Calcipotriene and Betamethasone Dipropionate (ENSTILAR) Foam 0.005% / 0.064%

National Drug Monograph
July 2016
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 when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Combination of a synthetic vitamin D_3 analog (calcipotriene hydrate (CAL); a.k.a. calcipotriol by its International Nonproprietary Name) and synthetic corticosteroid (betamethasone dipropionate, BDP). Compared with CAL/BDP ointment (TACLONEX, DAIVOBET in EU), CAL/BDP foam contains no new excipients except for the addition of propellants (dimethyl ether and butane).[1] After evaporation of the propellants, the product remaining on the skin differs from the ointment in structure.[2] The exact mechanisms of CAL and BDP in plaque psoriasis are unknown, although corticosteroids affect gene transcription that leads to antiinflammatory, antiproliferative and immunosuppressive effects.
Indication(s) Under Review in This Document	Topical treatment of plaque psoriasis in patients 18 years of age and older.
Dosage Form(s) Under Review	Foam, 0.005% / 0.064% Each gram of foam contains 52.2 mcg of CAL (equivalent to 50 mcg of calcipotriene) and 0.643 mg of BDP (equivalent to 0.5 mg of betamethasone)
REMS	☐ **REMS** ☒ **No REMS** ☒ **Postmarketing Commitments** See Other Considerations for additional REMS information
Pregnancy Rating	Category C

Executive Summary

Efficacy	• One vehicle-controlled, phase III randomized clinical trial showed that CAL/BDP foam was efficacious in terms of treatment success rate at Week 4; the effect size was large (NNT = 2.1). • A phase II trial showed that CAL/BDP foam was superior to CAL foam monotherapy (NNT = 3.3; moderate–large additional benefit) and BDP foam monotherapy (NNT = 7.0; small additional benefit) in treatment success rate at Week 4. • Another phase II trial showed that CAL/BDP foam had a small additional benefit over CAL/BDP (TACLONEX) ointment in treatment success rate at Week 4 (NNT = 8.6).
Safety	• There are no contraindications to CAL/BDP foam therapy; however, treatment has been associated with hypercalcemia, hypercalciuria, endocrine effects due to topical absorption of a potent corticosteroid, and allergic contact dermatitis. • The safety profile of CAL/BDP foam was similar to that of CAL/BDP (TACLONEX) ointment. • Nasopharyngitis occurred in 1.1% of treated patients. • Treatment was well tolerated, with 0.5% of patients discontinuing treatment because of an adverse reaction.
Other Considerations	• CAL/BDP foam was approved for use on the body and was not specifically approved or labelled for use on the scalp, although one of the clinical trials included patients with scalp PPsO. • CAL aerosol foam 0.005% is available as a proprietary product, but BDP is not available in an aerosol foam.

	• The topical corticosteroid potency of CAL/BDP foam has not been determined.
Projected Place in Therapy	• In addition to having a recommended role as initial therapy of mild to moderate plaque psoriasis, topical antipsoriatic therapy in general may be useful as an adjunct to second- or third-line systemic therapies or as the main mode of treatment for patients who refuse or are inappropriate for systemic therapies. • CAL/BDP foam may be considered in patients with mild to moderate plaque psoriasis of the body who have had problems adhering to one of the following: calcitriol ointment 3 mcg/g (formulary proprietary product) plus BDP ointment 0.05% base (formulary generic), CAL ointment 0.005% (nonformulary generic) plus BDP ointment (formulary generic), fixed combination CAL/BDP ointment 0.05% / 0.064% (nonformulary generic) or CAL foam 0.005% (proprietary) plus BDP ointment 0.05% (formulary generic) or gel 0.05% (nonformulary generic).

Background

Purpose for Review

Recent FDA approval, new formulation submitted through FDA's full New Drug Application process

Issues to be determined:

- ✔ Evidence of need
- ✔ Does this product offer efficacy advantages to available alternatives?
- ✔ Does this product offer safety advantages over available alternatives?
- ✔ Does this product require criteria for use?

