Research Review
PRODUCT REVIEW

Daivobet® (Calcipotriol/Betamethasone Dipropionate) Gel in Mild-to-Moderate Plaque Psoriasis

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Expert contributor

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Abbreviations used in this review

AE = adverse event
BSA = body surface area
CI = confidence interval
DLQI = Dermatology Life-Quality Index
EQ-5D = EuroQoL-5D
FDC = fixed-dose combination
IGA = Investigators' Global Assessment
IL = interleukin
OR = odds ratio
PASI = Psoriasis Area and Severity Index
PBS = Pharmaceutical Benefits Scheme
PDI = Psoriasis Disability Index
PGA = Patients' Global Assessment
PhGA = Physicians' Global Assessment
PRO = patient-reported outcomes
PSO-TOP = PSOriasis Treatment OPtimisation
QoL = quality of life
Th = T-helper
TNFα = tumour necrosis factor-α
UV = ultraviolet

This review is a summary of evidence in support of calcipotriol/betamethasone dipropionate gel (Daivobet® 50/500; LEO Pharma Pty Ltd, Bowen Hills, Brisbane, QLD) use on adults with mild-to-moderate plaque psoriasis on the body, or on patients with scalp psoriasis.

Important therapeutic advantages for the topical fixed-dose combination (FDC) of calcipotriol/betamethasone, particularly the gel formulation, comprise improvements in clinical efficacy,[1] quality of life (QoL), patient convenience and acceptability,[2] patient adherence to treatment,[3] patient and dermatologist preference,[4,5] tolerability, and cost savings.[6–10] Moreover, the calcipotriol constituent of the FDC has been shown to work against the atrophogenic activity of betamethasone on the skin.[11]

In large, well-designed clinical studies, calcipotriol/betamethasone demonstrated superior efficacy to placebo, calcipotriol and betamethasone monotherapies in the treatment of plaque psoriasis of the trunk/limbs and scalp. Improvements in QoL have also been reported with calcipotriol/betamethasone, and predictive pharmacoeconomic analyses suggest that the FDC is more cost-effective than other topical antipsoriatic treatments.[7] A German analysis, based on a Markov model and a simulated treatment duration of 48 weeks, revealed that calcipotriol/betamethasone FDC was more cost-effective than the two agents administered together.[9]

Based on overall therapeutic profile for the calcipotriol/betamethasone FDC, and on the accumulation of data endorsing use of gel and ointment formulations of the FDC, calcipotriol/betamethasone is now likely to consolidate and extend its already well-established place in the antipsoriatic armamentarium in Australia. In Europe and America, psoriasis treatment guidelines already advocate calcipotriol/betamethasone as a first-line intervention for management of mild-to-moderate plaque psoriasis of the body and scalp.[12]

Introduction

Plaque psoriasis (psoriasis vulgaris), the most common type of psoriasis, is characterised by chronicity, with exacerbations and remissions,[13] dermal inflammation, and the presence of red, scaly patches shed from the skin; the condition is not contagious.[14] Psoriasis may be mild and barely noticeable, or so severe that it sometimes requires hospitalisation.[13] Approximately 80% of patients with psoriasis have mild-to-moderate disease, and are therefore candidates for topical antipsoriatic therapy.[15]

Psoriatic lesions generally vary in size and extent of inflammation, but are typically well defined; they may be itchy, but are rarely painful.[13] The most frequently affected regions are the elbows, knees and scalp, but the condition can occur anywhere on the body. In some patients, dermal plaques may develop into uncomfortable fissures and cracks.[14] The psychosocial burden and stigma of having 'mild' psoriasis is often underestimated,[16] and QoL is impaired as much as having a chronic cardiac problem.[17]

The causes of psoriasis are not fully recognised, although the condition is considered to develop due to interaction of an individual's immune system, genetic susceptibility, and specific environmental factors.[18] Several psoriasis-susceptibility gene loci (e.g. *PSOR1*) and genes associated with interleukin (IL)-23 signalling (*IL23A, IL23R, IL12B*), modulation of T-helper (Th)-2 immune responses (*IL4, IL13*) and activated B-cell signalling (*TNIP1, TNFAIP3*) have been identified.[18] Various disease 'triggers' are present in genetically susceptible individuals: alcohol ingestion; cigarette smoke; drug treatments (e.g. antimalarials, β-blockers, lithium, nonsteroidal anti-inflammatory drugs); general illness; human immunodeficiency virus; inappropriate diet; lack of exercise; and stress.[13,19,20]

Psoriasis: prevalence and pathophysiology

Worldwide, it is estimated that about 125 million people have psoriasis, although this statistic is likely an underestimate because it is based primarily on patient self-reporting.[21] Indeed, prevalence estimates in different regions vary widely from approximately 1% to 8.5%,[20] with mean prevalence cited as approximately 2–4%.[21–23] In Australia, psoriasis prevalence has been estimated at approximately 2.5–6.5%.[20] Up to 10–40% of patients with psoriasis may have nail involvement, and up to one-third will have concomitant psoriatic arthritis. Nail and scalp involvement are prognostic indicators of psoriatic arthritis, which may be associated with minimal skin disease; conversely, severe forms of psoriatic arthritis are usually accompanied by severe skin disease.[14,21,22]

When psoriasis manifests, patients are usually affected for most of their lives.[14] The peak ages of disease onset are 30–39 years and 60–69 years, although the condition can first appear at any age.[24] Females, and patients with a family history of psoriasis, often develop the condition at an earlier age, and early onset tends towards more severe disease.[25] Patients with severe disease have a greater risk of mortality than the general population.[18] Individuals living at higher latitudes rather than equatorial regions, and Caucasians relative to other races, have a greater prevalence of psoriasis.[20,21] Indigenous Australians and Samoans are rarely affected by the disorder.[26,27]

Over time, pathophysiological beliefs have changed from considering psoriasis as a disorder of keratinocyte dysregulation to the concept of immune system dysregulation mediated by cytokines. Fundamental considerations are now that Th-1, Th-17 and Th-22 cell populations expand and stimulate release of inflammatory cytokines, including ILs 17 and 22, and tumour necrosis factor-α (TNFα).[18]

