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ADIS DRUG EVALUATION

Calcipotriol/Betamethasone Dipropionate Foam: A Review in Plaque Psoriasis

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Abstract Calcipotriol/betamethasone dipropionate foam (Enstilar®) is a once-daily synthetic vitamin D_3 analogue and synthetic corticosteroid fixed-dose combination foam formulation that is indicated for the topical treatment of plaque psoriasis in adults. In randomized, multicentre trials, treatment with calcipotriol/betamethasone dipropionate foam for 4 weeks resulted in greater proportions of patients achieving treatment success [of the body (i.e. trunk and/or limbs), as assessed by a physician] compared with 4 weeks' treatment with the foam vehicle, individual components as foam, or calcipotriol/betamethasone dipropionate fixed-dose combination as an ointment, or 8 weeks' treatment with the fixed-dose combination as a topical suspension. Treatment with calcipotriol/betamethasone dipropionate foam resulted in significantly lower modified psoriasis area and severity index scores and, where assessed, greater improvements from baseline to week 4 in itch-related sleep loss and health-related quality of life than its comparators; results were mixed for patient-assessed improvements in itch. Overall, adverse events were mostly mild or moderate in severity, and the most commonly reported treatment-related adverse events were application-site events. Notably, there were no reports of clinically relevant effects on calcium homeostasis or the hypothalamic-pituitary-adrenal axis. Calcipotriol/betamethasone dipropionate foam is a useful new option for patients with plaque psoriasis.

Calcipotriol/betamethasone dipropionate foam: clinical considerations in plaque psoriasis in adults
Foam formulation of a synthetic vitamin D_3 analogue and synthetic corticosteroid fixed-dose combination
Offers convenience of once daily administration
Enhanced skin penetration compared with the fixed-dose combination as ointment
More effective in treating plaque psoriasis than the foam vehicle, individual components as foam, or fixed-dose combination as a topical suspension or ointment
Generally well tolerated, with no reports of clinically relevant effects on calcium homeostasis or the hypothalamic-pituitary-adrenal axis

1 Introduction

Psoriasis is a common, chronic, immune-mediated, potentially disfiguring and disabling inflammatory skin disease that affects over 100 million individuals worldwide [1, 2]. It is a disease in which new skin cells form in days instead of weeks in response to faulty signals from the immune system in genetically susceptible individuals, resulting in the accumulation of excess skin cells on the surface of the skin

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[3, 4]. The disease may be accompanied by extracutaneous involvement (e.g. ophthalmic symptoms, psoriatic arthritis) and an increased risk of comorbidities (e.g. cardiovascular disease, malignancy, metabolic syndrome) [3, 5, 6].

Plaque psoriasis (also known as psoriasis vulgaris) is the most common type of psoriasis (70–90 % of cases), characterized by well-defined, red lesions/plaques, covered in silvery-white scales [2, 7]. Common symptoms include itching and pain. While lesions can affect any anatomical site, including the nails, predilection sites include the elbows, knees and scalp, and lumbar, anogenital, and periumbilical areas [2, 7]. Histological changes are mediated mainly by dendritic cells and T cells through various cytokines [e.g. tumour necrosis factor (TNF)-α, interleukin (IL)-12, -23, -17, and -22] [2, 4, 8].

Topical therapies (e.g. corticosteroids, vitamin D analogues) are the mainstay of treatment for mild psoriasis, either as mono- or combination therapy, and they are often used in conjunction with phototherapy [e.g. narrow-band ultraviolet (UV)-B, psoralen plus UVA] or systemic therapy [traditional (e.g. acitretin, ciclosporin, methotrexate) or biological (e.g. T-cell inhibitors, TNF-α inhibitors, a monoclonal antibody blocking interleukins 12 and 23)] for the treatment of moderate to severe psoriasis [9–11]. Topical therapies are associated with lower adherence rates than those of systemic treatments, and adherence to treatment is a major challenge in psoriasis patients [12]. The visible and highly stigmatizing nature of psoriasis can severely impair patients' health-related quality of life (HR-QOL), even in patients with mild disease (≈70–80 % of patients) [2, 13], and adherence is critical for the successful management of the disease [12]. There is a need for other treatment options that can enhance patient acceptability and adherence, thereby improving efficacy and treatment success. One such option is calcipotriol/betamethasone dipropionate 0.005/0.064 % foam (Enstilar®), a novel emollient formulation of a well-established fixed-dose combination of a synthetic vitamin D_3 analogue (calcipotriol/calcipotriene) and synthetic corticosteroid (betamethasone dipropionate; referred to hereafter as betamethasone) that is indicated in the EU and USA for the topical treatment of plaque psoriasis in adults [14–17].