Other Therapeutic Options

- Alternative topical alternatives for the individual CAL/BDP foam drugs that are indicated **for the treatment of plaque psoriasis** (PPsO) or for the relief of inflammatory and pruritic manifestations of corticosteroid (CS)-response dermatoses are shown in the table below.
- Unlike topical CSs, vitamin D_3 analogs do not have restrictions on duration of use.
- Since the potency of CAL/BDP foam has not been determined, corticosteroids with group 1 / super high potency to group 3 / high potency are shown. Corticosteroid potencies were based on prescribing information, a potency table,[3] or both expressed as a range of potencies.

Topical Formulary Alternatives	Other Considerations
Vitamin D Analogs	
Calcipotriene 0.005% Cream (generics)	Not for use on the face. Dose: 2 times daily. Safety and efficacy shown in patients treated for 8 wks.
Calcitriol Ointment, 3 mcg/g (VECTICAL)	For mild to moderate PPsO in adults 18 yrs and older. Apply 2 times daily. Max. 200 g/wk. Not for use on eyes, lips, or face. Better in efficacy and tolerability than calcipotriene ointment for psoriasis in sensitive areas.
Betamethasone Dipropionate Products	
Betamethasone Dipropionate Cream, Augmented Cream (AF) Eq 0.05% Base (generics)	High potency (Class 2). More active than betamethasone valerate. Apply 1–2 times daily. Max. 45 g/wk.
Betamethasone Dipropionate Ointment Eq 0.05% Base (generics)	High to super-high potency (Class 1–2). Apply 1–2 times daily for up to 2 consecutive wks. Max. 50 g/wk. Avoid use on face, groin, or axillae.
Other Corticosteroids with High to Super High Potency (Classs 1–3)	
Betamethasone Valerate Ointment, (BETA-VAL, DERMABET, VALNAC, generics)	Ointment: High potency (Class 3)
Clobetasol Cream, Cream emollient, Ointment, Solution	Super high potency (Class 1)

(scalp) (CORMAX, EMBELINE, EMBELINE E, generics)	
Fluocinonide Cream 0.05%, 0.1%; Cream emulsified base 0.05%; Ointment 0.05%; Solution 0.05% (LIDEX, VANOS, generics)	Super high potency (Class 1)
Triamcinolone Acetonide Cream, 0.5%, Ointment 0.5% (generics)	Cream, Ointment 0.5%: High potency (Class 3)

Topical Nonformulary Alternatives	**Other Considerations**
Vitamin D Analogs	
Calcipotriene / Betamethasone Dipropionate (TACLONEX, generics) Ointment 0.005% / 0.064%	Equivalent to a potent CS. For patients 18 years and older. Not for use on face, arms or groin. Dose: 2 times daily for up to 4 wks. Max. 100 g/wk. Treatment of >30% BSA is not recommended. Common adverse reaction (>1%): scaly rash. May cause hypercalcemia, hypercalciuria and adrenal suppression (15.6%). Associated with pustular psoriasis and rebound effect. Pregnancy category C.
Calcipotriene / Betamethasone Dipropionate (TACLONEX SCALP, TACLONEX) Topical Suspension 0.005% / 0.064%	For scalp in patients 12–17 yrs and for scalp and body in patients 18 yrs and older. Dose: 1 time daily for up to 8 wks. Max 100 g/wk for adults (60 g/wk for 12–17 yr olds). Avoid use on face, groin or axillae. Common adverse reactions (>1%): folliculitis, burning sensation of the skin. May cause hypercalcemia, hypercalciuria and adrenal suppression (15.6%). Pregnancy category C.
Calcipotriene Ointment 0.005% (generic)	Dose: 1–2 times daily. Avoid use on face.
Calcipotriene Solution 0.005% (generics)	For moderately severe psoriasis of the scalp. Dose: 2 times daily. Safety and efficacy shown in patients treated for 8 wks.
Calcipotriene **Foam** 0.005% (SORILUX)	For scalp and body in patients 18 years and older. Dose: 2 times daily.
Betamethasone Dipropionate Products	
Betamethasone Dipropionate Augmented Cream (AF) Eq 0.05% Base (DIPROLENE AF, generic); Augmented Gel, Augmented Lotion, Augmented Ointment (DIPROLENE, generics)	Augmented Cream: High potency (Class 2) Cream: High potency (Class 3) Augmented Gel, Augmented Lotion, Augmented Ointment: Super high potency (Class 1) Dose: 1–2 times daily.
Other Corticosteroids with High or Super High Potency (Classs 1–3)	
Amcinonide Cream, Lotion, Ointment 0.1% (generic)	Ointment: High potency (Class 2) Cream, Lotion: High potency (Class 3) Dose: 2–3 times daily.
Betamethasone Valerate **Foam** 0.12% (LUXIQ, generic)	Medium to high potency (Class 3–4) CS for use on the scalp. Dose: 2 times daily.
Clobetasol Propionate **Foam**, Gel, Lotion, Shampoo, Aerosol Spray (all 0.05%) (CLOBEX, EMBELINE, OLUX (scalp), OLUX E, generics)	Foam, Gel, Lotion: CRD Spray: PPsO up to 20% BSA. All formulations: Super high potency (Class 1)
Desoximetasone Cream 0.05%, 0.25%, Ointment and Spray 0.25%, Gel 0.05% (TOPICORT, TOPICORT LP)	Cream, Ointment, Spray 0.25% and Gel 0.05%: High potency (Class 2) Cream 0.05% (TOPICORT LP): High potency (Class 3)