Psoriasis: comorbidities and disease burden

The inflammatory aspects of psoriasis pathophysiology are associated with several comorbidities with detrimental effects on QoL: for example, psoriatic arthritis, cardiovascular disease, depression, diabetes, dyslipidaemia, hypertension, obesity, and stroke.[13,18,28] In addition, patients with psoriasis are at increased risk of developing other immune-mediated disorders with overlapping pathology: for example, inflammatory bowel disease and rheumatoid arthritis.[18]

In a US university dermatology practice, comorbidities were present in 551 of 773 patients with psoriasis (73%). Furthermore, in a large US study in more than 100,000 patients with psoriasis, reported incidences of hyperlipidaemia, hypertension, depression, diabetes and cardiovascular disease were 27.3%, 25.4%, 9.2%, 8.7%, and 8.6%, respectively.[28,29] In patients with severe psoriasis, such comorbidities have been estimated to reduce life expectancy by 3–4 years.[18]

In a UK cross-sectional study, more than 9,000 individuals with psoriasis, and aged 25–64 years, were compared with more than 90,000 controls without psoriasis and who were matched for age and medical practice. Adjustments were made for age, sex and duration of follow-up and, in patients with versus those without psoriasis, significantly increased risks were documented for the following concurrent conditions: chronic obstructive pulmonary disease (+8%; p=0.02); diabetes (+22%; p<0.001); peptic ulcer disease (+27%; p=0.04); renal disease (+28%; p=0.005); diabetes with complications (+34%; p=0.006); myocardial infarction (+34%; p=0.03); peripheral vascular disease (+38%; p=0.02); mild liver disease (+41%; p=0.008); and rheumatological disease (+104%; p<0.001).[30]

A survey undertaken by the US National Psoriasis Foundation in 405 patients with psoriasis, two-thirds of whom had moderate-to-severe disease, revealed that approximately one-third spent about half an hour each day caring for their disease, whereas about one-quarter spent more than 1 hour doing so.[31] In a European survey of 17,000 patients with psoriasis, 50% reported that the time-consuming nature of treatment for their disease was the most bothersome aspect of treatment.[32] Such time issues in relation to psoriasis management may be less problematic for convenient FDC topical antipsoriatic preparations rather than single-agent formulations. That is, FDCs have the distinct therapeutic advantages of greater convenience, reduced application time for two treatments combined, a potentially reduced need for switching between treatments, and improved patient acceptability, adherence and satisfaction (see *Calcipotriol/betamethasone gel in Australia*).[2,4,5,33–35]

As psoriasis is a chronic and considerably noticeable condition often associated with psychiatric comorbidity, personal interactions (e.g. those requiring skin contact), activities of daily living, and work ability and performance can all be adversely affected.[14,23] The costs to patients, healthcare systems and society are therefore enormous.[20] In Australia, large cross-sectional studies have endorsed the major burden posed by psoriasis: substantial proportions of patients admitted to energetically concealing their condition from the public (83%), friends (58%), family (40%), or a partner (20%). A significant detrimental effect on QoL was also evident from a mean EQ-5D scale score of only 0.73. In the three-quarters of patients with concurrent conditions, the EQ-5D score was further reduced to a mean of only 0.64.[36]

Mild-to-moderate plaque psoriasis: treatment trends

Body psoriasis

Psoriasis cannot be cured, but can be controlled with appropriate intervention. In mild-to-moderate plaque psoriasis not affecting the face, genitalia, palms or soles, topical formulations such as calcipotriol, corticosteroids (e.g. betamethasone) and coal tar are frontline treatments (**Figure 1**).[19] Indeed, most patients with psoriasis have limited mild disease (<5% body surface area [BSA]).[15] Typically, they respond well to topical agents such as corticosteroids, which possess anti-inflammatory, immunosuppressive and antiproliferative activity, vitamin D analogues, tar products, and moisturisers, which all usually have a marked efficacy-to-safety ratio;[15] generally, about three-quarters of patients with psoriasis (70–80%) respond adequately to topical therapy alone.[37]

To reduce comorbidities and stress, patients should be encouraged to optimise lifestyle factors:

- Maintain good sleep habits (at least 8 hours sleep per night).
- Use stress management strategies.
- Undertake regular, vigorous exercise.
- Ensure weight management through a healthy diet rich in fresh fruit and vegetables.

Emollients should be regularly applied to skin that is prone to dryness and scaling.[31] Trauma can exacerbate psoriasis: scratches, and areas prone to trauma such as the elbows and knees, are favoured sites (Koebner phenomenon).[38] Hence, patients should be advised not to pick the scales off their plaques or loofah them in the shower. One study showed that covering psoriasis with occlusive dressings for protection led to healing.[39] Hence, the use of an occlusive emollient may be effective.

Overall, successful disease management depends on tailoring therapeutic strategies to the specific needs of patients.[40] It should be emphasised to patients that psoriasis is a chronic condition; treatment aims to control rather than cure the disorder, and complete clearance of psoriatic lesions is often unattainable. When selecting a treatment, patient preferences are important, especially concerning time taken for topical application.[13] This can be reduced by using a FDC formulation, where two agents can be applied simultaneously, rather than single agents separately, with the likely consequences of improved patient adherence and satisfaction. Conversely, some patients with mild psoriasis may prefer simply to 'cope' with their condition and not apply creams every day.[13] Patients who do prefer treatment typically appreciate a simple schedule (e.g. use of a FDC formulation).[31]

Sunshine may clear psoriasis in some cases, but sunburn may cause flares; fair-skinned patients should be clearly warned about avoiding sunburn and that long-term overexposure to the sun leads to an accelerated risk of skin cancers.[31] A low vitamin D level has been associated with more severe psoriasis;[41] hence, it is clinically prudent to check vitamin D status and administer supplementation if necessary.[42]