This narrative review discusses the use of calcipotriol/betamethasone foam in the topical treatment of adults with plaque psoriasis. The gel and ointment formulations of this fixed-dose combination were reviewed in *Drugs* previously [18].

2 Pharmacodynamic Properties

Calcipotriol can promote epidermal differentiation and inhibit the proliferation of keratinocytes, and betamethasone can decrease the mitotic rate of the epidermis [19]. In addition, calcipotriol and betamethasone have anti-inflammatory properties [19]. Although the clinical and pharmacological effects of calcipotriol and betamethasone are known, their exact mechanisms of action in plaque psoriasis are not completely understood [14].

A mode-of-action study investigated the effects of calcipotriol, betamethasone and a combination of the two drugs on immune modulatory effects in ex vivo psoriatic skin cultures and in in vitro cultures of primary human cell subsets relevant to psoriasis [20]. In psoriasis skin explants, calcipotriol/betamethasone reduced IL-8, -17A and -22 gene expression, and TNF-α and IL-8, -17A and -22 protein levels to a significantly greater extent than calcipotriol and/or betamethasone alone. In vitro, calcipotriol/betamethasone reduced inflammatory responses in keratinocytes stimulated with T helper 17 cell-related cytokines, and exhibited additive inhibitory effects on the secretion of TNF-α and IL-23 by dendritic cells and TNF-α and IL-17A by T cells [20].

In patients with plaque psoriasis, calcipotriol/betamethasone foam improves erythema, lesional thickness and scaling associated with psoriasis [21]. In patients with plaque psoriasis ($n = 24$), intra-individual comparisons using a modified psoriasis plaque test showed a significantly greater reduction from baseline to week 4 in mean total clinical score (TCS; the sum of scores for erythema, lesional thickness and scaling) with once-daily calcipotriol/betamethasone foam than with once-daily calcipotriol/betamethasone ointment ($p = 0.038$), betamethasone foam ($p = 0.005$) or foam vehicle ($p < 0.001$) [21]. In this study, calcipotriol/betamethasone foam reduced total skin thickness significantly compared with the foam vehicle ($p < 0.001$), and reduced superficial dermis inflammation significantly compared with betamethasone foam ($p = 0.037$) and foam vehicle ($p < 0.001$) [21].

Enhanced skin penetration of calcipotriol/betamethasone foam compared with calcipotriol/betamethasone ointment was shown in an in vitro skin penetration study using pig ear skin ($n = 6$) [22]. Twenty-one hours after topical application, higher total levels of calcipotriol ($p < 0.001$) and betamethasone ($p = 0.002$) were found within skin samples with the calcipotriol/betamethasone foam than with the ointment. A stable, supersaturated solution of calcipotriol and betamethasone that forms once the propellants of the foam have evaporated accounts for the improved drug delivery and is a potential explanation for the improved clinical efficacy [22].

In healthy volunteers ($n = 35$), calcipotriol/betamethasone foam showed significantly ($p \leq 0.001$) greater vasoconstrictor potential (as assessed by a skin blanching response detected visually by trained observers over 32 hours) than calcipotriol/betamethasone ointment or a moderately potent steroid (fluocinolone acetonide 0.25 mg/g ointment) but significantly ($p < 0.001$) lower vasoconstrictor potential than a

very potent steroid (clobetasol propionate 0.05 % cream) [23]. In another study ($n = 213$), calcipotriol/betamethasone foam was found to have no skin sensitization potential and low skin irritation [24].