Diflorasone Diacetate Cream emollient, Ointment 0.05% (generics)	High potency (Class 2–3) Dose: 1–3 times daily.
Fluocinonide Gel 0.05% (generics)	High potency (Class 2)
Fluticasone Propionate Ointment 0.005% (generics)	Ointment: High potency (Class 3) Dose: 2 times daily
Halcinonide Cream, Ointment 0.01% (HALOG)	High potency (Class 2) Dose: 2–3 times daily
Halobetasol Propionate Cream, Ointment (ULTRAVATE, generic), Lotion (ULTRAVATE) (all 0.05%)	Super high potency (Class 1) Dose: 1–2 times daily
Mometasone Furoate Ointment 0.1% (ELOCON, generics)	Ointment: High potency (Class 3)
Retinoids	
Tazarotene Cream, Foam, Gel 0.05%, 0.1% (TAZORAC, AVAGE cream, FABIOR foam)	Cream: Mild to moderate PPsO. Gel: Stable PPsO up to 20% BSA. Fast onset. Effects continue for up to 12 weeks after therapy is discontinued. Often used in combination with corticosteroids such as BDP cream to reduce skin irritation. Retinoids and High-dose Vitamin A (Highly Teratogenic) Criteria for Use
Calcineurin Inhibitors	
Tacrolimus Ointment 0.03%, 0.1% (PROTOPIC, generic)	Off-label use in psoriasis. Useful for facial or intertriginous areas, or for CS-sparing effects.
Pimecrolimus Cream 1% (ELIDEL)	Same as for tacrolimus.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to May 2016) using the search terms calcipotriene and betamethasone dipropionate. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials and long-term (>1 year) observational studies published in peer-reviewed journals were included. Study results were also obtained from the FDA Medical Review and the manufacturer's Academy of Managed Care Pharmacy (AMCP) dossier.

Review of Efficacy

- The FDA review of the efficacy of CAL/BDP foam was based on two (one phase III and one phase II) major clinical trials and one supportive phase II trial. Seven clinical trials were included in the New Drug Application (Table 1).
- **Treatment success** was defined as Investigator Global Assessment of disease activity (IGA) of 0 / Clear or 1 / Almost Clear with at least 2-grade improvement from baseline (5-point scale).

