Drug Design, Development and Therapy Dovepress

Open Access Full Text Article REVIEW

Clinical Utility of Various Formulations of Calcipotriene and Betamethasone Dipropionate for the Treatment of Plaque Psoriasis in Patients Aged 12 Years or Older

Kamila Kędra[1,2], Adam Reich[1]

[1]Department of Dermatology, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszów, 35-055, Poland; [2]Doctoral School, University of Rzeszow, Rzeszow, Poland

Correspondence: Adam Reich, Email adamandrzejreich@gmail.com

Abstract: Plaque-type psoriasis is a chronic immune-mediated inflammatory skin disease of uncertain etiology, significantly impacting patient well-being. This chronic condition not only contributes to stigmatization and mental health challenges but also poses an independent risk for cardiovascular and other comorbid diseases. Affecting approximately 60 million people globally, psoriasis manifests primarily as mild-to-moderate disease in about 80% of cases, where topical therapy is pivotal. The most commonly used topical antipsoriatic therapy involves a combination of vitamin D3 analog (calcipotriene – Cal) and a synthetic potent corticosteroid (betamethasone dipropionate – BD). Various formulations of Cal/BD, including ointment, gel (topical suspension), and aerosol foam, have been approved by the US Food and Drug Administration (FDA). The cream based on the PAD (Polyaphron Dispersion) technology is another formulation of this combination drug, expanding the therapeutic options for patients with psoriasis. This article summarizes the most relevant published studies concerning the efficacy and safety of different calcipotriol and betamethasone formulations treating of plaque-type psoriasis in patients aged 12 or older.

Keywords: psoriasis vulgaris, calcipotriene, betamethasone dipropionate, topical therapy, vitamin D derivatives, corticosteroids

Introduction

Plaque-type psoriasis is a chronic, immune-mediated, inflammatory skin disease of uncertain etiology with a great impact on patient's well-being.[1] Psoriasis, through lowered self-esteem, feeling of stigmatization, and loneliness, leads to difficulties in interpersonal relationships and withdrawal from many activities, which negatively affects patients' quality of life (QoL). Moreover, psoriasis burdens not only the patient's mental sphere but also has been identified as an independent contributor to the cardiovascular risk due to persistent systemic inflammation. The disease has been linked to various comorbidities, such as arterial hypertension, diabetes, Crohn's disease, dyslipidemia and cerebrovascular disease.[1] Psoriasis affects approximately 60 million individuals worldwide and its prevalence in the adult population ranges between 0.09% and 11.4% depending of the studied populations.[2] Approximately 80% of patients with psoriasis present with mild-to-moderate disease, for which topical therapy is the cornerstone of treatment. Alternative therapeutic options, particularly in more severe cases, include systemic non-biological treatments, biologics and phototherapy, depending on the patient's preferences, the severity of the disease and the success of previous therapies.[3] However, access to biological treatment remains challenging due to the high costs associated with this therapy.[4] In addition, as the use of systemic medications registered for the treatment of psoriasis, such as methotrexate, cyclosporine, acitretin, or apremilast, carries the risk of potential side effects and requires regular monitoring, topical therapy is often favored as the initial therapeutic option.[5] So far, many patients perceive existing topical treatments as ineffective, uncomfortable, and time-consuming to apply. Therefore, non-compliance poses a significant obstacle to achieving treatment success. Since

Received: 12 July 2024
Accepted: 30 November 2024
Published: 8 December 2024

there is currently no cure of psoriasis, a compelling need exists for ongoing enhancement of topical drug formulations to achieve both high efficacy and satisfactory user-friendliness.[6] There are numerous topical treatments for psoriasis, available in different formulations such as lotions, creams, ointments, gels and foams. The selection of a topical agent from the wide range of options depends on the course of the disease itself (including the morphological variant and location of psoriatic lesions) as well as patients' preferences.[7] Topical therapies for psoriasis include: topical corticosteroids, calcineurin inhibitors (used off-label), vitamin D3 analogues (such as calcitriol, calcipotriol, tacalcitol), tazarotene and recently approved by the US Food and Drug Administration (FDA): tapinarof (Aryl hydrocarbon receptor, AhR, agonist) and roflumilast (phosphodiesterase 4, PDE4, inhibitor).[7–9] According to the American, Canadian and European treatment guidelines, the fixed-dose combination of calcipotriol (Cal), a vitamin D3 analogue, and betamethasone dipropionate (BD), a potent corticosteroid, are recommended as the initial therapy for mild-to-moderate psoriasis. The combination of these two substances in a single product enhances disease control due to their potent effects and minimizes therapy-associated side effects. However, therapeutic success relies not only on the drug's efficacy but also on patient adherence. The incorporation of betamethasone and calcipotriol into one formulation simplifies the treatment regimen, reducing the time required for application, which may enhance patient satisfaction and, consequently, improve adherence.[10] Currently, Cal/BD preparations are available in four distinct formulations: ointment, gel, foam and cream based on PAD (polyaphron dispersion) technology.[11] This article summarizes the most relevant published studies concerning efficacy and safety of different Cal/BD formulations in the treatment of plaque-type psoriasis in patients aged 12 or older. Our paper focuses on the most recent and relevant clinical trials and literature. We aimed to summarize previously published studies and do not include any new clinical data generated by the authors specifically for this paper.

Cal/BD Ointment Formulation

Calcipotriol Ointment

Calcipotriol (Cal), a synthetic analog of vitamin D3, binds to the vitamin D receptor, a ligand-activated transcription factor found in target cells such as epidermal keratinocytes and lymphocytes.[12] It was found out that Cal inhibits cellular proliferation, which is increased in psoriasis, and stimulates cell differentiation, both in vitro and in patients with psoriasis. The first formulation of Cal used in the treatment of psoriasis was an ointment with a concentration of 50 μg/g, applied twice daily. According to published studies, Cal ointment has been shown to reduce the accumulation of epidermal T-cells and polymorphonuclear leukocytes in psoriatic lesions after a 4-week treatment period. Additionally, in normal human skin, Cal altered the morphology and reduced the number of Langerhans cells (dendritic skin cells) and inhibited their capacity to stimulate T-cell proliferation.[13] In studies lasting from 4 to 12 week, topical Cal ointment demonstrated equal or superior efficacy compared to other vitamin D3 analogs, some topical corticosteroids, dithranol and coal tar. The mean reduction of psoriasis severity scores evaluated by investigators in short term clinical trials enrolling at least 50 adult patients with chronic psoriasis ranged from 53% to 73% with twice-daily application of Cal ointment (50 μg/g).[14–18] Furthermore, Cal therapy generally provided superior efficacy to twice daily betamethasone valerate 1 to 1.2 mg/g. Cal ointment administered twice daily for up to 52 weeks in several trials involving over 3000 adult patients with psoriasis, demonstrated a favorable safety profile.[14] The most common side effects associated with Cal ointment included mild and transient lesional or perilesional irritations. Symptoms, such as itching, burning, and stinging, occurred in 12 to 20.1% of patients, while 2 to 4.2% patients with non-scalp psoriasis experienced face and scalp irritation.[14–18] The nature of adverse events (AE) observed in long-term studies was consistent with those identified in short-term trials, and Cal ointment resulted in a significantly higher incidence ($p<0.001$) of lesional and perilesional irritation compared to treatment with betamethasone valerate.[17]