3 Pharmacokinetic Properties

Calcipotriol/betamethasone foam is systemically absorbed, but systemic exposure following topical application is low [14, 15]. Following systemic uptake, calcipotriol is metabolized rapidly in the liver to MC1046, then MC1080, then calcitroic acid [14]. These metabolites are less potent than calcipotriol. Betamethasone dipropionate is metabolized via hydrolysis to betamethasone, betamethasone 17-propionate (B17P) and the respective 6β-hydroxy derivatives [14]. In adults with extensive, moderate to severe plaque psoriasis ($n = 35$) treated with calcipotriol/betamethasone foam once daily for 4 weeks (mean weekly dose of 61.8 g), plasma concentrations of calcipotriol and its main metabolite (MC1080) were quantifiable in 2.9 and 8.6 % of patients, and plasma concentrations of betamethasone and its main metabolite (B17P) were quantifiable in 14.3 and 77.1 % of patients [14, 15]. However, the clinical significance of these results is unknown [14].

4 Therapeutic Efficacy of Calcipotriol/Betamethasone Foam

The efficacy of once-daily calcipotriol/betamethasone foam in the treatment of adults with plaque psoriasis was examined in large ($n > 100$), randomized, single- [25, 26] or double-blind [16, 27], multicentre [16, 25–27] (multinational [26]), phase II [25, 27] or III (PSO-FAST [16] and PSO-ABLE [26]) trials. The main objectives of these trials were to compare the efficacy of calcipotriol/betamethasone foam with that of the foam vehicle [16], the individual components as foam [27], and the fixed-dose combination as topical suspension (a gel formulation) [26] or ointment [25]. Three of the trials included vehicle (i.e. placebo) controls [16, 25, 26]. Some data are from abstracts and/or posters [28–31].

Eligible patients were aged ≥18 years with plaque psoriasis of at least mild severity [according to the physician's global assessment of disease severity (PGA)], affecting 2–30 % of their body surface area (BSA) [generally the trunk and/or limbs], and a modified (head excluded) psoriasis area and severity index (mPASI) score of ≥2 [16, 25–27]. Exclusion criteria [16, 25–27] included other types of psoriasis, other inflammatory skin disorders, skin infections, hypercalcaemia-associated disorders of calcium metabolism, severe hepatic or renal disorders (where specified [16, 25, 27]), and recent treatment with biologicals, other systemic treatments with a possible effect on psoriasis, topical antipsoriatic therapy [16, 25, 27], and phototherapy.

The primary efficacy endpoint was the proportion of patients who achieved treatment success (defined in Table 1) at week 4 [16, 25, 27] or at the end of the approved treatment period for each active formulation [26]. Treatment success of the scalp was evaluated as an additional efficacy endpoint in the phase II trial [27]. Efficacy analyses were performed in the ITT populations.

4.1 Comparison with the Foam Vehicle

In PSO-FAST, patients were randomized to receive calcipotriol/betamethasone foam or the foam vehicle once daily for up to 4 weeks [16]. At baseline, the mean duration of disease was 15.9 years (range 1–67 years), and the distribution of patients with mild, moderate and severe disease was 15.3, 74.9 and 9.9 %, respectively. The mean duration of treatment was 4.0 weeks in calcipotriol/betamethasone foam recipients and 4.1 weeks in foam vehicle recipients. The majority of patients (97 % of calcipotriol/betamethasone foam and 96 % of foam vehicle recipients) completed the trial, with full compliance reported in 76.2 and 86.3 % of patients, and the weekly amount of treatment used was 29.8 and 32.1 g [16].