Scalp psoriasis

In children and adults with psoriasis, the scalp is the most commonly affected body area; approximately 50–80% of patients have scalp involvement.[40] Although such involvement represents only 4–5% of total BSA, the treatment of scalp psoriasis is more difficult than that on other areas of the body:[40]

- Scalp psoriasis, because of its visibility and scales and dandruff falling onto clothes and carpets, has marked detrimental effects on patient self-confidence and social acceptance. Patients require fast and durable symptom improvement produced by an easy-to-use treatment. If these factors are not met by the selected treatment, then patient adherence is unlikely to be adequate.
- Any deleterious effects of topical therapy on scalp hair (e.g. oiliness, dryness, discolouration, odour) are likely to reduce patient compliance with instructions to maintain the frequency and regularity of product use.
- Cutaneous absorption of the active constituent from a prescribed preparation must be adequate for clinical efficacy. This is often difficult to attain, given that exposure of scalp skin may be 20–100 times less than exposure of scalp hair to an active ingredient. However, calcipotriol/betamethasone gel, which is alcohol and water free, is the only lipophilic antipsoriatic gel available on the market. Increased drug lipophilicity is generally associated with increased cutaneous absorption and increased drug bioavailability.
- Cosmetic acceptability of the base used in topically applied preparations is also important. How easily a base can be 'washed out' after the active ingredient has exerted its therapeutic effect is a significant factor for patients. Water-in-oil emulsions are not readily washed out, they make hair softer and greasier, and sometimes have a disagreeable smell; therefore, they are not well accepted by patients. Conversely, gels are readily washed out after therapeutic activity, and are generally advocated for the outpatient treatment of scalp psoriasis.

Topical therapies, with prudent selection of formulation base, are the treatments of choice for scalp psoriasis.[40] First-choice agents are steroids and vitamin D analogues, or their use together in a FDC formulation (**Figure 1**). Typically, but depending on base, concentration, and potency, steroids are effective, easy to use, and without major cosmetic restrictions. Alcohol-based preparations should be avoided, since they can exacerbate scalp drying and itching and can cause burning. Calcipotriol has anti-inflammatory activity, normalises keratinisation, and restricts epidermal proliferation. Numerous clinical trials have confirmed the short- and long-term clinical efficacy of calcipotriol; however, potent steroids are generally more effective in scalp psoriasis. Nevertheless, unlike topical steroids, calcipotriol can be used for periods of up to 12 months. Considerable evidence from controlled clinical trials exists of the safety, efficacy and cost-effectiveness of once-daily calcipotriol/betamethasone FDC gel in the short-term (8 weeks) and long-term (12 months) management of scalp psoriasis.[1,2,8,43–47] In the latter setting, the FDC gel is not associated with cumulative toxicity or a changing tolerability profile.[40]

Salicylic acid is a keratolytic that is sometimes used to treat severe scaling and enhance absorption of other topical treatments.[40] When used, it should be applied as initial therapy, at a strength of 3–10%, for no more than a few days. Vitamin D analogues should not be administered concurrently because of incompatibility, and salicylic acid should not be used in children. Tar-based preparations are also sometimes used to treat scalp psoriasis; however, their efficacy has been questioned due to lack of evidence, and their smell is often cosmetically unacceptable. Besides topical therapy for scalp psoriasis, patients will

also often require cosmetic products, such as zinc pyrithione shampoo to reduce scaling, or various general-use shampoos to reduce dryness, oiliness, etc.[40] Steroid-based shampoos, such as ones containing clobetasol propionate, are available on prescription for scalp psoriasis, and on authority for body psoriasis. Studies attest to their efficacy,[48,49] and they can be used in combination with *Daivobet®*.

If symptomatic improvement does not occur with topical therapies, then systemic therapy may be appropriate (e.g. acitretin, apremilast, cyclosporin, methotrexate, or an injectable biologic).[40] However, while the utility of systemic treatments in body psoriasis is fully endorsed by clinical-trial data, corresponding specific data for systemic therapies in scalp psoriasis are particularly lacking.[40]

Specific topical therapies

Topical treatments are appropriate for patients with mild-to-moderate plaque psoriasis, and also for patients with severe plaque psoriasis who are receiving systemic therapy. Emollients (e.g. emulsifying ointment, vaseline, 10% urea cream, salicylic acid-based formulations, coal tar/pine tar solutions and bath oils) are useful for reducing itch, for facilitating movement in thick, scaly areas, and for restricting the appearance of scales.[31]

First-line therapy for mild-to-moderate plaque psoriasis may commence with cautious use of the following, remembering of course that for Pharmaceutical Benefits Scheme (PBS) reimbursement of *Daivobet®*, psoriasis must be inadequately controlled with either a vitamin D analogue or potent topical corticosteroid monotherapy (**Figure 1**):[12,50]