Betamethasone Dipropionate

Betamethasone dipropionate (BD) is a potent steroid of class III potency, that exerts its effects by binding to glucocorticoid receptors in the cell cytoplasm, translocating to the nucleus and inhibiting the transcription of specific genes. This results in significant anti-inflammatory effect and suppression of cytokines production (including IL-1, IL-6, IL-8, tumor necrosis factor-α, interferon-γ). In psoriasis, it leads to reduction of erythema, oedema, suppression of the

inflammatory infiltrate and improvement of keratinocyte differentiation.[19,20] However, the use of potent steroids, such as betamethasone, can lead to the skin atrophy, which manifests itself as reduced skin thickness and elasticity, purpura and telangiectasia. Glucocorticoids suppress collagen synthesis in fibroblasts and decrease the level of HA through regulation of HAS-2 in fibroblasts and keratinocytes, which plays a great role in maintaining epidermal and dermal structure and skin flexibility.[21] A study with healthy volunteers showed that the biological activity of BD in the combined ointment was similar to that in a single-component ointment with the same concentration of BD.[22] BD as a strong glucocorticoid should be used in the treatment of psoriasis for a relatively short time to minimize the risk of side effects such as skin thinning. According to studies performed in mice, it was suggested that vitamin D receptor agonists have antagonistic effects on various molecular and cellular mechanisms underlying glucocorticoid-induced skin atrophy.[23] Therefore, a fixed-dose combination ointment formulation containing 50 µg/g of Cal (as monohydrate) and 0.5 mg/g of betamethasone (as dipropionate) [Daivobet; Dovobet] was successfully developed for once-daily application.[24]

Cal/BD Ointment

The FDA and European Medicines Agency (EMA) approved the use of Cal/BD at concentrations of 0.005%/0.064% and 50 µg/0.5 mg per gram, respectively, in an ointment formulation for the topical treatment of psoriasis in adults aged ≥18 years in 2006 (USA) and 2010 (Europe). Literature data concerning use of Cal/BD in ointment formulation is extensive and unequivocally confirms the product's efficacy and its crucial role in psoriasis treatment. Cal/BD fixed combination was shown as an effective topical treatment of psoriasis vulgaris with a very low risk of skin atrophy up to a year. Regarding the effectiveness, the Cal/BD combination was superior in the treatment of psoriasis than the use of these substances separately.[25] A review of six Phase III clinical trials, involving 6050 psoriasis patients, was conducted to evaluate the consistency of the outcomes associated with Cal/BD ointment. The findings revealed that the efficacy of Cal/BD ointment was both higher and faster than that of its individual components used alone. Significant reductions in the Psoriasis Area and Severity Index (PASI) were observed within the first week of treatment, and this rapid response was consistent for both once-daily and twice-daily application regimens.[26] A post-hoc meta-analysis encompassing 1534 patients treated with Cal/BD ointment presented efficacy data from four international multicenter studies. The findings confirmed a significant, rapid, and high efficacy of Cal/BD in both, mild and severe form of psoriasis. The mean PASI reduction after four weeks was comparable across different patients groups (with mild and severe form of disease), ranging from 67.2% in mild cases to 71.2% in severe cases. Additionally, a rapid response was observed, with PASI scores reducing by 38.5% to 41.2% after just one week of treatment.[27] Moreover, a multicenter, prospective, randomized, partly double-blind study, which included 972 patients, compared the efficacy of different treatment regimens with the two-compound product and Cal ointment.[25] According to this study, the two-compound product demonstrated rapid and significant clinical efficacy in the treatment of psoriasis vulgaris. Eight weeks of continuous treatment with the two-compound product applied once daily was more effective than eight weeks of treatment with Cal ointment applied twice daily. Furthermore, two-compound product was found to be better tolerated, as AEs within lesional or perilesional areas were reported less frequently compared to treatment with Cal alone.[25]

Cal/BD Gel vs Ointment Formulation

In 2008 FSA and EMA have approved Cal/BD gel, initially, for the treatment of scalp psoriasis in patients aged 18 years and older. Later, its approval was extended also to other body regions. The conventional treatment regimen recommends once-daily application of Cal/BD gel on both the body and scalp for up to 8 weeks. Several clinical trials have evaluated the efficacy and safety of Cal/BD gel for the treatment of psoriasis on the scalp and body.[25,28] A comparison of Cal/BD gel versus Cal/BD ointment in a long-term (52 weeks) real-life observation study was reported by Lambert et al.[29] A study was conducted among 328 patients. This research primarily highlighted the easier application of the gel compared to the ointment, and therefore greater satisfaction with the therapy. The main endpoint was to evaluate the difference in effectiveness between the gel and ointment formulations after 12 weeks. Effectiveness was assessed based on the proportion of patients whose disease was classified as mild or very mild according to the Patient's Global Assessment (PaGA). Secondary endpoints included the comparison of effectiveness between the gel and ointment at 4 weeks and the number of patients achieving controlled disease at 4 and 12 weeks compared to baseline in both treatment groups. Improvement in psoriasis severity was comparable between the two groups, with a higher percentage of patients showing "mild/very mild" disease status compared to baseline. For the

Cal/BD gel group, 60.2% of patients achieved this status at week 52. In the Cal/BD ointment group, 58.8% of patients reached "mild/very mild" disease status at week 52.[28] This study also examined patient adherence; 11.6% at week 12 admitted that "often" or "always" not using the ointment due to its being too great burden, compared with 0% of the gel-treated patients. Additionally, more patients reported spending over 5 minutes daily applying the ointment (23.3%) compared to the gel (11.8%). A total of 66.7% of patients described the application of the gel as "easy", while among people using the ointment it was 45.2%. In terms of adherence and treatment satisfaction, patients favored the gel, finding it more convenient, faster to apply and simple to use. These studies show that the introduction of Cal/BD in the form of a gel has made progress in the treatment of psoriasis in terms of patient adherence, and thus satisfaction and a better therapeutic effect.[29]

Cal/BD Gel Formulation in the Treatment of Scalp Psoriasis

The efficacy and safety of the fixed combination gel for the treatment of scalp psoriasis was assessed in 7 clinical trials, both as a short-term treatment (8-week) as well as a long-term (52-week) therapy.[30–40] In two 8-week Phase 3 studies on scalp psoriasis, significantly more patients achieved treatment success, defined as "absent" or "very mild" disease according to the Investigator's Global Assessment (IGA) with the fixed combination gel compared to the active control (71.2% and 68.4%, respectively).[34,35] A pooled analysis of two large phase 3 trials involving 2920 patients revealed that Cal/BD gel was more effective and faster-acting compared to its individual components and the vehicle alone. Clinical benefits were evident as early as week 1 and persisted through 8 weeks. At week 1, 30.6% of patients using Cal/BD gel achieved "absent" or "very mild" disease, compared to 24.1% for BD, 10.0% for Cal, and 6.9% for the vehicle, with this trend continuing until the study completion.[41] A comparison between Cal/BD gel and Cal scalp solution was conducted in a 4-week Chinese clinical trial.[42] After four weeks of treatment, a significantly higher proportion of subjects in the two-compound gel group (87.5%) achieved controlled disease compared to 50.8% in the Cal group. A post hoc analysis revealed that significant improvement with the two-compound gel was noticeable as early as week 1. At that time, 40.8% of subjects using the two-compound gel achieved controlled disease, compared to just 2.4% of those using Cal scalp solution. Moreover, the mean TSS (redness, thickness, scaliness) on the scalp showed greater and faster improvement with the two-compound gel compared to the Cal scalp solution.[42] Another study (12 week) on 885 patients by Saraceno et al[38] on Cal/BD gel in adults showed that maintenance therapy with twice-weekly applications was more effective and resulted in a lower relapse rate compared to on-demand treatment. Cal/BD gel was also characterized by a favorable safety profile.[38] Reports on the greater effectiveness of proactive therapy were also confirmed in another phase 3 clinical trial involving 650 patients.[43] The primary endpoint was the time to the first relapse. Patients in the proactive treatment group on average experienced an additional 41 days of remission over 52 weeks compared to the control on demand group. The two-compound gel had significantly lower overall AE rates compared to other treatments. However, the reduction in skin-specific AE rates was not statistically significant.[43] The systematic review by Guenther reports no changes in serum calcium levels, skin atrophy, or the development of striae in any of the six reviewed trials, which included 4494 patients with scalp psoriasis.[44] To sum up, the two-compound gel has shown superior efficacy in various studies compared to the vehicle, its individual components, and Cal scalp solution.