Treatment success rates were significantly higher with calcipotriol/betamethasone foam than with the foam vehicle at week 4 (Table 1). Of note, treatment success rates were generally similar across all body mass indices and bodyweights [30]. At week 4, mPASI scores were significantly lower in calcipotriol/betamethasone foam than foam vehicle recipients (Table 1), reflecting mean reductions from baseline of 71.9 % in calcipotriol/betamethasone foam recipients and 25.8 % in foam vehicle recipients. A significant between-group difference ($p < 0.001$) in mPASI scores was seen from week 1 [16]. By week 4, significantly greater proportions of calcipotriol/betamethasone foam recipients achieved reductions in mPASI scores of ≥75 % (PASI75) or ≥50 % (PASI50) than foam vehicle recipients (Table 1).

Patient perceptions of treatment success were consistent with investigator-reported results [16]. On the patient's global assessment of disease severity (PaGA) scale, significantly more calcipotriol/betamethasone foam than foam vehicle recipients (65.2 vs. 22.2 % of patients; $p < 0.001$) achieved treatment success (defined as clear or very mild disease) at week 4 [16]. Among patients who reported itch or itch-related sleep loss at baseline (96.2 and 79.8 % of patients overall), significantly greater improvements in both conditions [on a visual analogue scale (VAS)] were reported with calcipotriol/betamethasone foam than with the foam vehicle from day 3 (first assessment; $p = 0.01$)

Table 1 Efficacy of calcipotriol/betamethasone foam in adults with plaque psoriasis of the body (i.e. trunk and/or limbs). Results of large, multicentre trials at the end of treatment[a]

Trial	Treatment (od)	No. of pts[b]	Treatment success[c] (% pts)	Mean mPASI score [BL]	PASI75 (% pts)	PASI50 (% pts)
Versus vehicle						
PSO-FAST (NCT01866163) [16]	CAL/BET foam	323	53.3*	2.0* [7.4]	52.9*	82.3*
	Foam vehicle	103	4.8	5.5 [7.9]	8.2	28.0
Versus individual components						
NCT01536938 [27]	CAL/BET foam	100	45.0††,‡	2.37††,‡‡‡ [8.8]	49.0††	80.0†,‡‡
	CAL foam	101	14.9	4.39 [8.6]	18.0	44.0
	BET foam	101	30.7	3.37 [8.1]	34.0	59.0
Versus other formulations[d]						
PSO-ABLE (NCT02132936) [26, 31]	CAL/BET foam	185	38.3§§§	2.18§ [7.1]	52.1§§§	NA
	CAL/BET topical suspension	188	22.5	2.77 [6.6]	34.6	NA
	Foam vehicle	47	5.0	NA [7.2]	0.0	NA
	Topical suspension vehicle	43	0.0	NA [7.4]	3.0	NA
NCT01536886 [25]	CAL/BET foam	141	54.6§	1.82§§ [7.0]	50.4	80.9
	CAL/BET ointment	135	43.0	2.46 [6.7]	40.7	74.8
	Foam vehicle	49	6.0	4.3 [6.7]	NA	NA
	Ointment vehicle	51	8.0	4.3 [6.6]	NA	NA

BET betamethasone dipropionate, *BL* baseline, *CAL* calcipotriol, *mPASI* modified psoriasis area severity index, *NA* not available, *od* once daily, *PASI50* reduction in mPASI scores of ≥50 %, *PASI75* reduction in mPASI scores of ≥75 %, *pts* patients

* $p < 0.001$ vs. vehicle

† $p < 0.01$, †† $p < 0.001$ vs. CAL foam

‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$ vs. BET foam

§ $p < 0.05$, §§ $p < 0.01$, §§§ $p < 0.001$ vs. other CAL/BET formulation

[a] Results for topical suspension combination and vehicle are at week 8 of treatment; all other results are at week 4

[b] ITT population

[c] Primary efficacy endpoint [for the body (i.e. trunk and/or limbs) unless otherwise specified]; defined according to the physician's global assessment of disease severity as clear skin in patients with mild disease at baseline and clear or almost clear skin in patients with moderate to severe disease at baseline [16, 27], or clear to almost clear skin with at least a two-step improvement from baseline [25, 26]

[d] Apart from BL, values for vehicle-only arms were estimated from bar charts where available; no statistical analyses were reported

through to week 4 ($p < 0.001$) of treatment. The proportions of calcipotriol/betamethasone foam recipients achieving 70 % reductions in itch or itch-related sleep loss increased from day 3 ($p < 0.04$ vs. foam vehicle recipients) to week 4 ($p < 0.001$) [16].