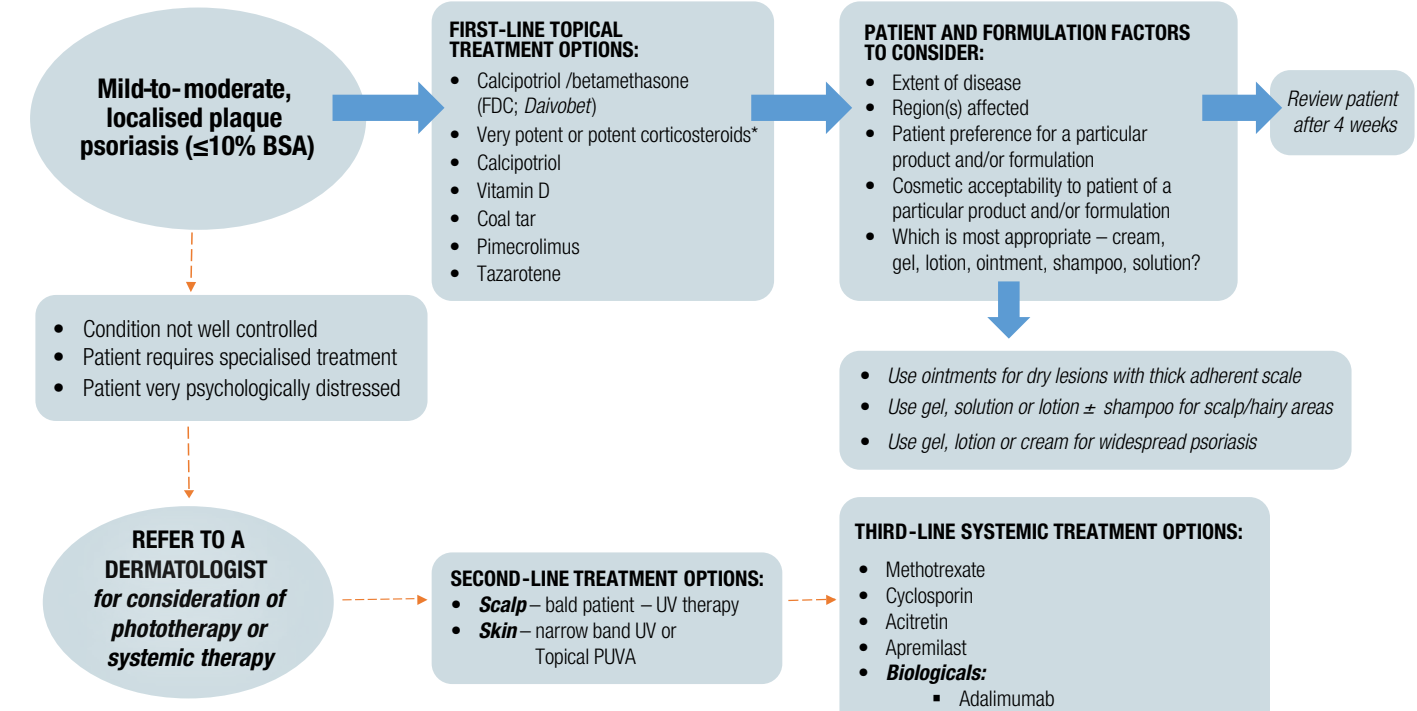
1. topical corticosteroids of varying potency (e.g. betamethasone, clobetasol, hydrocortisone, mometasone);
2. topical vitamin D analogues (e.g. calcipotriol);
3. FDC calcipotriol/betamethasone gel (*Daivobet®*), which is a safe, effective and cost-effective option in adults;[53–55]
4. coal tar or pine tar;
5. pimecrolimus; and/or
6. tazarotene.

Topical agents can be used intermittently or continuously.[15] However, dermatologists typically advocate breaks from topical steroid treatment to reduce skin atrophy. Topical vitamin D analogues may irritate areas of delicate skin (e.g. intertriginous or facial regions), and plasma calcium levels need to be monitored if large quantities of these analogues are applied.[31]

Generally, when topical steroids are used, the least potent agent that controls symptoms should be prescribed.[15] Low-potency steroids are usually used for short periods in infants and on the face, whereas in adults, moderate- to high-potency steroids are often used as the initial treatment. Coal tar 1% lotion is less messy than other tar formulations.[13,31]

In Australia, calcipotriol/betamethasone gel (*Daivobet®*) is PBS-subsidised for the treatment of scalp psoriasis, as are coal tar preparations. For psoriasis on the face, genitals, and in the flexures, most dermatologists prescribe mild topical steroids (e.g. hydrocortisone) intermittently (e.g. weekly), or as short-term treatment only.[56] However, pimecrolimus cream is another alternative for mild disease on the face and genitals, and avoids the risk of steroid-induced skin atrophy.[57] Long-term outcome studies have found no increased risk of skin malignancy and lymphoma with topical calcineurin inhibitors, including pimecrolimus.[58,59] Tazarotene is sometimes used to treat plaque psoriasis. It is as effective as topical steroids, but typically produces a longer disease-free interval. Unfortunately, as a retinoid, it is potentially teratogenic and is also frequently associated with perilesional adverse events (AEs) such as burning and pruritus.[50] For nail psoriasis, topical steroid lotions can be applied under the affected nails, or referral to a dermatologist for systemic therapy may be appropriate. To assess the efficacy and acceptability of topical treatment, patients with psoriasis should ideally be followed-up 4 weeks after starting or changing topical therapy;[51] however, this is not always possible because of additional patient costs, and a 50% decrease in Psoriasis Area and Severity Index (PASI) score often takes up to 8 weeks to manifest. Patients need to be told that areas covered with thick, silvery-white scale will turn beefy red in the process of healing; patients should not stop topical therapy, as this is a normal sign of response and it can take 4–8 weeks for plaques to heal.

If topical therapy fails, secondary care treatment options comprise phototherapy, oral agents (acitretin, apremilast, cyclosporin, methotrexate), and injectable biologics. The latter injectable preparations are becoming increasingly used in patients with extensive skin, facial, hand and foot psoriasis, or joint involvement.[15] Most of these systemic therapies need to be prescribed by a dermatologist,[31] and patients have to be excluded from having latent tuberculosis or hepatitis B and update their live vaccines before it is safe to start these therapies. Clearly, before systemic schedules are started in psoriatic patients without joint involvement, it should be remembered that fundamental reasons for perceived failure of topical therapy are poor patient adherence to treatment and ineffective or incorrect use of topical preparations.[6] Nonetheless, some patients will have >10% BSA involvement, in which case systemic therapy is usually needed.[60,61]



*Generally, topical steroids should not be used continuously for >4 weeks (very potent) or >8 weeks (potent) for body psoriasis; for scalp psoriasis, topical steroids should not be used continuously for >4 weeks. Consider an interval of ≥4 weeks between courses of very potent or potent topical steroids.

