Apremilast in Mild–Moderate Plaque Psoriasis National Drug Monograph Addendum October 2022

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

- Phosphodiesterase 4 inhibitor.[1]
- Apremilast was previously approved for treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy as well as treatment of adults with active psoriatic arthritis and treatment of adults with oral ulcers associated with Behcet's disease.
- In December 2021, apremilast gained approval for an expanded indication, mild to moderate plaque psoriasis, making it the first systemic medication approved for all severities of the disease.
- Generic apremilast by Alkem Labs, Amneal, and Zydus Pharms are FDA-approved but not marketed to date.

Indication Under Review in This Document

- Treatment of adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy.

Dosage Regimen and Dosage Form(s) Under Review

- Initiated with a 5-day upward dosage titration to a maintenance dose of 30 mg orally twice daily starting on Day 6.

Clinical Evidence Summary

Efficacy Considerations

- There are no direct comparisons between apremilast and alternative therapies for mild to moderate (aka limited) chronic plaque psoriasis to inform place in therapy.
- The results of a single randomized clinical trial (RCT), Apremilast as a Direct Treatment for Mild-to-Moderate Plaque Psoriasis Versus Placebo (ADVANCE), supported the approval of apremilast in mild to moderate plaque psoriasis.[2]

Randomized Clinical Trials

Methods

Table 1 Methods of Phase 3 RCT

Topic	ADVANCE
Study Design	16-week multicenter, double-blind, placebo-controlled phase 3 RCT Randomization was stratified by baseline sPGA (2 = mild, 3 = moderate) Hierarchical ranked testing to control multiplicity
Major Entry Criteria	Adults ≥ 18 years with chronic plaque psoriasis for ≥ 6 months Mild–moderate plaque psoriasis (sPGA 2–3, BSA 2%–15%, PASI 2–15) Inadequate response or intolerance to ≥ 1 topical therapy No prior biologic therapy No csIMMs or phototherapy within 4 weeks prior
Interventions	Apremilast 30 mg BID (Weeks 16–32) following a one-week titration period Placebo BID 16 weeks Allowed concomitant therapy: Unmedicated moisturizers
Maintenance Phase or Long-term Extension	None reported
Primary Efficacy Measure(s)	Percentage of patients who achieved an sPGA response at Week 16. SPGA response was defined as static PGA of 0 / Clear or 1 / Almost Clear with at least a 2-point reduction from baseline.
Baseline Patient Characteristics	Mean age 49 yrs (range, 18–85 yrs) Male 54.6% Mean BSA involvement 6.4% PASI 6.5, WBI-NRS 6.2, DLQI total score 9.9 Scalp involvement 69.1% sPGA score of 2 / Mild and 3 / Moderate: 30.6% and 69.4%, respectively Prior treatment: ≥ 1 csIMM 10.9%; ≥ 1 biologic 0.2%

BSA, Body surface area; **DLQI**, Dermatology Life Quality Index (range 0–30; minimal clinically important change = 4; scores of 6–10 correspond to a moderate effect)[3]; **sPGA**, Static Physician Global Assessment; **WBI-NRS**, Whole body itch numerical rating scale (range 0–10; minimal clinically important change = –4)[4]

Results

Primary Outcome Measures

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

Table 2 ADVANCE study efficacy results at Week 16

Outcome Measure	Apremilast	PBO	Relative Risk (95% CI)	Difference (95% CI)
Primary				
sPGA response, n/N (%)	64/297 (21.6)	12/298 (4.1)	5.4 (3.0, 9.7)	17.5 (12.3, 22.8)
Secondary				
BSA-75 response, n/N (%)	98/297 (33.0)	22/298 (7.4)	4.5 (2.9, 6.9)	25.6 (19.4, 31.7)
WBI-NRS-4 response, n/N (%)	128/297 (43.2)	55/298 (18.6)	2.3 (1.8, 3.1)	24.6 (17.3, 31.6)
ScPGA-0/1 response, n/N (%)	93/212 (44.0)	33/199 (16.6)	2.6 (1.9, 3.7)	27.4 (18.7, 35.5)
LSM CFB in DLQI [N]	–5.2 [297]	–2.4 [298]	NA	–2.8 (NC)

BSA-75, ≥ 75% reduction in involved body surface area; **CFB**, Change from baseline; **DLQI**, Dermatology Life Quality Index total score; **LSM**, Least square mean; **NC**, Not calculable; **ScPGA**, Scalp Physician Global Assessment score of 0/Clear or 1 Almost Clear (baseline ScPGA ≥ 2); **WBI-NRS-4**, ≥ 4-point reduction in Whole Body Itch Numerical Rating Scale (range 0–10; minimal clinically important change = –4)[4]