Table 1 Summary of Clinical Trials and Findings

TRIAL	PURPOSE / INTERVENTIONS	POPULATION, N RANDOMIZED / COMPLETED	DESIGN	PRIMARY FINDINGS
Leonardi (2015), PSO-FAST[4] LP0053-1001	Assess safety and efficacy Major efficacy-safety trial CAL/BDP foam Foam vehicle (VEH) Applied once daily	PPsO on body (mostly moderate PPsO) ≥18 yo, IGA ≥2, 2%–30% BSA, mPASI ≥2 (body) 426 / 412	4-wk phase III, 27-center DB VC RCT ITT (US)	CAL/BDP foam was significantly better than VEH in terms of *treatment success rate* at Wk 4: 172/323 (53.3%) vs. 5/103 (4.8%) (p < 0.001). **NNT = 2.1** (large effect size).
LEO 90100-7, FDA Medical Review (2015)[1]	Assess safety and efficacy, proof of concept Major efficacy-safety trial CAL/BDP foam BDP in foam VEH CAL in foam VEH Applied once daily	PPsO on body and scalp (mostly moderate PPsO) ≥18 yo, IGA ≥2, 2%–30% BSA, ≥10% of scalp, mPASI ≥2 (body) 302 / 281	4-wk phase II, 28-center DB, AC RCT ITT (US)	CAL/BDP foam was significantly better than CAL foam and BDP foam in terms of *treatment success rate* at Wk 4: 45/100 (45.0%) vs. 15/101 (14.9%) (p < 0.001; **NNT = 3.3**) and 31/101 (30.7%) (p = 0.047; **NNT = 7.0**), respectively.
Koo (2016)[5] LEO 90100-35	Assess safety and efficacy Supportive efficacy-safety trial CAL/BDP foam CAL/BDP (TACLONEX) ointment Foam VEH Ointment VEH Applied once daily	PPsO on body ≥18 yo, IGA ≥2, 2%–30% BSA, mPASI ≥2 (body) 376 / 358	4-wk phase II, 35-center investigator-blinded, AC VC RCT (US); post hoc comparison of CAL/BDP foam and foam VEH	CAL/BDP foam was significantly superior to TACLONEX ointment in • *Treatment success rate*: 77/141 (54.6%) vs. 58/135 (43.0%); mean diff 11.6% (p = 0.025), OR 1.7 (95% CI 1.1–2.8). **NNT = 8.6**. • Mean mPASI scores at Wk 1 and Wk 4 (diffs –0.7 and –0.6, respectively; p ≤ 0.005); 43.4% and 74.2% relative decreases from baseline. CAL/BDP foam was similar to TACLONEX ointment in • PASI75 response at Wk 4: 50.4% vs. 40.7%; p = 0.052 (NSD). • Mean reductions in itch VAS scores. The authors speculated that the greater efficacy of the foam product may be related to higher CAL and BDP concentrations in skin with foam than ointment, as observed in an unpublished preclinical trial.[6]
LEO 90100-30	Assess maximum use systemic exposure (MUSE) – HPA axis test, calcium metabolism, pharmacokinetics (PK) CAL/BDP foam Applied once daily	Extensive PPsO on trunk, limbs, scalp 37 / 35	OL, 8-center, noncontrolled, PK (CA)	Low quantifiable plasma levels of CAL and its metabolite MC1080 were seen in only a few subjects. There was no evidence of effects on calcium metabolism after daily topical application for up to 4 wks, indicating no or only minimal systemic exposure.

TRIAL	PURPOSE / INTERVENTIONS	POPULATION, N RANDOMIZED / COMPLETED	DESIGN	PRIMARY FINDINGS
LP0053-69	Vasoconstriction CAL/BDP foam Clobetasol (DERMOVAL / DERMOVATE) cream CAL/BDP (TACLONEX) ointment Fluocinolone Acetonide (SYNALAR) ointment BDP in foam VEH Foam VEH	Healthy subjects 35 / 35	Single-center, investigator-blinded, single-dose, intra-individual comparison RCT (FR)	This study was deemed unacceptable to establish product potency by FDA.
LP0053-66	Assess dermal safety (skin irritation and sensitization potential) CAL/BDP foam Foam VEH White petrolatum	Healthy subjects 218 / 214	Single-center, phase I, 16-application with semi-occlusive patches, intra-individual comparison DB RCT (FR)	CAL/BDP foam showed no potential for sensitization. Repeated applications showed limited potency for irritancy.
LEO 90100-01	Exploratory psoriasis plaque test CAL/BDP foam CAL/BDP (TACLONEX) ointment BDP Foam VEH	PPsO on body 24 / 24	4-wk, single-center, investigator-blinded, AC VC repeat-dose, intra-individual comparison RCT (FR)	No information available.