Figure 1. **Suggested algorithm for the management of mild-to-moderate plaque psoriasis of the body or scalp in adults in primary care.[19,50–52]**

Clinical rationale for a topical FDC formulation

Numerous potential advantages exist for combining a potent steroid with a vitamin D analogue in one formulation for the treatment of both body and scalp psoriasis.[62] Fundamentally, a FDC provides a complementary, dual mechanism of action, and a reduced application time relative to separate application of the individual product constituents.[33] Time savings also occur for prescribers, who can generate only one, rather than several, prescriptions for the treatment of both body and scalp psoriasis. Cost savings are also likely because, besides the potential for improved efficacy and tolerability with FDCs, patients will need to collect fewer repeat prescriptions than if individual components were prescribed separately. Overall, these benefits of FDC therapy will likely translate into substantial improvements in patient convenience, acceptability, satisfaction and, importantly, adherence to treatment.[2,4,5,33–35,62] This is particularly pertinent given that some surveys suggest that up to half of all patients with psoriasis may fail to collect their prescriptions for antipsoriatic medication.[63]

Significantly, the calcipotriol/betamethasone FDC has been associated with enhanced clinical efficacy,[1] QoL, patient convenience and acceptability,[2] patient adherence to treatment,[3] patient and dermatologist preference,[4,5] tolerability, and cost savings.[6–10] Regarding a complementary mechanism of action, the calcipotriol constituent of the FDC has been shown to work against the atrophogenic activity of betamethasone on the skin.[11]

As shown in **Table 1**, some of the key therapeutic advantages for calcipotriol/betamethasone gel are that it is available as a simple, once-daily treatment for both body and scalp psoriasis, and it increases patients' QoL, minimises impact on patients' daily routines, and encourages patient adherence.[34,35,64,65]

Table 1. **Key therapeutic attributes for FDC calcipotriol/betamethasone gel**

- Simple, once-daily treatment[34,35]
- Specifically designed to treat psoriasis[65]
- Effective in both body and scalp psoriasis[34,35,64,65]
- Improves patients' QoL, minimises impact on daily routines, encourages patient adherence[34,35,64,65]
- Dual mechanism of action[64,65]
- Easy and fast to use[33]
- Provides faster, more effective symptom relief than a potent steroid used alone[43]
- High levels of patient convenience and acceptability[2]
- High levels of patient and dermatologist preference, and patient satisfaction[4,5,33]
- Associated with major cost savings,[6–10] and is more cost-effective than other topical antipsoriatic treatments[7–9]
- Well tolerated — rare occurrence of steroid-related AEs or skin irritation.[34]

AE, adverse event; FDC, fixed-dose combination; QoL, quality of life.

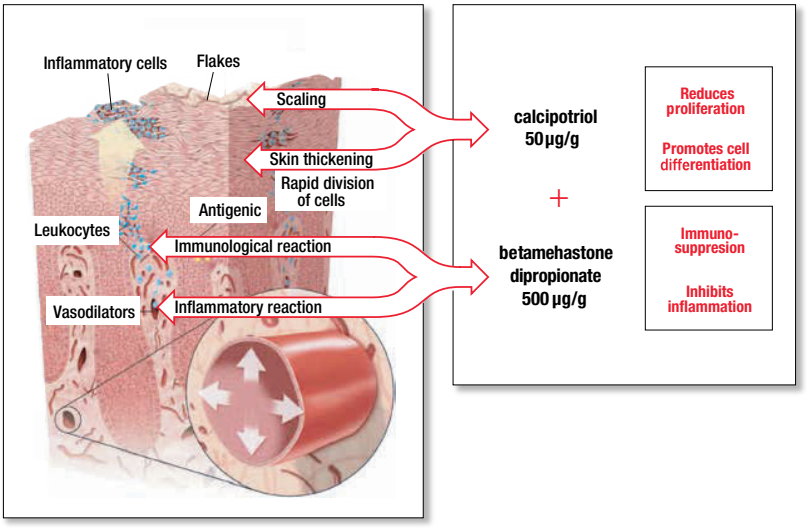


Figure 2. **Calcipotriol/betamethasone gel: mechanism of action.**

Product 'in brief': calcipotriol/betamethasone gel

Mechanisms of action

Calcipotriol, a nonsteroidal antipsoriatic agent, is derived from vitamin D and competes for 1,25-dihydroxycholecalciferol [1,25$(OH)_2D_3$] receptors. It is as potent as 1,25$(OH)_2D_3$, the naturally occurring form of vitamin D, in regulating cell differentiation and proliferation; however, its effects on calcium metabolism are much less than those of 1,25$(OH)_2D_3$. Calcipotriol stimulates keratinocyte differentiation and suppresses proliferation, without cytotoxicity, thereby counteracting aberrant changes in keratinocytes in patients with psoriasis and normalising epidermal growth.[66]

Betamethasone dipropionate is a potent topical steroid that has rapid, marked and prolonged anti-inflammatory activity, through a mechanism that has not been clearly elucidated, and antipruritic, immunosuppressive and vasoconstrictive activity; however, betamethasone does not cure underlying conditions. The activity of betamethasone can be increased approximately 10-fold under occlusion because of increased penetration of the stratum corneum.[66]

The calcipotriol/betamethasone FDC is specifically designed to treat psoriasis, and the dual action of calcipotriol plus corticosteroid in a single, once-daily solution reduces keratinocyte proliferation and inflammation (**Figure 2**).[64,65]

Pharmacokinetic properties

In rats and minipigs, systemic exposure to calcipotriol and betamethasone from topical calcipotriol/betamethasone gel is 13–45% less than that from the corresponding FDC ointment. After administration of radiolabelled ointment, the systemic absorption of calcipotriol and betamethasone is <1% of the dose (2.5 g) when applied to normal skin (625 cm^2) for 12 hours. After systemic exposure, calcipotriol and betamethasone are rapidly and extensively metabolised; in animals (rats, mice, minipigs), the main route of excretion is via faeces. In 34 patients with extensive body and scalp psoriasis, 4–8 weeks' administration of calcipotriol/betamethasone gel and ointment led to undetectable levels of calcipotriol and betamethasone in all blood samples; one metabolite of calcipotriol, and one of betamethasone, was detected in blood samples from some patients.[66]