Calcipotriol/betamethasone foam treatment improved HR-QOL, as assessed using the dermatology life quality index (DLQI) and generic five-dimension EuroQOL (EQ-5D-5L) questionnaires [28]. Improvements from baseline in mean DLQI scores were significantly greater in calcipotriol/betamethasone foam than foam vehicle recipients at all assessed time points (weeks 1, 2 and 4) [all $p < 0.001$]. Overall, 48.2 % of calcipotriol/betamethasone foam recipients compared with 21.2 % of foam vehicle recipients ($p < 0.001$) reported no impairment (DLQI scores of 0 or 1) by week 4. In patients with baseline DLQI scores of ≥5 (more than a mild impact), 81.2 % of calcipotriol/betamethasone foam recipients compared with 57.3 % of foam vehicle recipients ($p < 0.001$) achieved a minimal clinically important difference from baseline (defined as a ≥5-point improvement). In addition, the change from baseline to week 4 in EQ-5D-5L scores was significantly ($p \leq 0.005$) more favourable with calcipotriol/betamethasone foam than with the foam vehicle [28].

4.2 Comparison with the Individual Components

In a phase II trial (NCT01536938), patients were randomized to receive calcipotriol/betamethasone foam, calcipotriol foam or betamethasone foam once daily for 4 weeks [27]. At baseline, the majority of patients had moderate plaque psoriasis of the body (76 % of patients) and scalp (66 %). The majority of patients (94, 92 and 93 % of fixed-combination foam, calcipotriol foam and betamethasone foam recipients, respectively) completed the trial [27].

Calcipotriol/betamethasone foam was more effective than calcipotriol foam or betamethasone foam in treating plaque psoriasis of the trunk and limbs, and it was more effective than calcipotriol foam in treating plaque psoriasis

of the scalp [27]. The proportion of patients with treatment success on the trunk and limbs was significantly greater with calcipotriol/betamethasone foam than with calcipotriol foam or betamethasone foam at week 4 (Table 1). At week 4, a significant ($p = 0.021$) percentage of calcipotriol/betamethasone foam recipients (53 %) had treatment success of the scalp compared with calcipotriol foam recipients (35.6 %) but not with betamethasone foam (47.5 %) recipients [27]. By week 4, mean mPASI scores were significantly lower in calcipotriol/betamethasone foam than calcipotriol foam or betamethasone foam recipients, and significantly greater proportions of calcipotriol/betamethasone foam than calcipotriol foam or betamethasone foam recipients achieved PASI75 or PASI50 (Table 1).

Patient-reported outcomes supported these results [27]. A significantly greater proportion of calcipotriol/betamethasone foam recipients (60 % of patients) reported combined body and scalp PaGA treatment success at week 4 than calcipotriol foam (30 %; $p < 0.001$) or betamethasone foam (41 %; $p = 0.005$) recipients. At week 4, a significant between-group difference in itch intensity VAS scores was seen with calcipotriol/betamethasone foam and calcipotriol foam ($p < 0.001$), but not with calcipotriol/betamethasone foam and betamethasone foam [27].

4.3 Comparison with Other Formulations

4.3.1 Comparison with the Topical Suspension

In PSO-ABLE, patients were randomized to receive calcipotriol/betamethasone foam, calcipotriol/betamethasone topical suspension, the foam vehicle or the topical suspension vehicle once daily for up to 12 weeks [26]. The objective of the trial was to compare the efficacy of calcipotriol/betamethasone foam at week 4 with that of calcipotriol/betamethasone topical suspension at week 8 (reflecting treatment durations approved for each formulation by the FDA and the European Medicines Agency) [15, 32]. At baseline, the majority of patients (58.9–74.4 %) had moderate disease [26].