Cal/BD Foam

The Cal/BD 0.005%/0.064% foam is a relatively newly approved treatment for plaque psoriasis. It was approved by the FDA in 2015 and by the EMA in 2016.[45] Due to its properties, the foam allows for better penetration through the skin, which guarantees its greater bioavailability and, therefore, better clinical effect. Its mechanism of action is based on dimethyl ether (DME), which is the solvent for the vehicle base. When applied to the skin, DME evaporates and delivers both active ingredients to the skin as a supersaturated solution without crystal formation. Imaging studies demonstrated that Cal and BD crystals (which limit skin penetration) are absent for at least 26 h after application, which ensures better permeability, leading to superior clinical efficacy.[46] Cal/BD foam has been evaluated in several studies as the treatment of psoriasis. The efficacy of Cal/BD foam was compared to the Cal/BD gel in the PSO-ABLE phase 3 trial. In this 12-week study, 463 patients with mild to severe psoriasis were randomized to receive Cal/BD foam, Cal/BD gel, foam vehicle and gel vehicle (allocated in the proportion 4:4:1:1, respectively). The primary end point concerned the proportion of patients with a ≥2 grade improvement in the Physician's Global Assessment (PGA), at week 4 for those using Cal/BD foam and

at week 8 for those using Cal/BD gel, following the treatment duration guidelines of the US FDA and EMA. By week 4, Cal/BD foam showed significantly higher treatment success rate (38% vs 22%; p<0.001) compared to Cal/BD gel at week 8. The secondary endpoints were the proportion of patients achieving at least 75% reduction in the modified PASI (mPASI75) and the duration required to reach treatment success. Secondary endpoints revealed a significantly larger decrease of mPASI in patients using Cal/BD foam at week 4, compared to those using Cal/BD gel at week 8 (2.18 vs 2.77). The mean percentage reduction in mPASI from baseline to week 12 was 63.8±40.7% with Cal/BD aerosol foam and 50.8±55.2% with Cal/BD gel. Treatment success rates were higher for foam compared with gel at all evaluated time points (weeks 1, 2, 4, 8 and 12) (p=0.0089), including sub-group of patients with more severe disease manifestations.[47] Another phase 3 clinical trial also evaluated the impact of foam and gel formulations on the quality of life. In a prospective multicenter study PSO-INSIGHTFUL the authors compared the effects of a foam containing Cal with those of a gel containing the same active ingredient. Cal/BE foam was used once daily for 7 days and then was substituted by the gel or the opposite. Patients assessed the foam product markedly higher for "feeling soothing" and "providing immediate relief" upon application (p<0.001 for both), compared to their current topical therapy.[48] These results are consistent with previous research concerning preferences for foams and solutions over other formulations among psoriatic patients.[49] Furthermore, there have also been conducted studies comparing the effectiveness of Cal/BD foam with other psoriasis therapies, including systemic ones. In one study, a matching adjusted indirect comparison (MAIC) was conducted to compare the efficacy of Cal/DB in the treatment of psoriasis with systemic non-biological treatment. The statistical approach outlined by Signorovitch et al included 749 individuals treated with Cal/BD foam from four randomized clinical.[50] These participants were aligned with summarized data from another study including: 148 patients treated with apremilast in the UNVEIL trial, 218 patients treated with methotrexate, 41 patients treated with acitretin and 115 patients treated with fumaric acid esters (FAE). According to results, Cal/BD foam provided a comparable results to FAE and enhanced effectiveness compared to apremilast, methotrexate, or acitretin.[50]

PAD Technology – Cal/BD Cream

The PAD technology enhances the stability of Cal and BD in an aqueous cream by forming a multimolecular shell structure. It also increases the penetration of both active ingredients into the epidermis and dermis. Additionally, this technology improves cosmetic acceptability and provides desirable sensory properties for a topical psoriasis treatment.[51] In order to assess the diffusion/penetration of Cal/BD through the epidermis and dermis, two studies (one in vivo and one in vitro) have been conducted. In both studies, Cal/BD PAD cream was compared with Cal/BD gel. The in vitro cell analysis showed, that the cumulative amount of BD that permeated the epidermis was significantly higher for the Cal/BDP cream compared to the Cal/BD gel at all observed time points. Furthermore, at 1, 2, 4, and 8 hours post-application, the amount of BD recovered was consistently greater following the application of Cal/BD cream than after Cal/BD gel application, as measured using the in vivo tape stripping method. In an in vivo study with 10 healthy female participants, the Cal/BD PAD-cream consistently demonstrated superior delivery of BD to both the upper (stratum corneum) and lower (epidermis) skin layers compared to the CAL/BD gel.[52] Moreover, two phase 3 trials with the Cal/BD PAD-cream: MC2-01-C2, NCT03308799 and MC2-01-C7, NCT03802344 have been conducted. Patients with mild-to-moderate psoriasis were randomly distributed in a 3:1:3 ratio to receive either the Cal/BD PAD-cream, the PAD-cream vehicle, or the Cal/BD gel once daily over a period of 8 weeks. Both studies were characterized by similar design, however their primary endpoints were different. In the US trial (MC2-01-C2), the primary endpoint was focused on the proportion of patients in each treatment group achieving treatment success according to the PGA by Week 8. Conversely, the primary endpoint for the European trial (MC2-01-C7) was the percentage change in the mPASI from baseline at Week 8. PGA treatment success was achieved in both phase 3 clinical trials. A significantly higher percentage of patients using the Cal/BD PAD-cream reached PGA treatment success at Week 8 compared to those using the Cal/BD gel, with 43.2% versus 31.9% respectively (p<0.001). By Week 1, a significantly greater number of patients in the Cal/BD PAD-cream group compared to the PAD-cream vehicle group had achieved various measures of treatment success. These included PGA treatment success (3.6% vs 0.0%; p<0.0001), PGA controlled disease (7.8% vs 1.3%; p<0.0001), and a ≥1-grade improvement in PGA (36.0% vs 12.6%; p<0.0001. Additionally, in one study (MC2-01-C7) 50.8% of patients in the Cal/BD PAD-cream group achieved PGA treatment success on the scalp, compared to 9.3% in the PAD-cream vehicle

group (p=0.0001). In the US trial (MC2-01-C2), the improvement of itch was assessed using an 11-point Numeric Rating Scale (NRS). An improvement of 4 points or more on this scale was considered clinically meaningful. Already by Week 1, a higher percentage of patients in the Cal/BD PAD-cream group achieved a ≥4-point improvement in itch compared to those in the Cal/BD gel group (44.0% vs 36.9%; p=0.024).[53–55] One of the studies also compared the Cal/BD foam preparation to PAD-cream through an anchored MAIC analysis (type of robust indirect comparison). No significant differences were observed in PGA success, mPASI75, or DLQI scores between Cal/BD PAD-cream and Cal/BD foam following their recommended treatment periods of 8 weeks for the cream and 4 weeks for the foam. According to the participants, Cal/BD was characterized as "easily incorporated into daily routine" and therefore has achieved greater results in terms of treatment satisfaction in comparison with Cal/BD foam.[56] To sum up, Cal/BD cream represents an effective drug based on PAD technology, which is characterized by high effectiveness and, thanks to its formula, increased patient adherence. However, it demands further investigation.