Pharmacodynamic properties

In vitro studies showed calcipotriol to counteract betamethasone-induced suppression of collagen I synthesis, and calcipotriol and betamethasone to have opposite effects on matrix metalloproteinase expression in fibroblasts and keratinocytes. *In vivo*, application of the FDC calcipotriol/betamethasone gel to minipigs prevented betamethasone-induced epidermal thinning.[11] Moreover, in 18 patients with plaque psoriasis treated with FDC calcipotriol/betamethasone or either monotherapy, immunohistochemical staining of skin biopsies taken at 4 and 6 weeks revealed a greater reduction in dermal and epidermal T-cell markers and human β-defensin-2 with the FDC relative to both monotherapies.[67]

Calcipotriol/betamethasone gel in Australia

Calcipotriol/betamethasone gel, the only lipophilic gel available on the market, is indicated for the treatment of scalp psoriasis, and for the treatment of mild-to-moderate plaque psoriasis on the body in adults.[66] It was previously PBS-subsidised (as a 30 g or 60 g bottle) for patients with chronic stable plaque psoriasis of the scalp inadequately controlled with monotherapy with a vitamin D analogue or potent topical corticosteroid;[68] however, from 1 March 2016, calcipotriol/betamethasone gel is now PBS-subsidised for both body and scalp psoriasis.

Reimbursement of calcipotriol/betamethasone gel

Calcipotriol/betamethasone is available in Australia as a gel or ointment (50/500 µg/g). It is reimbursed on the PBS, and stipulations for PBS subsidy are:[68]

- *Gel 30g or 60g* — for patients with chronic stable plaque psoriasis of the scalp inadequately controlled with monotherapy with a vitamin D analogue or potent topical corticosteroid. *[From 1 March 2016, the gel is now also subsidised for the treatment of body psoriasis.]*
- *Ointment 30g* — for patients with chronic stable plaque type psoriasis inadequately controlled with either calcipotriol or potent topical corticosteroid monotherapy.

On the PBS, calcipotriol/betamethasone gel has a *Restricted benefit* reimbursement. That is, the condition must be inadequately controlled with either a vitamin D analogue or potent topical corticosteroid monotherapy.[68]

Although randomised controlled clinical trials are the standard by which new treatments are evaluated and efficacy confirmed, the strict, inflexible design of such studies can often lead to overestimation of patient-reported outcomes (PROs) such as QoL and satisfaction with treatment. Patient adherence to treatment may also be overestimated. Thus, for decision-making processes, healthcare payers and professionals are starting to rely more heavily on PRO data generated from observational studies. Such studies better mimic 'real-life' clinical practice and better define treatment effectiveness because they have flexible study protocols, heterogeneous patient populations, and personalised treatment schedules.[69]

A recent, postmarketing surveillance study of calcipotriol/betamethasone gel revealed that one 60 g bottle was sufficient to provide 5 weeks' treatment in the real-life setting in 579 patients with mild-to-moderate psoriasis on the trunk and limbs. That is, the mean quantity of calcipotriol/betamethasone gel used during the study was 0.98 of a 60 g bottle per patient. Significant improvements were evident in Physicians' Global Assessment (PhGA) of efficacy (39.6%; p<0.0001) and QoL (Dermatology Life-Quality Index [DLQI], 63.2%; p<0.0001).[33] Importantly, in patients needing to treat large BSAs, the 30 g bottle of gel may be insufficient for one monthly prescription treatment cycle. The consequence is that some patients may fail to pick up a second gel prescription, not use any treatment, and simply try to cope with symptoms, because of the major bother of having to frequently return to a pharmacy to collect repeat prescriptions.[34] Indeed, a Danish survey revealed that approximately one-third of patients with dermatological disorders failed to collect their prescription of any medication; this fraction was greater (almost 50%) in patients with psoriasis.[63]

Key phase III trials in body psoriasis

In two, well-designed, well-controlled, short-term (8-week) clinical trials in a total of 1,610 patients with mild-to-moderate plaque psoriasis of the body, FDC calcipotriol/betamethasone gel was significantly more effective than monotherapy with each of tacalcitol ointment, betamethasone gel, calcipotriol gel, and gel vehicle. This applied at weeks 4 and 8 regarding the proportion of patients with controlled disease (Investigators' Global Assessment [IGA]), and the percentage change in PASI score from baseline. The proportion of patients with treatment success (Patients' Global Assessment [PGA]) was also numerically greater for FDC calcipotriol/betamethasone gel than for tacalcitol ointment and gel vehicle. The FDC also improved QoL, as measured on the DLQI scale, to a significantly greater extent than betamethasone gel and gel vehicle (**Table 2**).[35,70]

Table 2. **Key phase III trials of FDC calcipotriol/betamethasone gel in mild-to-moderate plaque psoriasis of the body**

Reference	Treatment	No. of pts	Outcomes at week 8		
			IGA-controlled disease (% pts)[a]	PASI score (% change)	PGA-treatment success (% pts)[b]
Langley et al.[70]	FDC CAL/BET	183	39.9	–53.1	40.4
	TAC ointment	184	17.9**	–41.9**	21.5
	Gel vehicle	91	5.5**	–17.9**	21.9
					DLQI score change
Menter et al.[35]	FDC CAL/BET	482	29.0	–55.8	–6.4
	BET gel	479	21.5*	–48.6**	–5.4*
	CAL gel	96	14.6*	–43.6**	–5.9
	Gel vehicle	95	6.3**	–20.9**	–2.7**

[a] Defined as 'clear' or 'almost clear', based on the IGA scale, plus a minimum 2-point change from baseline.

[b] Proportion of patients with 'marked improvement', 'almost clear' or 'clear', based on PGA.

Statistical significance: *p<0.01, **p<0.001 vs calcipotriol/betamethasone gel.

BET, betamethasone; CAL, calcipotriol; DLQI, Dermatology Life-Quality Index; FDC, fixed-dose combination; IGA, Investigators' Global Assessment; PASI, Psoriasis Area Severity Index; PGA, Patients' Global Assessment; pts, patients; TAC, tacalcitol.