Treatment with calcipotriol/betamethasone foam for 4 weeks was significantly more effective than treatment with calcipotriol/betamethasone topical suspension for 8 weeks, in terms of treatment success, mPASI and PASI75 (Table 1) [26]. Of note, significantly greater proportions of calcipotriol/betamethasone foam recipients at week 4 than calcipotriol/betamethasone topical suspension recipients at week 8 achieved PASI90 (22.2 vs. 10.7 % of patients; $p = 0.009$) [26]. Both calcipotriol/betamethasone foam and calcipotriol/betamethasone topical suspension provided itch relief, but the difference in mean itch VAS scores at the respective assessment timepoints was not statistically significant [31].

At week 12, treatment with calcipotriol/betamethasone foam or calcipotriol/betamethasone topical suspension resulted in treatment success in 44.1 and 34.3 % of patients, and PASI75 in 60.6 and 45 % of patients [26]. The median time to treatment success was 6 weeks in calcipotriol/betamethasone foam recipients and could not be determined in calcipotriol/betamethasone topical suspension recipients (because <50 % of these patients had achieved treatment success by week 12) [$p < 0.001$] [26].

Improvements in HR-QOL, as assessed by the DLQI and EQ-5D, were significantly greater with calcipotriol/betamethasone foam than with calcipotriol/betamethasone topical suspension at week 4 ($p \leq 0.005$), but not at weeks 8 and 12 [29]. Results of a patient preference questionnaire at week 4 showed that the majority of calcipotriol/betamethasone foam or topical suspension recipients preferred these treatments over previous topical (83.7 and 69.3 %) or systemic (65.2 and 55.3 %) therapies [26]. The majority of calcipotriol/betamethasone foam or topical suspension recipients also agreed/strongly agreed with statements in the topical therapy questionnaire regarding treatment satisfaction at weeks 4–12, including speed of improvement in skin condition (89.7–93.3 and 66.1–72.5 % of patients), satisfaction with how quickly treatment took effect (92.9–94.9 and 78.0–79.4 %), acceptability of time spent on daily treatment (94.2–96.9 and 94.3–96.1 %), and that they would continue or repeat therapy (90.2–95.5 and 81.1–90.4 %) [26].

4.3.2 Comparison with the Ointment

In a phase II trial (NCT01536886), patients were randomized to receive calcipotriol/betamethasone foam, calcipotriol/betamethasone ointment, foam vehicle or ointment vehicle once daily for 4 weeks [25]. At baseline, the majority of patients (71.4–79.4 %) had moderate disease [25]. Calcipotriol/betamethasone foam was significantly more effective than calcipotriol/betamethasone ointment in treating plaque psoriasis, in terms of treatment success rates and mPASI scores, but not in terms of PASI75 or PASI50 (Table 1). Both the foam and ointment formulations of calcipotriol/betamethasone provided itch relief starting from the first week of treatment; the mean change from baseline to week 4 in VAS itch scores was −39.8 in calcipotriol/betamethasone foam recipients (baseline score was 52.7) and −36.5 in calcipotriol/betamethasone ointment recipients (baseline score of 52.1) [*p*-values not stated] [25].

4.4 Pooled Analysis

An analysis pooling data from trials of 4 weeks' duration [16, 25, 27] (descriptive analyses only) showed treatment