Table 3 Absolute Effects for Achieving sPGA Response at Week 16

Outcome Measure	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
sPGA response	177 (81, 350) more	6 (5, 9)	High

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

Secondary efficacy measures

- Apremilast showed statistically significant, clinically meaningful benefits in all secondary efficacy outcomes at Week 16, including
    - BSA-75 response, BSA ≤ 3% response, BSA ≤ 1% response, change from baseline in BSA;
    - change from baseline in Psoriasis Area and Severity Index (PASI);
    - ScPGA response;
    - WBI-NRS response;
    - change from baseline in DLQI total score, minimal clinically important change in DLQI (≥ 4-point reduction), DLQI ≤ 5 response, DLQI of 0 or 1, and ≥ 5-point reduction in DLQI.

Subgroup Analyses

- None

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference) and duration of an adequate therapeutic trial are summarized by outcome measure in Table 4.

Table 4 Onset of Benefit and Adequate Therapeutic Trial

Outcome Measure	Onset of Significant Treatment Benefit (Wks)	Duration of an Adequate Therapeutic Trial (Wks)
sPGA response	2	≥ 16
DLQI total score	2	12

- Overall, the duration of an adequate therapeutic trial seems to be 16 weeks.

Durability of Response

- No information reported

Evidence Gaps

- Functional ability / Disability
- Patient Satisfaction
- Long-term maintenance of response

Network Meta-analyses

- No relevant network meta-analyses were found for mild to moderate psoriasis.
- A network meta-analysis of studies evaluating systemic induction therapies for moderate to severe psoriasis showed that apremilast was not significantly different from methotrexate and cyclosporine in achieving PASI90.

Indirect Comparative Efficacy

- A study used matching-adjusted indirect comparisons to compare topical calcipotriene 0.005% / betamethasone diproprionate 0.05% (Cal/BD) aerosol foam with nonbiologic systemic agents in terms of effectiveness.[5]

- Pooled individual patient data from four 4- to 12-week RCTs of Cal/BD foam (once daily application), one RCT of apremilast (30 mg twice daily), and three retrospective observational cohort studies of methotrexate (mean 12 mg/week), acitretin (mean 25 mg/d), or fumaric acid esters (30 mg) were included. (Note that Cal/BD foam is labeled for once daily use for up to 4 weeks with a maximum dose of 60 g every 4 days, and therapy should be discontinued when the condition is controlled.)
- The effective sample size for Cal/BD foam was 640 after reweighting. Data for apremilast were obtained from 148 patients in the UNVEIL trial. The number of patients who received methotrexate, acitretin, or fumaric acid esters were 218, 41, and 115, respectively.
- Patients had plaque psoriasis with mean PASI scores ranging from 7.3 to 11.9 or affected BSA of 7.2 (apremilast) or 7.3 (Cal/BD) (not reported for other treatments). Previous topical treatment was used by 85.1% and 82.4% of Cal/BD foam patients and apremilast patients, respectively. Previous systemic treatment had been used by 31.1% and 26.8% of Cal/BD foam patients and acitretin patients, respectively. Similar data were not reported for other treatments.
- The primary analysis was sPGA response, defined as achievement of sPGA score of 0 or 1 (clear or almost clear) with ≥ 2-grade improvement in disease severity on a 5-point scale (except the apremilast UNVEIL trial used a 6-point PGA scale).
- Cal/BD Foam vs Apremilast
    - Cal/BD foam at Week 4 was better than apremilast at Week 16 in achieving sPGA response (52.7% vs. 30.4%, respectively).[5]
    - The topical combination foam product at Week 4 was also better than apremilast at Week 16 in achieving at least 75% improvement in the Psoriasis Area and Severity Index (PASI-75): 51.1% vs 21.6%, respectively.
- Cal/BD Foam vs Other Nonbiologic Systemic Agents
    - Cal/BD foam at Week 4 showed significantly better PASI-75 response rates than methotrexate (50.8% vs 33.5%, respectively) and acitretin (50.9% vs 31.7%, respectively) at Week 12.
    - Cal/BD foam at Week 4 was comparable in PASI-75 response relative to fumaric acid esters (42.4% vs 47.0%, respectively).
- Other Considerations
    - The study was funded by LEO Pharma (manufacturer of ENSTILAR [Cal/BD foam]).