Studies Among Adolescents Aged 12-17 Years

In Europe, the prevalence of psoriasis among adolescents ranges from 1.2% to 2.0%, showing a roughly linear increase throughout adolescence. As teenage psoriasis has a huge impact on the quality of life, appropriate treatment is crucial. However, the limited number of clinical trials focusing on pediatric psoriasis and the absence of standardized guidelines significantly hinder effective treatment.[57] As for the preparations approved for use in the pediatric population (patients between 12 and 17 years old), the Cal/BD gel was licensed for the treatment of scalp psoriasis in 2014 and for body psoriasis in 2019.[58,59] To date, two open-label trials have been conducted to assess the efficacy and safety of Cal/BD gel in adolescents aged 12–17 years. Both studies confirmed the effectiveness of Cal/BD in gel form. The first conducted study was an 8-week-open-label trial (n=78). At week 8, 66 patients (85%) achieved an IGA score of 1 or 2, indicating significant improvement. The mean Total Symptom Score (TSS) showed an 80% reduction from baseline to the end of treatment. Regarding the assessed safety of Cal/BD, 37 patients (35%) reported at least one AE. However, side effects were predominantly mild or moderate. Notably, there were no reports of serious AEs or hypercalcemia. In a second 8-week open-label trial involving adolescents with scalp psoriasis, 55% (17 patients) achieved treatment success by week 8, defined as an IGA score of 1 or 2. Moreover, the mean TSS improved from 6.9 at baseline to 2.9 at the end of treatment. 52% patients (16) experienced at least one AE, but none of these were classified as serious. In both trials, no serious AEs were reported. In the US trial, 70% of AEs (14 out of 16) were mild, while in the multinational trial, 52% of AEs (33 out of 64) were classified as mild. The most common AEs in the US trial, each occurring in at least 4% of patients, included cough (3 patients), oropharyngeal pain (3 patients), nasopharyngitis (2 patients), and upper respiratory tract infection (2 patients). In the multinational trial, the most frequently reported AEs were headache (4 patients), pharyngitis (4 patients), upper respiratory tract infection (4 patients), and decreased urine calcium (3 patients).[60,61] Cal/BD in foam form was approved for use in children over 12 years of age in 2019. The safety and effectiveness of Cal/BD in the form of foam applied once a day for ≤4 weeks was examined in a Phase 2, open-label, study (NCT02387853) in adolescent patients (12 to <18 years) with at least mild psoriasis. The study group ultimately included 106 people, including 34 patients with more severe psoriasis assigned to the HPA-axis cohort, in which assessment of HPA-axis function post-ACTH challenge was also a secondary endpoint. The primary endpoints were the occurrence of treatment-emergent adverse events (TEAEs) and the change in albumin-corrected serum calcium levels from baseline to week four. In the treatment group (n=106), 32 TEAEs were reported in 22 patients, which constituted 20.8% of patients. All TEAEs were mild, except two of moderate severity: erythema and myopia. The most frequent TEAEs were upper respiratory tract infection, reported in 8 patients (7.5%), nasopharyngitis, reported in 4 patients (3.8%), and acne, reported in 2 patients (1.9%). In the HPA-axis cohort, no change in the urinary calcium-to-creatinine ratio was observed, and the responses to the adrenocorticotropic hormone (ACTH) challenge did not indicate any disruption of the HPA axis. Cal/BD in the form of foam turned out to be an effective preparation in psoriasis in adolescents, At week 4 (W4), 71.8% of patients achieved treatment success on the body, and 75.7% achieved treatment success on the scalp, according to the PGA. Mean PASI decreased by 82.0% vs baseline at Week 4. However, this study contains several limitations. First of all, the 4-week observation period for perturbations of calcium homoeostasis or HPA-axis may be too short. Moreover, the lack of a control group may make it difficult to assess the

efficacy and safety of the drug in adolescents. Additional studies are necessary to determine the maximum tolerated dose in adolescent psoriasis patients and to evaluate the safety for those with severe disease by PGA.[62]

Safety

Safety of Cal/BP fixed combination has been assessed in multiple studies. As for the AEs associated with the use of topical vitamin D analogues, the milder ones include pruritus, erythema and itching, while the more severe ones incorporate allergic contact dermatitis and hypercalcemia.[63] Topical glucocorticoid therapy has been associated with skin atrophy, telangiectasia, folliculitis and acneiform dermatitis, and to a lesser extent with more serious AEs such as Cushing syndrome, HPA axis suppression, immunosuppression, and hyperglycemia.[64] According to the findings from selected studies, the combined use of Cal/BP is considered better tolerated than using Cal. It seems that Cal may prevent the skin atrophy, which is a significant complication of long-term glucocorticoid therapy. A study, which was conducted on ex vivo pig and human skin after topical application of the calcipotriol/betamethasone fixed-combination product, showed that Cal mitigates the suppression of collagen I synthesis caused by betamethasone. Moreover, Cal can reverse the reduction in hyaluronic acid (HA) synthesis in keratinocytes caused by BP and prevent betamethasone-induced epidermal thinning in minipigs when treated with the Cal/BP gel.[65] Furthermore, a systematic review involving more than 11,000 patients from clinical trials confirmed the short- and long-term tolerability of the dual-compound formulation. The most common AEs were local skin reactions, such as itching. These occurred less frequently compared to other products, a result attributed to the inclusion of a potent steroid in the formulation.[66] The fixed-combination therapy was found to be better tolerated than either Cal alone or when alternated with Cal in 4-week cycles. Long-term side effects of corticosteroid use were reported in 22 patients. AEs with an incidence greater than 1% included skin atrophy, affecting 7 patients, and folliculitis, affecting 4 patients.[67] In the Phase 3, a multicenter, double- blind, vehicle-controlled 4-week study, the primary objective was to compare the efficacy and safety of Cal/BD foam with aerosol foam vehicle in psoriatic patients. In total, 78 AEs were reported during the trial with similar incidence between treatment group: 15.8% in the Cal/BD group (51 patients) and 11.7% in the vehicle group (12 patients). Most noted events were mild or moderate in severity. The most common AEs were nasopharyngitis, which occurred in six patients (1.9%), all in Cal/BD aerosol foam group) and application-site pain, noted by three patients (0,9%) in the Cal/ BD group and two patients (1,9~%) in the vehicle group. Cal/BD was well tolerated, with only a few local reactions reported such as burning (Cal/BD, seven patients [2.2%]; vehicle, four patients [4.0%]) and erythema (Cal/BD, six patients [1.9%]; vehicle, two patients [2.0%]). There were no clinically significant alterations in the average albumin-corrected serum calcium levels or the urinary calcium ratio in either of the treatment groups. Five severe AES were reported only in Cal/ BD aerosol foam group and two of these events were noted as serious (bipolar disorder and substance-induced psychotic disorder).[68] Similar safety data have been reported in studies using Cal/BD as an ointment,[14] gel,[69] and more recently cream.[14,70]

Summary

Combining vitamin D3 analogs with potent corticosteroids enhances the clinical response and increases the overall efficacy of the treatment (Table 1). The synergistic effects and complementary mechanisms of action of combining treatments improve tolerability and ultimately lead to better patient adherence. Moreover, many studies have proven the safety of the combination of Cal/BP, which can also be successfully used in children over 12 years of age. Studies have confirmed that the combination of these two substances prevents skin atrophy caused by long-term use of steroids and long-term use did not indicate a disruption of the HPA axis. Randomized clinical trials have shown that a fixed combination of Cal and BP used in the form of foam and gel are characterized by high effectiveness, and through ease of application and convenient formulation they contribute to greater patient adherence and, therefore, better therapeutic effects. Taking into account the effectiveness of these two substances in the treatment of psoriasis and their high safety profile, Cal/BD combination remains a valuable treatment in mild and moderate psoriasis.

