determine prevalence of psoriasis by disease severity, it was 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.[22] A UK study reported the incidences of mild (≤ 2 % BSA), moderate (3%–10% BSA), and severe (> 10% BSA) psoriasis to be 51.8%, 35.8%, and 12.4%, respectively.[23]
- **Potential Place in Therapy Based on the Evidence**. A very low quality, active-controlled trial showed that tapinarof in the petrolatum-containing benvitimod cream product produced a small but statistically significant benefit over calcipotriol ointment in PASI-75 and PASI-90 responses but with higher risk of intolerance (DAEs). Moderate-quality evidence from two phase 3 vehicle-controlled trials supports the use of tapinarof cream in patients with any severity (mainly moderate) plaque psoriasis who may or may not have had prior exposure to other topical or systemic therapies. Tapinarof may be more preferable than tazarotene because of its low risks of skin irritation and burning / stinging and lack of desquamating

effects and less preferable than alternative antipsoriatic topical therapies in patients with a significant history of folliculitis.

- **Potential Place in Therapy in VHA**. Tapinarof cream 1% may be used in patients with plaque psoriasis who require topical nonsteroidal therapy (e.g., for treatment of lesions in sensitive areas or to limit corticosteroid use or complications) and have had an inadequate response or intolerance to topical roflumilast unless medically inadvisable and either (1) ≥ 2 other classes of topical antipsoriatics (e.g., topical corticosteroids, vitamin D analogs, calcineurin inhibitors, retinoids / tazarotene, or coal tar, etc.); OR (2) 1 other class of topical antipsoriatics and 1 class of systemic antipsoriatics (e.g., phototherapy, conventional immunomodulator such as methotrexate, or biologic). Issues for consideration include the unknown safety and efficacy of using tapinarof cream in combination with other antipsoriatic topical, systemic (including biologic) or ultraviolet light therapies and the limited long-term safety data and real-world experience with topical tapinarof.

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References

1 VTAMA (tapinarof) topical cream [prescribing information online]. Long Beach, CA: Dermavant Sciences. May 2022. Available at: https://www.vtama.com/hcp/PI/ . Accessed 17 January 2023.

2 Smith SH, Jayawickreme C, Rickard DJ, et al. Tapinarof Is a Natural AhR Agonist that Resolves Skin Inflammation in Mice and Humans. J Invest Dermatol. 2017 Oct;137(10):2110-2119. doi: 10.1016/j.jid.2017.05.004.

3 Stein Gold L, Rubenstein DS, Peist K, Jain P, Tallman AM. Tapinarof cream 1% once daily and benvitimod 1% twice daily are 2 distinct topical medications. J Am Acad Dermatol. 2021 Sep;85(3):e201-e202. doi: 10.1016/j.jaad.2021.04.103.

4 Cai L, Chen GH, Lu QJ, et al. A double-blind, randomized, placebo- and positive-controlled phase III trial of 1% benvitimod cream in mild-to-moderate plaque psoriasis. Chin Med J (Engl). 2020 Nov 9;133(24):2905-2909. doi: 10.1097/CM9.0000000000001221.

5 Stein Gold L, Bhatia N, Tallman AM, Rubenstein DS. A phase 2b, randomized clinical trial of tapinarof cream for the treatment of plaque psoriasis: secondary efficacy and patient-reported outcomes. *J Am Acad Dermatol*. 2021; **84**(3): 624- 631. doi:10.1016/j.jaad.2020.04.181

6 Ehsan M, Rehman AU, Athar F, et al. Benvitimod for the treatment of psoriasis: A systematic review and meta-analysis of randomized controlled trials. Dermatol Ther. 2022 Dec;35(12):e15957. doi: 10.1111/dth.15957.

7 Lebwohl MG, Stein Gold L, Strober B, et al. Phase 3 Trials of Tapinarof Cream for Plaque Psoriasis. N Engl J Med. 2021 Dec 9;385(24):2219-2229. doi: 10.1056/NEJMoa2103629.

8 Strober B, Stein Gold L, Bissonnette R, et al. One-year safety and efficacy of tapinarof cream for the treatment of plaque psoriasis: Results from the PSOARING 3 trial. J Am Acad Dermatol. 2022 Oct;87(4):800-806. doi: 10.1016/j.jaad.2022.06.1171.

9 Bissonnette R, Bolduc C, Maari C, et al. Efficacy and safety of topical WBI-1001 in patients with mild to moderate psoriasis: results from a randomized double-blind placebo-controlled, phase II trial. J Eur Acad Dermatol Venereol. 2012 Dec;26(12):1516-21. doi: 10.1111/j.1468-3083.2011.04332.x.

10 Robbins K, Bissonnette R, Maeda-Chubachi T, et al. Phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of plaque psoriasis. J Am Acad Dermatol. 2019 Mar;80(3):714-721. doi: 10.1016/j.jaad.2018.10.037.

11 Jett JE, McLaughlin M, Lee MS, et al. Tapinarof Cream 1% for Extensive Plaque Psoriasis: A Maximal Use Trial on Safety, Tolerability, and Pharmacokinetics. Am J Clin Dermatol. 2022 Jan;23(1):83-91. doi: 10.1007/s40257-021-00641-4.

12 Center for Drug Evaluation and Research (CDER). Multi-discipline review of tapinarof (VTAMA). Food and Drug Administration (FDA). May 2022

13 VTAMA® (tapinarof) cream, 1% and Plaque Psoriasis standard response letter (e-mail communication dated 26 January 2023), Medical Information, Dermavant Sciences.

14 Center for Drug Evaluation and Research (CDER). Multi-discipline review of roflumilast (ZORYVE). Food and Drug Administration (FDA). May 2022

15 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 Feb;84(2):432-470. doi: 10.1016/j.jaad.2020.07.087.

16 Coal Tar, In-Depth Answers. In: IBM Micromedex DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ . Accessed 24 January 2023.

17 Feldman SR. Treatment of psoriasis in adults. In: UpToDate, Dellavalle RP, Duffin KC (Eds), UpToDate, Waltham, MA, 2023. (Accessed on 24 January 2023.)

18 Plaque Psoriasis – Drug Therapy Guideline. In: IBM Micromedex DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ . Accessed 24 January 2023.

19 Lebwohl MG, Kircik LH, Moore AY, et al. Effect of Roflumilast Cream vs Vehicle Cream on Chronic Plaque Psoriasis: The DERMIS-1 and DERMIS-2 Randomized Clinical Trials. JAMA. 2022 Sep 20;328(11):1073-1084. doi: 10.1001/jama.2022.15632.

[20] Kowalzick L. Clinical experience with topical calcitriol (1,25-dihydroxyvitamin D3) in psoriasis. Br J Dermatol. 2001 Apr;144 Suppl 58:21-5. doi: 10.1046/j.1365-2133.2001.144s58021.x.

[21] Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017 Feb;31(2):205-212. doi: 10.1111/jdv.13854.

[22] Papp KA, Gniadecki R, Beecker J, et al. Psoriasis Prevalence and Severity by Expert Elicitation. Dermatol Ther (Heidelb). 2021 Jun;11(3):1053-1064. doi: 10.1007/s13555-021-00518-8.

[23] Yeung H, Takeshita J, Mehta NN, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol.* 2013;149:1173–1179. doi: 10.1001/jamadermatol.2013.5015.