Safety Considerations

- Safety findings in the ADVANCE study population were similar to those observed in previous trials of apremilast in patients with moderate–severe psoriasis or psoriatic arthritis.

Other Considerations

- No FDA multidisciplinary review was available.

Other Therapeutic Options

- For patients who inadequately respond to topical therapies for mild–moderate plaque psoriasis, localized UVB phototherapy is an option if it is available, feasible, and not inadvisable.
- Apremilast is the only systemic drug treatment approved for mild–moderate plaque psoriasis in patients who are candidates for systemic therapy or phototherapy (Table 13). Other systemic therapies such as methotrexate, cyclosporine, retinoids, and targeted biologic agents (TNF inhibitors, interleukin [IL]-12/23 inhibitor, IL-17A inhibitors, IL-17A receptor inhibitor, and IL-23 inhibitors) are guideline-recommended for moderate to severe disease[6] and could therefore be considered for mild to moderate psoriasis recalcitrant to therapies approved for treatment of mild–moderate plaque psoriasis including apremilast.

Table 5 Systemic Treatment for Mild–Moderate Plaque Psoriasis

Drug	Formulary	Current CFU Place in Therapy	FDA Place in Therapy	AAD-NPF (2020)[6] Guideline Place in Therapy	Safety Considerations	Other Considerations
Apremilast	VANF PA-F, CFU in moderate–severe psoriasis, psoriatic arthritis, and Behçet's disease	Moderate–severe psoriasis After trials of MTX and phototherapy (unless inadvisable, not available or not feasible) AND TNFI is medically inadvisable (prior trial of TNFI is not required)	Plaque psoriasis and candidate for phototherapy or systemic therapy	Preceded approval of apremilast for mild–moderate psoriasis Recommended for treatment of moderate–severe psoriasis in adults Appropriate for pts who prefer to avoid frequent injections and lab monitoring and willing to accept delayed onset and lower chance of skin clearance	GI AEs / diarrhea (dehydration in elderly) –slowly up-titrate dosage in first 5 days Decrease dose for renal impairment Weight loss Depression Avoid strong CYP3A4 inducers	Used as monotherapy Favorable safety profile No routine lab monitoring Also effective for psoriatic arthritis

AAD, American Academy of Dermatology; **CFU**, Criteria for Use; **MTX**, Methotrexate; **NPF**, National Psoriasis Foundation; **TNFI**, Tumor necrosis factor inhibitor

Projected Place in Therapy

- **Epidemiology and Prevalence of Mild–Moderate Plaque Psoriasis in US**. About 2% to 4% of Western populations have psoriasis, with an estimated 50% and 78% of patients having BSA < 3% and < 10%, respectively.
- **Place in Therapy Based on Medical Society Guidelines**. No relevant guidelines included apremilast for mild–moderate plaque psoriasis.
- **Potential Place in Therapy Based on the Evidence**. Although no head-to-head trials comparing apremilast with other systemic therapies were available, high-quality evidence from a single placebo-controlled trial supported the short-term efficacy and safety of apremilast monotherapy in patients with mostly moderate plaque psoriasis with or without scalp involvement who have had an inadequate response to ≥ 1 topical therapy or for whom topical therapies are medically inadvisable. The majority of patients had no prior exposure to systemic therapies. Short-term results consistently showed clinically meaningful benefits in measures of physician global assessment, involved BSA, itch, and dermatology-related quality of life. Apremilast is unique in being the only systemic drug therapy approved for treatment of all severities of plaque psoriasis (mild, moderate, or severe). No new safety concerns were identified. Long-term studies beyond 16 weeks are lacking in patients with mild–moderate psoriasis; however, acceptable safety profiles have been established in trials of ≥ 156 weeks for patients with moderate to severe psoriasis.[7]
- **Potential Place in Therapy in VHA**. Apremilast may be used in patients cared for by a VA / VA Community Care dermatologist and who have a documented diagnosis of plaque psoriasis for ≥ 6 months. Apremilast may be used when BOTH of the following situations apply:
- Inadequate response to 2 or more topical therapies; for example, corticosteroids in different potencies, vitamin D analogs (e.g., calcipotriene or calcitriol), calcineurin inhibitors (e.g., tacrolimus or pimecrolimus) for sensitive areas, or retinoids (e.g., tazarotene); AND
- Phototherapy is medically inadvisable, not available, not feasible, not tolerated, or not adequate.

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Contact person: Francine Goodman, PharmD, BCPS, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

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