https://doi.org/10.2147/DDDT.S240867 DovePress

Table 1 Most Relevant Clinical Trials Concerning Different Calcipotriol and Betamethasone Dipropionate (Cal/BD) Formulations

Author (year)	N	Study design	Duration	Treatment	Study outcomes
Guenther et al[40] (2002)	828	Randomized, double-blind, vehicle-controlled study	4 weeks	1) Combined ointment formulation Cal/BD once daily 2) Combined ointment formulation Cal/BD twice daily 3) Calcipotriol ointment twice daily 4) Vehicle ointment twice daily	PASI reduction in Cal/BD (68.6% once daily, 73.8% twice daily) was higher vs the twice daily calcipotriol group (58.8%) and the vehicle group (26.6%).
Kragballe et al[67] (2006)	634	A 52-week randomized safety study of a Cal/BD two-compound product in the treatment of psoriasis vulgaris	52 weeks	1) Cal/BD ointment 2) Cal/BD ointment (52 weeks) followed by Cal ointment (4 weeks) – alternating group 3) Cal/BD ointment (4 weeks) followed by Cal ointment (48 weeks)	Adverse drug reactions (ADRs) occurred in 45 (21.7%) patients in Cal/BD group, 63 (29.6%) in the alternating group, and 78 (37.9%) in the Cal group.
Jemec et al[34] (2008)	541	Multicenter, randomized, double-blind study (scalp psoriasis)	8 week	1) Cal/BD gel 2) Cal gel 3) BD gel 4) Vehicle gel	More patients achieved "absent" or "very mild" disease at week 8 with Cal/BD gel (71.2%) compared with BD gel (64.0%, p=0.011), Cal gel (36.8%, p<0.0001), or the vehicle (22.8%, p<0.0001)
Kragballe et al[37] (2009)	312	International, multicenter, prospective, randomized, investigator-blind, two-arm, parallel-group study (scalp psoriasis)	8 week	1) Cal/BD gel 2) Cal solution	The proportion of patients with "clear" or "minimal" disease at week 8 was significantly greater in the Cal/BD scalp gel group (68.6%) vs the Cal scalp solution group (31.4%; p<0.001).
Fleming et al[30] (2010)	162 83 79 40	Randomized, double-blind, active and vehicle controlled	8 weeks	1) Fixed combination gel 2) Betamethasone dipropionate gel 3) Calcipotriol gel 4) Gel vehicle	PASI percentage change at week 4 and 8 – 48.1 and −55.3 – 40.9 and −49.8 – 32.7 and −41.2 – 16.9 and −11.9
Langley et al[31] (2011)	183 184 91	Randomized, investigator-blind, active and vehicle controlled	8 weeks	1) Fixed combination gel 2) Tacalcitol ointment 3) Gel vehicle	PASI percentage change at week 4 and 8 – 53.1 and −57.0 – 37.3 and −41.9 – 13.3 and −17.9
Menter et al[32] (2013)	482 479 96 95	Phase IIIRandomized, double-blind, active and vehicle controlled	8 weeks	1) Fixed combination gel 2) Betamethasone dipropionate gel 3) Calcipotriol gel 4) Gel vehicle	PASI percentage change at week 4 and 8 – 46.4 and −55.8 – 42.7 and −48.6 – 32.2 and −43.6 – 17.4 and −20.9

Lambert et al[33] (2014)	6789	Interim results	52-week	1) Cal/BD ointment 2) Cal/BD gel	No significant difference in the proportion of patients with controlled disease in the gel vs ointment group at week 12.
Saraceno et al[38] (2014)	885	National, multicenter, randomized trial		1) maintenance of two applications per week 2) on-demand therapy	At weeks 8 and 12, group 1 demonstrated a higher clinical response compared with group B ($p < 0.05$).
Gooderham et al[60] (2014)	78	Phase II, multicentre, single-arm, open-label, 8-week trial, patients aged 12–17 years	8 weeks	Application once-daily Cal/BD gel to the scalp for up to 8 weeks.	IGA "clear" or "almost clear" at the end of treatment in 85% of patients.Twenty-seven patients (35%) reported 64 AEs.No clinically relevant increases in albumin-corrected serum calcium, 24 h urinary calcium excretion or urinary calcium-to-creatinine ratio.
Reich et al[69] (2015)	1803	Phase 4, multicentre, prospective, randomized, controlled, parallel-group, open-label clinical trial	8 weeks	Cal/BD gel once a day	PGA at 8 weeks: 36.5% of patients were "almost clear" or "clear".
Leonardi et al[68] (2015)	426	Phase III, multicentre doubleblind, randomized	4 weeks	1) Cal/BD aerosol foam 2) Aerosol foam vehicle once daily	At week 4, significantly more patients using Cal/BD foam achieved treatment success versus vehicle (53.3 versus 4.8%; OR 30.3; $p<0.001$)
Eichenfield et al[61] (2015)	31	Phase II, multicenter, open-label, single-arm,	8 weeks	Application once-daily Cal/BD gel to the scalp for up to 8 weeks.	The mean TSS improved from 6.9 at baseline to 2.9 at the end of treatment (59% improvement)
Lebwohl et al[71] (2016)	302	Phase II, randomized, double-blind, multicenter	4 weeks	1) Cal/BD foam (n=100) vs 2) Cal (n=101) 3) BD foam (n=101)	Treatment success: 45% vs 31% (BD foam; p=0.047) and 15% (Cal foam; $p<0.001$)
Koo et al[72](2016)	376	Phase II, multicenter, investigator-blinded study	4 week	1) Cal/BD aerosol foam 2) Cal/BD ointment, 3) aerosol foam vehicle 4) ointment vehicle	At week 4, significantly more patients using Cal/BD aerosol foam achieved treatment success (54.6% versus 43.0% [ointment]; p=0.025)
Paul et al[47] (2017)	85 188	Phase III randomized, parallel-group, investigator-blinded	12 weeks	1) Cal/BD aerosol foam 2) Cal/BD gel	Percentage of patients achieving PASI75 at week 4 52.1% 24.3%
Hong et al[48] (2017)	213	Phase IIIb, prospective, multicentre, open-label, randomized, two-arm crossover study	2 weeks	Once-daily Cal/BD foam for 1 week, followed by Cal/BD gel for 1 week, or vice versa.	Based on the Subject's Preference Assessment, 50% of patients preferred Cal/BD foam and 50% preferred Cal/BD gel.

(*Continued*)

https://doi.org/10.2147/DDDT.S240867 DovePress

Table 1 (Continued).

Author (year)	N	Study design	Duration	Treatment	Study outcomes
Queille –Roussel et al[73] (2017)	35	Phase IIa, singlecenter, investigato r-blinded, within patient controlled, randomized	6 days per week, for a total of 28 days	1) Cal/BD foam 2) BVmedicated plaster	Mean change in total skin thickness from baseline to the end of treatment. Cal/BD group −1.0 mm, vs BV-medicated plaster −0.6 mm (difference −0.4 mm; 95% CI −0.5 to −0.3; p<0.001)
Pinter et al[74] (2023)	490	Phase 3, multicentre, randomized, investigator-blind, active and vehicle-controlled	8 weeks	1) Cal/BD cream 2) Cal/BD gel 3) Cal/BD vehicle cream	The percentage mean change from baseline to Week 8 in mPASI for CAL/BDP PAD-cream (67.5%) was superior compared to PAD-cream vehicle (11.7%; p<0.0001) and non-inferior to CAL/BDP gel (63.5%).
Stein Gold et al[75] (2021)	796	Phase 3, multicenter, randomized, investigator-blind, active, and vehicle-controlled trial	8 weeks	1)Cal/BD cream 2)Cal/BD topical solution 3)Cream vehicle	The proportion of patients achieving PGA treatment success after 8 weeks was statistically significantly greater for CAL/BDP cream (37.4%) compared to CAL/BDP TS (22.8%, p<0.0001), and vehicle (3.7%, p<0.0001).
Guenther et al[76] (2022)	521	Phase 3, randomized, double-blind study	52 weeks	1)Cal/BD foam 2)Foam vehicle	Fixed-dose combination Cal/BD foam used for long-term management of psoriasis significantly reduces psoriasis-related work productivity and activity impairment

Disclosure

Dr Kamila Kędra has nothing to disclose.