success rates of 51.4 % with calcipotriol/betamethasone foam, 43.0 % with calcipotriol/betamethasone ointment, 14.9 % with calcipotriol foam, 30.7 % with betamethasone foam, 5.3 % with the foam vehicle and 7.8 % with the ointment vehicle at week 4 [33]. Among calcipotriol/betamethasone foam recipients, treatment success rates in patients who had mild, moderate or severe disease at baseline were 30.1, 57.5 and 33.3 %, respectively. Mean percentage improvements (reductions) in mPASI scores from baseline to week 4 were 71.5 % with calcipotriol/betamethasone foam, 63.4 % with calcipotriol/betamethasone ointment, 43.2 % with calcipotriol foam, 53.3 % with betamethasone foam, 31.8 % with foam vehicle and 32.9 % with ointment vehicle, and PASI75 was achieved in 50.7, 40.7, 17.8, 33.7, 7.2 and 9.8 % of patients, respectively. The mean change in itch VAS scores from baseline to week 4 was −41.4 with calcipotriol/betamethasone foam, −36.3 with calcipotriol/betamethasone ointment, −30.3 with calcipotriol foam, −44.8 with betamethasone foam, −23.4 with the foam vehicle and −14.6 with the ointment vehicle (baseline values not provided) [33].

5 Tolerability of Calcipotriol/Betamethasone Foam

Calcipotriol/betamethasone foam was generally well tolerated in patients with plaque psoriasis. In the four trials discussed in Sect. 4, adverse events (AEs) were mostly of mild or moderate severity [16, 25–27] and infrequently led to treatment discontinuations [16, 25, 27, 31].

In the trial comparing calcipotriol/betamethasone foam with the foam vehicle (PSO-FAST), 15 treatment-related adverse events (TRAEs) were reported in ten (3.1 %) calcipotriol/betamethasone foam recipients and two (1.9 %) foam vehicle recipients [16]. In calcipotriol/betamethasone foam recipients, TRAEs were discolouration, irritation, pruritus (all application-site events), application-site reaction, folliculitis, psoriasis, skin irritation and increased blood calcium (one patient each). Application-site dryness, erosion, erythema and oedema were reported with the vehicle foam (one patient each) and application-site pain was reported by two calcipotriol/betamethasone foam recipients and one vehicle foam recipient. Two serious AEs (single occurrences of bipolar disorder and substance-induced psychotic disorder) were reported in calcipotriol/betamethasone foam recipients; whether or not these events were related to treatment was not stated. AEs did not lead to treatment discontinuations [16].

In a pooled analysis ($n = 1099$; safety analysis set) of patients from PSO-FAST [16] and the two other trials of 4 weeks' duration [25, 27] mentioned in Sect. 4, at least one TRAE was reported in 2.7 % of calcipotriol/betamethasone foam recipients, 3.0 % of calcipotriol/betamethasone ointment recipients, 6.1 % of calcipotriol foam recipients and 7.1 % of betamethasone foam recipients (poster presentation) [34]. In patients receiving calcipotriol/betamethasone foam, the most common TRAEs (occurring in at least two patients) were application-site pruritus and application-site pain (0.4 and 0.5 % of patients); hypersensitivity (occurring in one patient) was the only serious AE that was considered possibly related to treatment. Two patients (0.4 %) receiving calcipotriol/betamethasone foam discontinued treatment because of AEs, but they were not reported as treatment-related [34].

In the longer-term trial of up to 12 weeks' duration (PSO-ABLE), at least one TRAE was reported in 8 % of calcipotriol/betamethasone foam recipients and 4 % of calcipotriol/betamethasone topical suspension, 9 % of foam vehicle and 5 % of topical suspension vehicle recipients [26, 31]. The most commonly reported TRAE (incidence of ≥0.5 % of patients and in numerically more calcipotriol/betamethasone foam than calcipotriol/betamethasone topical suspension or vehicle groups) was itch (2.7 % of calcipotriol/betamethasone foam recipients, 0.5 % of calcipotriol/betamethasone topical suspension recipients, 2.1 % of foam vehicle recipients and 0 % of topical suspension vehicle recipients) [26, 31]. AEs led to treatment discontinuations in 2 % of calcipotriol/betamethasone foam recipients and 2 % of calcipotriol/betamethasone topical suspension recipients, but they were not reported as treatment-related [31].