The pooled mean age of patients across the three major efficacy trials ranged from 45.9 to 50.7 years. The majority of patients were white (81.8% to 91.9%) and male (52.0% to 64.9%). The median weekly dose of CAL/BDP foam was 24.8 g.

Indirect Efficacy Comparisons
The literature search found one Cochrane systematic review / meta-analysis of topical treatments for PPsO[7]; however, it did not specify formulations and preceded FDA approval of CAL/BDP aerosol foam.

Potential Off-Label Use

No published reports of off-label use were found. The following potential off-label uses are based on indications for similar products and clinical judgment:

- PPsO of the scalp.
- Corticosteroid-responsive dermatoses other than PPsO.
- Subtypes of psoriasis other than PPsO.

Safety

For more detailed information, refer to the prescribing information.

Boxed Warning	• None
Contraindications	• None
Warnings / Precautions	• Flammability of propellants • Hypercalcemia and Hypercalciuria • Effects on Endocrine System – HPA axis suppression, clinical glucocorticosteroid insufficiency during treatment or upon withdrawal of topical corticosteroid; Cushing's syndrome, hyperglycemia, glucosuria.

	• Allergic Contact Dermatitis • Risks of Ultraviolet Light Exposures – avoid excessive exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc.

Safety Considerations

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression	• None of 35 subjects showed HPA axis suppression in a maximal use pharmacokinetic study assessed HPA axis suppression following once daily application of CAL/BDP foam for 28 days.
Effects on Calcium Metabolism	• In the major safety-efficacy trials, a shift increase in albumin-corrected calcium from normal at baseline to high value (reference range, 2.15–2.55) at Wk 4 was seen in 3 patients on CAL/BDP (values ranged from 2.58 to 2.63) and 1 on TACLONEX ointment (value of 2.58); all values returned to normal or low at follow-up and none exceeded the threshold for clinically significant increase in albumin-corrected calcium of >2.9 mmol/l. • Urinary Calcium / Creatinine Ratio: No remarkable differences among all treatment groups. • In the same pharmacokinetic study mentioned above, none of the 35 subjects showed any effects on calcium metabolism.
Adverse Events Rated *Severe* in Intensity	• 6/78 (8%) of patients with adverse events on CAL/BDP foam vs. 1/14 (7%) of patients with adverse events on TACLONEX ointment. Of these, only one (psoriasis flare / exacerbation) was assessed as possibly related, starting about 1 week after completing study treatment.
Direct Safety Comparison of CAL/BDP Foam and TACLONEX Ointment (Phase II trial, Koo (2016)[5]	• Serious adverse events: 0/141 vs. 2/134; none deemed treatment-related. • Discontinuations Due to Adverse Events: 0/141 vs. 1/134; deemed not treatment-related. • Incidences of adverse events were similar between foam and ointment: 11.3% vs. 10.4% • Adverse drug reactions (adverse events assessed as related to study drug): 1/141 (0.7%, application site itch) vs. 4/134 (3.0%; application site dryness (n = 1), pain and psoriasis (1), itch (2)). • Albumin-corrected serum calcium and spot urinary calcium:creatinine ratio remained within normal limits in the foam and ointment groups at Wk 4; however, during treatment no foam-treated patient and 1 ointment-treated patient developed high albumin-corrected serum calcium concentrations (>2.55 mmol/l). • Shift from normal at baseline to high urinary calcium:creatinine ratio at Wk 4: 4/141 vs. 3/134. • None of the increases in calcium values were considered clinically relevant or reported as adverse events.
Indirect Comparison of CAL/BDP Foam and TACLONEX Ointment and Topical Suspension: Short- and Long-Term Safety	• Using the results of short-term (4 wks for body, 8 wks for scalp) major safety-efficacy trials for CAL/BDP foam and historical trials for TACLONEX ointment and topical suspension, the manufacturer concluded that there was no indication that CAL/BDP foam was associated with adverse events, adverse drug reactions and lesional / perilesional adverse events that were either higher in frequency or severity than with the two approved TACLONEX products. In addition, no adverse events were identified that were unique to CAL/BDP foam. • Based on long-term clinical trials with TACLONEX ointment and topical suspension, the adverse reactions seen during long-term treatment were predictable and consistent with the pharmacologic class effects, with no increase in frequency or severity of adverse reactions over time and no serious adverse reactions with treatment up to 52 weeks.