Professor Adam Reich reports personal fees from AnaptysBio, personal fees from Arcutis, personal fees from Argenx, personal fees from Celltrion, personal fees from Galderma, personal fees from Inflarx, personal fees from Dice, personal fees from Incyte, personal fees from Janssen, personal fees from LeoPharma, personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, personal fees from Trevi Therapeutics, personal fees from Eli Lilly, personal fees from UCB, personal fees from Horizon, personal fees from MetrioPharm, personal fees from AbbVie, personal fees from Bioderma, personal fees from Celgene, personal fees from BMS, personal fees from Boehringer Ingelheim, personal fees from Pierre Fabre Medicament, personal fees from Medac GmbH, personal fees from Sandoz, personal fees from MC2 Therapeutics, during the conduct of the study. The authors report no other conflicts of interest in this work.

References

1. Luna PC, Chu CY, Fatani M, et al. Psychosocial burden of psoriasis: a systematic literature review of depression among patients with psoriasis. *Dermatol Ther*. 2023;13(12):3043–3055. doi:10.1007/s13555-023-01060-5
2. Raharja A, Mahil SK, Barker JN. Psoriasis: a brief overview. *Clin Med*. 2021;21(3):170–173. doi:10.7861/clinmed.2021-0257
3. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60:643–659. doi:10.1016/j.jaad.2008.12.032
4. Nyholm N, Schnack H, Danø A, Skowron F. Cost per responder of biologic drugs used in the treatment of moderate-to-severe plaque psoriasis in France and Germany. *Curr Med Res Opin*. 2023;39(6):833–842. doi:10.1080/03007995.2023.2214046
5. Sbidian E, Chaimani A, Garcia-Doval I, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev*. 2022;5(5):CD011535. doi:10.1002/14651858.CD011535.pub5
6. Vasconcelos V, Teixeira A, Almeida V, et al. Patient preferences for attributes of topical anti-psoriatic medicines. *J DermatolTreat*. 2019;30 (7):659–663. doi:10.1080/09546634.2018.1544410
7. Le Roux E, Frow H. Diagnosis and management of mild to moderate psoriasis. *Prescriber*. 2020;31(7–8):9–17. doi:10.1002/psb.1855
8. Chat VS, Kearns DG, Uppal SK, Han G, Wu JJ. Management of psoriasis with topicals: applying the 2020 AAD-NPF guidelines of care to clinical practice. *Cutis*. 2022;110(2 Suppl):8–14. doi:10.12788/cutis.0573
9. Nogueira S, Rodrigues MA, Vender R, Torres T. Tapinarof for the treatment of psoriasis. *Dermatol Ther*. 2022;35(12):e15931. doi:10.1111/dth.15931
10. Narbutt J, Czajkowski R, Lesiak A, Owczarek W, Reich A, Szepietowski JC. Calcipotriene/betamethasone dipropionate foam: primary evidence supporting its use in patients with psoriasis vulgaris. A narrative review. *Postepy Dermatol Alergol*. 2021;38(5):727–733. doi:10.5114/ada.2021.110062
11. Rudnicka L, Olszewska M, Goldust M, et al. Efficacy and safety of different formulations of calcipotriol/betamethasone dipropionate in psoriasis: gel, foam, and ointment. *J Clin Med*. 2021;10(23):5589. doi:10.3390/jcm10235589
12. Zhao Y, Asahina A, Asawanonda P, et al. Systematic review and practical guidance on the use of topical calcipotriol and topical calcipotriol with betamethasone dipropionate as long-term therapy for mild-to-moderate plaque psoriasis. *J Dermatol*. 2021;48(7):940–960. doi:10.1111/1346-8138.15806
13. Guilhou JJ. The therapeutic effects of vitamin D3 and its analogues in psoriasis. *Expert Opin Investig Drugs*. 1998;7:77–84. doi:10.1517/13543784.7.1.77
14. Scott LJ, Dunn CJ, Goa KL. Calcipotriol ointment. A review of its use in the management of psoriasis. *Am J Clin Dermatol*. 2001;2:95–120. doi:10.2165/00128071-200102020-00008
15. Highton A, Quell J. Calcipotriene ointment 0.005% for psoriasis: a safety and efficacy study. Calcipotriene study group. *J Am Acad Dermatol*. 1995;32:67–72. doi:10.1016/0190-9622(95)90186-8
16. Bruce S, Epinette WW, Funicella T, et al. Comparative study of calcipotriene (MC 903) ointment and fluocinonide ointment in the treatment of psoriasis. *J Am Acad Dermatol*. 1994;31(5 Pt 1):755–759. doi:10.1016/S0190-9622(94)70237-3
17. Cunliffe WJ, Berth-Jones J, Claudy A, et al. Comparative study of calcipotriol (MC 903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris. *J Am Acad Dermatol*. 1992;26(5 Pt 1):736–743. doi:10.1016/0190-9622(92)70103-M
18. Katz HI. Combined topical calcipotriene ointment 0.005% and various systemic therapies in the treatment of plaque-type psoriasis vulgaris: review of the literature and results of a survey sent to 100 dermatologists. *J Am Acad Dermatol*. 1997;37(3 Pt 2):S62–S68.
19. Castela E, Archier E, Devaux, et al. Topical corticosteroids in plaque psoriasis: a systematic review of risk of adrenal axis suppression and skin atrophy. *J Eur Acad Dermatol Venereol*. 2012;26(Suppl 3):47–51. doi:10.1111/j.1468-3083.2012.04523.x
20. Kolbe L, Kligman AM, Schreiner V, Stoudemayer T. Corticosteroid-induced atrophy and barrier impairment measured by non-invasive methods in human skin. *Skin Res Technol*. 2001;7:73–77. doi:10.1034/j.1600-0846.2001.70203.x
21. Bauer EA, Kronberger A, Valle KJ, Jeffrey JJ, Eisen AZ. Glucocorticoid modulation of collagenase expression in human skin fibroblast cultures. Evidence for pre-translational inhibition. *Biochim Biophys Acta*. 1985;825:227–235. doi:10.1016/0167-4781(85)90107-1
22. Traulsen J. Bioavailability of betamethasone dipropionate when combined with calcipotriol. *Int J Dermatol*. 2004;43(8):611–617. doi:10.1111/j.1365-4632.2004.01922.x
23. Hong SP, Oh Y, Jung M, et al. Topical calcitriol restores the impairment of epidermal permeability and antimicrobial barriers induced by corticosteroids. *Br J Dermatol*. 2010;162:1251–1260. doi:10.1111/j.1365-2133.2010.09760.x
24. Charakida A, Dadzie O, Teixeira F, et al. Calcipotriol/ betamethasone dipropionate for the treatment of psoriasis. *Expert Opin Pharmacother*. 2006;7(5):597–606. doi:10.1517/14656566.7.5.597
25. Megna M, Cinelli E, Camela E, Fabbrocini G. Calcipotriol/betamethasone dipropionate formulations for psoriasis: an overview of the options and efficacy data. *Expert Rev Clin Immunol*. 2020;16(6):599–620. doi:10.1080/1744666X.2020.1776116