Table 3. **Key phase III trials of FDC calcipotriol/betamethasone gel in plaque psoriasis of the scalp**

Reference	Treatment	No. of pts	Outcomes at week 8	
			IGA-treatment success (% pts)[a]	PGA-treatment success (% pts)[b]
Jemec et al.[43]	FDC CAL/BET	541	71.2	68.6
	BET gel	556	64.0*	62.5
	CAL gel	272	36.8†	38.3†
	Gel vehicle	136	22.8†	20.7†
van de Kerkhof et al.[44]	FDC CAL/BET	568	68.4	69.6
	BET gel	563	61.0**	59.9**
	CAL gel	286	43.4†	44.7†

[a] Defined as 'absent' or 'very mild disease' according to IGA.

[b] Proportion of patients with 'clear' or 'almost clear' disease, based on PGA.

Statistical significance: *p<0.05, **p<0.01, †p<0.0001 vs calcipotriol/betamethasone gel.

BET, betamethasone; CAL, calcipotriol; FDC, fixed-dose combination; IGA, Investigators' Global Assessment; PGA, Patients' Global Assessment; pts, patients.

In the larger of these two trials,[35] at week 4, significantly more patients treated with calcipotriol/betamethasone than calcipotriol or vehicle (13.3% vs 5.2% [p=0.019] vs 2.1% [p=0.001]) had IGA-assessed controlled disease ('clear' or 'almost clear' and a 2-point change from baseline). Corresponding rates of controlled disease at week 8 were 29.0% vs 14.6% (p=0.002) vs 6.3% (p<0.001). Also at week 8, the proportion of patients with a PASI 75 response (i.e. a 75% reduction in PASI score) was significantly greater in the FDC group than in all other groups: FDC 48.0%; betamethasone 34.9% (p=0.004 vs FDC); calcipotriol 20.7% (p<0.001); and vehicle 15.6% (p<0.001). Corresponding decreases in DLQI scores were 6.4 points, 5.4 points (p=0.005 vs FDC), 5.9 points (not significant), and 2.7 points (p<0.001). The incidence of AEs was similar in all four study groups: 20–26%. Most AEs were considered unrelated to study medication and were mild or moderate in intensity. *'Calcipotriene* [calcipotriol] *plus betamethasone dipropionate formulated in a nonalcoholic topical suspension provides the benefits of combination therapy in a formulation that may conveniently be applied once daily to psoriasis on the body as well as the scalp.'*[35]

Key phase III trials in scalp psoriasis

In two, well-designed, well-controlled, short-term (8-week) clinical trials in almost 3,000 patients with plaque psoriasis of the scalp, FDC calcipotriol/betamethasone gel was generally significantly more effective than monotherapy with each of betamethasone gel, calcipotriol gel, and gel vehicle. This applied at 8 weeks regarding the proportion of patients with IGA and PGA treatment success,[43,44] although in the Jemec *et al.* trial,[43] the difference between calcipotriol/betamethasone and betamethasone gel regarding PGA treatment success was not statistically significant (**Table 3**).[43,44] In a long-term (52-week) randomised, double-blind study in 869 patients with moderate-to-severe scalp psoriasis, and based on IGA-defined 'absent', 'mild' or 'very mild' disease, psoriasis was satisfactorily controlled at significantly more assessment timepoints in patients treated with calcipotriol/betamethasone rather than calcipotriol alone (92.3% vs 80.0% of assessments; p<0.001). The FDC was better tolerated than calcipotriol monotherapy: significantly fewer FDC recipients had AEs (17.2% vs 29.5%; odds ratio [OR] 0.5; 95% confidence interval [CI]: 0.36, 0.69; p<0.001) or lesional/perilesional skin irritation on the scalp (11.9% vs 21.6%; OR 0.49; 95% CI: 0.34, 0.72; p<0.001).[45]

In the larger of the two trials in **Table 3**,[43] calcipotriol/betamethasone FDC had a faster onset of efficacy, and was more effective, than betamethasone alone (**Figure 3**). That is, after 2 weeks with calcipotriol/betamethasone, the proportion of patients with an IGA assessment of 'absent' or 'very mild' disease was similar to that after 4 weeks with betamethasone alone (57.5% vs 54.7%). At week 4, calcipotriol/betamethasone was significantly more effective than betamethasone alone (66.9% vs 54.7%; p<0.001). The same was true at week 8 (71.2% vs 64.0%; p=0.011). The IGA response to calcipotriol alone was 23.5% at week 4 (p<0.0001 vs FDC gel) and 36.8% at week 8 (p<0.0001). In summary: *'Calcipotriene* [calcipotriol] *plus betamethasone dipropionate scalp formulation was more effective than either of the individual components or the vehicle alone.'*[43]

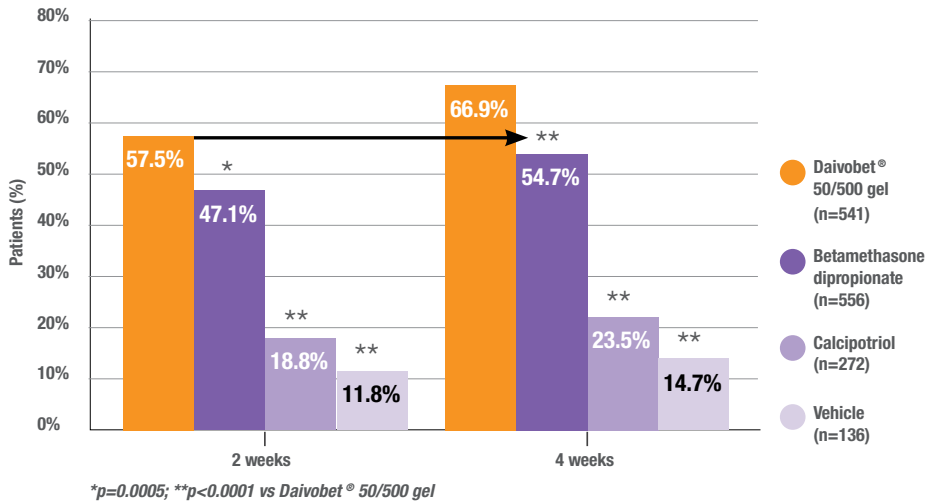


Figure 3. **Calcipotriol/betamethasone provides faster and more effective symptom relief than betamethasone alone in scalp psoriasis.[43]**

Data shown are the proportion of patients with IGA 'absent' or 'very mild' disease.