	• The FDA medical reviewer agreed with the manufacturer that a long-term study with CAL/BDP foam was unlikely to yield new safety information.

Adverse Reactions

Common Adverse Reactions	• CAL/BDP foam vs. TACLONEX Ointment: o Incidence of Adverse Events – 78/564 (13.8% vs. 14/134 (10.4%) o Incidence of Adverse Reaction (adverse events for which the investigator had not described the causal relationship with study treatment as *not related* – 15/564 (2.7%) vs. 4/134 (3.0%) • Common Adverse Reactions (>1%): Nasopharyngitis (1.1%) • Less Common Notable Adverse Reactions (<1%): Application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, urticarial, and exacerbation of psoriasis.
Deaths / Serious Adverse Reactions	• No deaths. • Nonfatal Serious Adverse Events (SAEs): 3/564 (0.5%) – severe hypersensitivity / urticarial (considered to be related to study drug and led to discontinuation), bipolar disorder and substance-induced psychotic disorder.
Discontinuations Due to Adverse Reactions	• 3/564 (0.5%) • Hypersensitivity / urticaria, substance-induced psychotic disorder, irregular menstruation

Drug Interactions

Drug-Drug Interactions	• No guidance in prescribing information.

Risk Evaluation

As of 9 May 2016

Sentinel Event Advisories	• None • Sources: ISMP, FDA, TJC
Look-alike / Sound-alike Error Potential	

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Calcipotriene/ betamethasone dipropionate 0.005% / 0.064% foam	None	None	None	Calcipotriene/betamethasone ***ointment*** Calcipotriene Calcitriol Calcitonin Capecitabine
ENSTILAR	None	None	None	EDLUAR ENSKYCE

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations	
Use of Corticosteroid Foam Products on the Body and Scalp	• CAL/BDP foam was approved for use on the body and was not specifically approved or labelled for use on the scalp, although one of the clinical trials included patients with scalp PPsO. • Generally, corticosteroid foam products (e.g., fluocinonide 0.05% or clobetasol propionate 0.05%) or solutions are used on the scalp or in the external ear canal. • Clobetasol 0.05% shampoo or spray may also be used on the scalp.
Use of Separate Products	• CAL aerosol foam 0.005% is available as a proprietary product, but BDP is not available in an aerosol foam.
Combination vs. Monotherapy	• Combination CAL/BDP formulations have been shown to be more effective and better tolerated than monotherapy with either agent alone. • The corticosteroid component seems to reduce the local skin reactions typically associated with CAL therapy. • CAL seems to augment the corticosteroid effect. • Once-daily application of the fixed combination product improves convenience over the twice-daily application of the monotherapy products.
Potency Testing – Postmarketing Commitments	• The topical corticosteroid potency of CAL/BDP foam has not been determined. • FDA suggested that the manufacturer conduct a study using a single point vasoconstriction assay to determine the topical corticosteroid potency classification for CAL/BDP foam in healthy subjects.

Dosing and Administration

- Instruct patients to shake can prior to using CAL/BDP foam and to wash their hands after applying the product.
- Apply CAL/BDP foam to affected areas once daily for up to 4 weeks. Rub in CAL/BDP foam gently. Discontinue use when control is achieved.
- Instruct patients not to use more than 60 g every 4 days.
- CAL/BDP foam should not be used with occlusive dressings unless directed by a physician. CAL/BDP foam is not for oral, ophthalmic, or intravaginal use.
- Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

Special Populations (Adults)	
Elderly	• In clinical trials, 97 patients were aged 65 years or older and 21 were 75 years or older. • Subgroup analyses in the clinical trials did not show age-dependent differences in safety or efficacy.
Pregnancy	• Pregnancy Category C. No adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefits outweigh the potential risks.
Lactation	• Use with caution. • It is not known whether topically administered calcipotriene or corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. • Do not apply CAL/BDP foam on breast when nursing.
Renal Impairment	• No guidance in prescribing information.
Hepatic Impairment	• No guidance in prescribing information.
Pharmacogenetics/genomics	• No data.