26. Kragballe K, van de Kerkhof PC. Consistency of data in six phase III clinical studies of a two-compound product containing calcipotriol and betamethasone dipropionate ointment for the treatment of psoriasis. *J Eur Acad Dermatol Venereol*. 2006;20(1):39–44. doi:10.1111/j.1468-3083.2005.01343.x
27. van de Kerkhof PC, Wasel N, Kragballe K, et al. A two-compound product containing calcipotriol and betamethasone dipropionate provides rapid, effective treatment of psoriasis vulgaris regardless of baseline disease severity. *Dermatology*. 2005;210:294–299. doi:10.1159/000084753
28. Kragballe K, Noerrelund KL, Lui H, et al. Efficacy of once-daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris. *Br J Dermatol*. 2004;150(6):1167–1173. doi:10.1111/j.1365-2133.2004.05986.x
29. Lambert J, Hol CW, Vink J. Real-life effectiveness of once-daily calcipotriol and betamethasone dipropionate gel vs. ointment formulations in psoriasis vulgaris: final analysis of the 52-week PRO-long Study. *J Eur Acad Dermatol Venereol*. 2015;29(12):2349–2355. doi:10.1111/jdv.13230
30. Fleming C, Ganslandt C, Guenther L, et al. Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a randomised, parallel group, double-blind, exploratory study. *Eur J Dermatol*. 2010;20:465–471. doi:10.1684/ejd.2010.0948
31. Langley RG, Gupta A, Papp K, et al. Calcipotriol plus betamethasone dipropionate gel compared with tacalcitol ointment and the gel vehicle alone in patients with psoriasis vulgaris: a randomized, controlled clinical trial. *Dermatology*. 2011;222:148–156. doi:10.1159/000323408
32. Menter A, Gold LS, Bukhalo M, et al. Calcipotriene plus betamethasone dipropionate topical suspension for the treatment of mild to moderate psoriasis vulgaris on the body: a randomized, double-blind, vehicle-controlled trial. *J Drugs Dermatol*. 2013;12:92–98.
33. Lambert J, Hol CW, Vink J. Real-life effectiveness of once-daily calcipotriol and betamethasone dipropionate gel vs ointment formulations in psoriasis vulgaris: 4- and 12-week interim results from the PRO-long study. *J Eur Acad Dermatol Venereol*. 2014;28(12):1723–1731. doi:10.1111/jdv.12387
34. Jemec GB, Ganslandt C, Ortonne J-P, et al. A new scalp formulation of calcipotriene plus betamethasone compared with its active ingredients and the vehicle in the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. *J Am Acad Dermatol*. 2008;59:455–463. doi:10.1016/j.jaad.2008.04.027
35. van de Kerkhof PC, Hoffmann V, Anstey A, et al. A new scalp formulation of calcipotriol plus betamethasone dipropionate compared with each of its active ingredients in the same vehicle for the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. *Br J Dermatol*. 2009;160:170–176. doi:10.1111/j.1365-2133.2008.08927.x
36. Buckley C, Hoffmann V, Shapiro J, Saari S, Cambazard F, Milsgaard M. Calcipotriol plus betamethasone dipropionate scalp formulation is effective and well tolerated in the treatment of scalp psoriasis: a Phase II study. *Dermatology*. 2008;217:107–113. doi:10.1159/000130425
37. Kragballe K, Hoffmann V, Ortonne JP, Tan J, Nordin P, Segaert S. Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. *Br J Dermatol*. 2009;161:159–166. doi:10.1111/j.1365-2133.2009.09116.x
38. Saraceno R, Camplone G, D'Agostino M, et al. Efficacy and maintenance strategies of two-compound formulation calcipotriol and betamethasone dipropionate gel (Xamiol gel) in the treatment of scalp psoriasis: results from a study in 885 patients. *J DermatolTreat*. 2014;25:30–33. doi:10.3109/09546634.2013.800182
39. Luger TA, Cambazard F, Larsen FG, et al. A study of the safety and efficacy of calcipotriol and betamethasone dipropionate scalp formulation in the long-term management of scalp psoriasis. *Dermatology*. 2008;217:321–328. doi:10.1159/000155642
40. Mrowietz U, Macheleidt O, Eicke C. Effective treatment and improvement of quality of life in patients with scalp psoriasis by topical use of calcipotriol/betamethasone (Xamiol-gel): results. *J Dtsch Dermatol Ges*. 2011;9:825–831. doi:10.1111/j.1610-0387.2011.07695.x
41. Jemec GB, van de Kerkhof PC, Enevold A, et al. Significant one-week efficacy of a calcipotriol plus betamethasone dipropionate scalp formulation. *J Eur Acad Dermatol Venereol*. 2011;25(1):27–32. doi:10.1111/j.1468-3083.2010.03682.x
42. Ma L, Yang Q, Yang H, et al. Calcipotriol plus betamethasone dipropionate gel compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized, controlled trial investigating efficacy and safety in a Chinese population. *Int J Dermatol*. 2016;55(1):106–113. doi:10.1111/ijd.12788
43. Lebwohl M, Kircik L, Lacour JP, et al. Twice-weekly topical calcipotriene/betamethasone dipropionate foam as proactive management of plaque psoriasis increases time in remission and is well tolerated over 52 weeks (PSO-LONG trial). *J Am Acad Dermatol*. 2021;84(5):1269–1277. doi:10.1016/j.jaad.2020.09.037
44. Guenther L, Van de Kerkhof PC, Snellman E, et al. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial. *Br J Dermatol*. 2002;147(2):316–323. doi:10.1046/j.1365-2133.2002.04967.x
45. Enstilar (calcipotriene and betamethasone dipropionate) Foam. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207589Orig1s000TOC.cfm. Accessed June 30, 2024.
46. Lind M, Nielsen KT, Schefe LH, et al. Supersaturation of calcipotriene and betamethasone dipropionate in a novel aerosol foam formulation for topical treatment of psoriasis provides enhanced bioavailability of the active ingredients. *Dermatol Ther*. 2016;6:413–425. doi:10.1007/s13555-016-0125-6
47. Paul C, Stein Gold L, Cambazard F, et al. Calcipotriol plus betamethasone dipropionate aerosol foam provides superior efficacy vs. gel in patients with psoriasis vulgaris: randomized, controlled PSO-ABLE study. *J Eur Acad Dermatol Venereol*. 2017;31(1):119–126. doi:10.1111/jdv.13859
48. Hong CH, Papp KA, Lophaven KW, Skallerup P, Philipp S. Patients with psoriasis have different preferences for topical therapy, highlighting the importance of individualized treatment approaches: randomized phase IIIb PSO-INSIGHTFUL study. *J Eur Acad Dermatol Venereol*. 2017;31:1876–1883. doi:10.1111/jdv.14515
49. Gottlieb AB, Ford RO, Spellman MC. The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of nonscalp regions. *J Cutan Med Surg*. 2003;7(3):185–192. doi:10.1177/120347540300700301
50. Bewley AP, Shear NH, Calzavara-Pinton PG, Hansen JB, Nyeland ME, Signorovitch J. Calcipotriol plus betamethasone dipropionate aerosol foam vs. apremilast, methotrexate, acitretin or fumaric acid esters for the treatment of plaque psoriasis: a matching-adjusted indirect comparison. *J Eur Acad Dermatol Venereol*. 2019;33(6):1107–1115. doi:10.1111/jdv.15369
51. Praestegaard M, Steele F, Crutchley N. Polyaphron dispersion technology, a novel topical formulation and delivery system combining drug penetration, local tolerability and convenience of application. *Dermatol Ther*. 2022;12(10):2217–2231. doi:10.1007/s13555-022-00794-y
52. Draelos ZD, Draelos MM, Steele F, Georgiou M, Praestegaard M. Enhanced skin deposition of betamethasone dipropionate from a novel formulation and drug delivery technology. *Dermatol Ther*. 2023;13(8):1763–1771. doi:10.1007/s13555-023-00959-3