In all four trials [16, 25–27], there were no clinically significant changes in mean albumin-corrected serum calcium levels or urinary calcium to creatinine ratios for any treatment group. In a multicentre, phase II, maximal-use systemic-exposure trial examining the effect of calcipotriol/betamethasone foam once daily in adults with extensive (moderate or worse) plaque psoriasis of the trunk, limbs and scalp, there were no reports of clinically relevant effects on calcium homeostasis or the hypothalamic-pituitary-adrenal (HPA) axis [35]. In the event of hypercalcaemia and hypercalciuria, treatment with calcipotriol/betamethasone foam should be discontinued until calcium metabolism parameters have normalized [14]. If suppression of the HPA axis is documented, treatment should be withdrawn, reduced (in frequency) or substituted with a corticosteroid of weaker potency [14].

6 Dosage and Administration

Calcipotriol/betamethasone (Enstilar®) 0.005/0.064 % [50 mcg/0.5 mg (as dipropionate per g)] foam is approved in the EU and USA for the topical treatment of plaque

psoriasis in adults (aged ≥18 years) [14, 15]. The foam, which is supplied in a pressurized spray can, is to be rubbed gently onto affected areas once daily for a maximum of 4 weeks, and usage should not exceed 15 g daily or 60 g (i.e. one can) every 4 days [14, 15].

Local prescribing information should be consulted for further, detailed information, including contraindications, warnings and precautions, drug interactions and use in special patient populations.

7 Place of Calcipotriol/Betamethasone Foam in the Management of Plaque Psoriasis

Vitamin D analogues and corticosteroids are recommended as first-line agents in the treatment of plaque psoriasis [11]. A meta-analysis has shown that corticosteroid/vitamin D analogue combination therapy has better efficacy than corticosteroid or vitamin D analogue monotherapy, and better tolerability than vitamin D analogue monotherapy [36]. In clinical trials in patients with plaque psoriasis, calcipotriol/betamethasone foam was more effective than the foam vehicle, individual components of the drug (i.e. calcipotriol or betamethasone foam), and other formulations of the drug (i.e. calcipotriol/betamethasone topical suspension or ointment), in providing treatment success [of the body (i.e. trunk and/or limbs)] and lowering mPASI scores. Where measured, patient perceptions of treatment success were consistent with investigator-reported results, and improvements from baseline to week 4 in itch-related sleep loss and HR-QOL were significantly greater with calcipotriol/betamethasone foam than with its comparators (Sect. 4); results were mixed for patient-assessed improvements in itch.

Calcipotriol/betamethasone foam was generally well tolerated, with AEs being mostly mild or moderate in severity and leading to few treatment discontinuations. The most commonly reported TRAEs were application-site events. Calcipotriol/betamethasone foam was not associated with an increased risk of TRAEs compared with the individual components as foam or the fixed-combination as topical suspension or ointment formulations. In addition, there were no reports of clinically relevant effects on calcium homeostasis or the HPA axis (Sect. 5).

Adherence to treatment is a major challenge in managing psoriasis patients, and treatment-related reasons for non-adherence include regimen inconvenience (e.g. time consuming or frequent application) and treatment formulation [e.g. poor cosmetic characteristics, vehicle issues (e.g. greasy, oily, sticky)] [12, 37]. Calcipotriol/betamethasone foam is applied to affected areas once daily using a pressurized spray can [14], and it is formulated as an alcohol-free foam with a non-skin-drying emollient vehicle [16]. Therefore, calcipotriol/betamethasone foam has the potential for greater patient acceptability, leading to greater adherence and treatment success than formulations that do not offer these characteristics.

In conclusion, calcipotriol/betamethasone foam is an effective and generally well tolerated treatment option that has the potential to increase patient adherence to therapy. As such, it represents a useful addition to the management of patients with plaque psoriasis.

Data selection sources: Relevant medical literature (including published and unpublished data) on calcipotriol/betamethasone dipropionate was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 5 September 2016], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Calcipotriol, calcipotriene, betamethasone, LEO-90100, Cal/BD, foam, Enstilar, psoriasis.
Study selection: Studies in patients with psoriasis who received calcipotriol/betamethasone dipropionate foam. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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Compliance with Ethical Standards

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