Projected Place in Therapy

- The place in therapy of CAL/BDP foam is not specifically addressed in clinical practice guidelines.
  - The 2012 NICE treatment guideline recommends offering topical agents as first-line therapies to patients with plaque psoriasis, and offering second- or third-line therapies (phototherapy or systemic therapy) to use concomitantly with topical therapies when topical monotherapy is unlikely to adequately control psoriasis, such as for extensive disease (e.g., ≥10% BSA), moderate disease, or nail psoriasis.[8]
  - The 2012 S-3 German treatment guideline for plaque psoriasis recommends the use of class III corticosteroids and vitamin D_3 derivatives for induction therapy for patients with mild to moderate plaque psoriasis (Evidence Level 1).[9] The guideline also recommends combination therapy with vitamin D_3 derivatives and corticosteroids in the first 4 weeks as induction therapy for patients with mild to moderate plaque psoriasis (Evidence Level 1).
  - The 2015 best practice recommendations on the treatment of nail psoriasis by the Medical Board of the National Psoriasis Foundation indicate that high-potency topical corticosteroids with or without calcipotriene are initial treatment options.[10]
  - UpToDate states that corticosteroids are the mainstay of topical treatment for psoriasis and may be used as the sole initial therapy.[11] Keeping the treatment regimen simple (e.g., a single topical formulation, less frequent dosing) and tailoring the choice of vehicle to patient preferences may be beneficial in promoting treatment adherence, probably the key factor in determining treatment effectiveness. Calcipotriene in combination with class 1 topical corticosteroids can be used for short-term control then reduced to intermittent (weekend) use, with calcipotriene monotherapy given daily. Thick plaques on extensor surfaces are indications for potent corticosteroids (e.g., betamethasone 0.05% or clobetasol propionate 0.05%). The combination of a vitamin D analog plus corticosteroid seems to be slightly more effective than monotherapy with a potent corticosteroid for scalp psoriasis. Many patients prefer lotion, solution, gel, foam or spray formulations over thicker creams and ointments for psoriasis on the scalp.
- In summary, in patients with mostly moderate plaque psoriasis, 4-week therapy with CAL/BDP aerosol foam showed a small efficacy advantage over CAL/BDP (TACLONEX) ointment, an established first-line treatment for psoriasis available as generic products. CAL/BDP foam and ointment have similar safety and tolerability profiles. After application of the foam and evaporation of the propellants, the product remaining on the skin is identical in ingredients to CAL/BDP ointment except it has a different structure and reportedly promotes greater drug absorption into the skin than the ointment formulation. The foam may be a more cosmetically acceptable formulation for patients than the ointment, which has been shown to lead to nonadherence with treatment in 11% of patients because of greasiness.[12] However, patient preference and adherence to treatment were not assessed in CAL/BDP foam clinical trials. In addition to having a recommended role as initial therapy of mild to moderate plaque psoriasis, topical antipsoriatic therapy in general may be useful as an adjunct to second- or third-line systemic therapies or as the main mode of treatment for patients who refuse or are inappropriate for systemic therapies. CAL/BDP foam may be considered in patients with mild to moderate plaque psoriasis of the body who have had problems adhering to one of the following: calcitriol ointment 3 mcg/g (formulary proprietary product) plus BDP ointment 0.05% base (formulary generic), CAL ointment 0.005% (nonformulary generic) plus BDP ointment (formulary generic), fixed combination CAL/BDP ointment 0.05% / 0.064% (nonformulary generic) or CAL foam 0.005% (proprietary) plus BDP ointment 0.05% (formulary generic) or gel 0.05% (nonformulary generic).

References

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Appendix A: GRADEing the Evidence

Quality of Evidence	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of theevidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.