53. Pinter A, Green LJ, Selmer J, et al. A pooled analysis of randomized, controlled, phase 3 trials investigating the efficacy and safety of a novel, fixed dose calcipotriene and betamethasone dipropionate cream for the topical treatment of plaque psoriasis. *J. Eur Acad Dermatol Venereol*. 2022;36 (2):228–236. doi:10.1111/jdv.17734
54. This trial is a randomised, multicentre, investigator-blind, vehicle and comparator-controlled, parallel-group trial With the purpose of evaluation efficacy, safety and convenience of the MC2-01 cream. Available from: https://clinicaltrials.gov/ct2/show/NCT03802344. Accessed June 30, 2024.
55. A clinical trial evaluating efficacy and safety of MC2-01 cream. Available from: https://clinicaltrials.gov/ct2/show/NCT03308799. Accessed June 30, 2024.
56. Bewley A, Barker E, Baker H, et al. An anchored matching-adjusted indirect comparison of fixed-dose combination calcipotriol and betamethasone dipropionate (Cal/BDP) cream versus Cal/BDP foam for the treatment of psoriasis. *J DermatolTreat*. 2022;33(8):3191–3198. doi:10.1080/09546634.2022.2116924
57. Seyhan M, Coşkun BK, Sağlam H, Ozcan H, Karincaoğlu Y. Psoriasis in childhood and adolescence: evaluation of demographic and clinical features. *Pediatr Int*. 2006;48(6):525–530. doi:10.1111/j.1442-200X.2006.02270.x
58. LEO pharma taclonex® topical ointment, prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021852s020lbl.pdf. Accessed March 2020.
59. LEO pharma taclonex® topical suspension, prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022185s027lbl.pdf. Accessed June 30, 2024.
60. Gooderham M, Debarre JM, Keddy-Grant J, Xu Z, Kurvits M, Goodfield M. Safety and efficacy of calcipotriol plus betamethasone dipropionate gel in the treatment of scalp psoriasis in adolescents 12-17 years of age. *Br J Dermatol*. 2014;171(6):1470–1477. doi:10.1111/bjd.13235
61. Eichenfield LF, Ganslandt C, Kurvits M, Schlessinger J. Safety and efficacy of calcipotriene plus betamethasone dipropionate topical suspension in the treatment of extensive scalp psoriasis in adolescents ages 12 to 17 years. *Pediatr Dermatol*. 2015;32(1):28–35. doi:10.1111/pde.12429
62. Seyger M, Abramovits W, Liljedahl M, Hoejen MN, Teng J. Safety and efficacy of fixed-dose combination calcipotriol (50 µg/g) and betamethasone dipropionate (0.5 mg/g) cutaneous foam in adolescent patients (aged 12 to <17 years) with plaque psoriasis: results of a phase II, open-label trial. *J Eur Acad Dermatol Venereol*. 2020;34(9):2026–2034. doi:10.1111/jdv.16233
63. McCormack PL. Spotlight on calcipotriene/betamethasone dipropionate in psoriasis vulgaris of the trunk, limbs, and scalp. *Am J Clin Dermatol*. 2011;12(12):421–424. doi:10.2165/11207670-000000000-00000
64. Lebwohl M. Topical application of calcipotriene and corticosteroids: combination regimens. *J Am Acad Dermatol*. 1997;37(3 Pt 2):S55–S58.
65. Norsgaard H, Kurdykowski S, Descargues P, et al. Calcipotriol counteracts betamethasone-induced decrease in extracellular matrix components related to skin atrophy. *Arch Dermatol Res*. 2014;306(8):719–729. doi:10.1007/s00403-014-1485-3
66. Taylor A, Singh R, Feldman SR. Review of calcipotriene and betamethasone dipropionate cream in the treatment of psoriasis. *Ann Pharmacother*. 2023;57(3):341–347. doi:10.1177/10600280221105508
67. Kragballe K, Austad J, Barnes L, et al. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product (Dovobet/Daivobet/Taclonex) in the treatment of psoriasis vulgaris. *Br J Dermatol*. 2006;154(6):1155–1160. doi:10.1111/j.1365-2133.2006.07236.x
68. Leonardi C, Bagel J, Yamauchi P, et al. Efficacy and safety of calcipotriene plus betamethasone dipropionate aerosol foam in patients with psoriasis vulgaris – a randomized phase III study (PSO-FAST). *J Drugs Dermatol*. 2015;14(12):1468–1477.
69. Reich K, Zschocke I, Bachelez H, et al. Efficacy of a fixed combination of calcipotriol/betamethasone dipropionate topical gel in adult patients with mild to moderate psoriasis: blinded interim analysis of a Phase IV, multicenter, randomized, controlled, prospective study. *J Eur Acad Dermatol Venereol*. 2015;29(6):1156–1163. doi:10.1111/jdv.12774
70. Kragballe K, van de Kerkhof P. Pooled safety analysis of calcipotriol plus betamethasone dipropionate gel for the treatment of psoriasis on the body and scalp. *J Eur Acad Dermatol Venereol*. 2014;28(Suppl 2):10–21. doi:10.1111/jdv.12444
71. Lebwohl M, Tyring S, Bukhalo M, et al. Fixed combination aerosol foam calcipotriene 0.005% (Cal) plus betamethasone dipropionate 0.064% (BD) is more efficacious than Cal or BD aerosol foam alone for psoriasis vulgaris: a randomized, double-blind, multicenter, three-arm, phase II study. *J Clin Aesthet Dermatol*. 2016;9(2):34–41.
72. Koo J, Tyring S, Werschler WP, et al. Superior efficacy of calcipotriene and betamethasone dipropionate aerosol foam versus ointment in patients with psoriasis vulgaris--A randomized phase II study. *J DermatolTreat*. 2016;27(2):120–127. doi:10.3109/09546634.2015.1083935
73. Queille-Roussel C, Rosen M, Clonier F, et al. Efficacy and safety of calcipotriol plus betamethasone dipropionate aerosol foam compared with betamethasone 17-valerate-medicated plaster for the treatment of psoriasis. *Clin Drug Investig*. 2017;37(4):355–361. doi:10.1007/s40261-016-0489-5
74. Pinter A, Reich A, Arenberger P, et al. Randomized phase 3 trial demonstrating high efficacy, favourable safety and convenience of a novel calcipotriol and betamethasone dipropionate cream for the treatment of psoriasis. *J Eur Acad Dermatol Venereol*. 2023;37(11):2327–2335. doi:10.1111/jdv.19330
75. Stein Gold L, Green LJ, Dhawan S, Vestbjerg B, Praestegaard M, Selmer J. A phase 3, randomized trial demonstrating the improved efficacy and patient acceptability of fixed dose calcipotriene and betamethasone dipropionate cream. *J Drugs Dermatol*. 2021;20(4):420–425. doi:10.36849/JDD.5653
76. Guenther L, Takhar A, Megna M, et al. Impact of fixed-dose combination Cal/BD foam on the work productivity of patients with psoriasis: results from the 52-week randomized, double-blind, PSO-LONG trial. *J Eur Acad Dermatol Venereol*. 2022;36(7):1054–1063. doi:10.1111/jdv.18053