*p=0.0005, **p<0.0001 vs calcipotriol/betamethasone gel.

Calcipotriol/betamethasone effective in 'real-life' studies

Besides demonstration of antipsoriatic efficacy in rigidly controlled clinical trials, confirmation of effectiveness in the real-life setting — where factors such as patient preference, satisfaction, and adherence to treatment become increasingly relevant — is also particularly important.[34] Several such large-scale, real-life studies have assessed the efficacy of calcipotriol/betamethasone gel in plaque psoriasis of the body and scalp (**Table 4**).[2,4,33,71]

Table 4. **Principal real-life studies of calcipotriol/betamethasone gel**

Reference	Treatment duration (area affected)	No. of pts	Key clinical outcomes	
Bagel et al.[71]	8 weeks (body)	147	PGA controlled disease: 60.2% of pts[a]	DLQI score change: –5.5 points**
Mrowietz et al.[2]	4 weeks (scalp)	721	% improvement in PGA: 41.8%**	% improvement in QoL: 69.5%**
Reich et al.[4] [PSO-TOP]	8 weeks (body)	1795[b]	PGA success:[c] 34.2% of pts	PhGA success:[c] 36.5% of pts
Sticherling et al.[33]	4 weeks (body)	579	% improvement in PGA: 39.6%**	% improvement in QoL: 63.2%**

[a] PGA score of 'clear' or 'very mild' disease.

[b] 48% of patients had failed treatment with potent steroids in the preceding 8 weeks.

[c] Lesions 'clear' or 'almost clear'.

Statistical significance: **p<0.0001 vs baseline.

DLQI, Dermatology Life-Quality Index; PGA, Patients' Global Assessment; PhGA, Physicians' Global Assessment; PSO-TOP, PSOriasis Treatment OPtimisation; pts, patients; QoL, quality of life.

As shown in **Table 4**, in real-life studies in a total of 3,242 patients with plaque psoriasis, calcipotriol/betamethasone gel demonstrated marked efficacy and major improvements in QoL: according to PGA, disease was controlled ('clear' or 'very mild') in approximately 60% of patients,[71] the actual improvement in PGA score was approximately 40% (p<0.0001),[2,33] and more than one-third of patients who had previously failed treatment with potent topical steroids had documented PGA or PhGA treatment success (lesions 'clear' or 'almost clear'; p<0.0001);[4] furthermore, statistically significant improvement was evident on the DLQI (p<0.0001),[71] and the actual improvement in QoL scores was reported as approximately 65–70% (p<0.0001).[2,33]

In the largest of these studies (the PSOriasis Treatment OPtimisation [PSO-TOP] study; n=1,795),[4] after 8 weeks' treatment with calcipotriol/betamethasone, slightly more than one-third of patients had improved according to a score of 'clear' or 'almost clear' on the PGA (34.2% of patients) or PhGA (36.5%; both p<0.001; **Figure 4**). Importantly, 48% of patients had received unsuccessful treatment with potent steroids during the 8 weeks before calcipotriol/betamethasone. The Patient Preference Questionnaire revealed that the FDC gel was highly preferred by patients (>85%) relative to previous topical therapy. Regardless of the previous treatment received, most patients 'agreed' or 'strongly agreed' that calcipotriol/betamethasone was more effective, easier to use, associated with fewer AEs and better tolerated, and preferred to previous treatment. Hence, this *'… interim analysis of a large patient population after 8 weeks of treatment indicated that the fixed combination calcipotriol/betamethasone dipropionate topical gel is highly efficacious and highly preferred by the patients compared with their previous treatments.'*[4]

Calcipotriol/betamethasone cost-effective in pharmacoeconomic studies

Medication cost is a fundamental consideration for many patients, prescribers and policy makers, and importantly, various pharmacoeconomic analyses have shown calcipotriol/betamethasone gel to be more cost-effective than other topical antipsoriatic therapies.[7,9] A cost-utility analysis in Scottish primary care projected that calcipotriol/betamethasone gel would produce an incremental gain of approximately 0.0025 quality-adjusted life-years, thus providing cost savings of £20–30 per patient per year.[8] Furthermore, because of its convenience in providing effective treatment for both body and scalp psoriasis, calcipotriol/betamethasone gel was more cost-effective than applying two separate treatments to different areas. That is, in a retrospective analysis of US claims data over a 6-month period for almost 2,000 patients with psoriasis, patients treated with calcipotriol/betamethasone gel (~20%), rather than multiple antipsoriatic therapies (~80%), had significantly lower total healthcare costs, fewer outpatient visits, and used fewer systemic treatments.[61]

A psoriasis-specific model was developed to predict 2-year outcomes of various topical treatment strategies in patients with moderately severe psoriasis.[54] Interestingly, the model projected that treatment with FDC calcipotriol/betamethasone, if administered to all patients with psoriasis in a UK population in a community setting, would produce potential cost savings in psoriasis care of £126 million over 2 years. A principal feature of this pharmacoeconomic model was to try to discover ways of reducing unnecessary referrals to hospital, thereby preserving secondary care resources for management of the most recalcitrant cases of psoriasis.[54]

Dosage

In adults with mild-to-moderate plaque psoriasis on the body, calcipotriol/betamethasone gel should be applied once daily for up to 8 weeks. If no improvement is evident after 4 weeks, treatment should be stopped. Steroid treatment of body psoriasis should be stopped after 8 weeks.[66]

In patients with scalp psoriasis, calcipotriol/betamethasone gel should be applied once daily for up to 4 weeks, after which it may be used, according to need, under medical supervision. Clinical experience exists for the intermittent use of calcipotriol/betamethasone gel for up to 1 year in patients with scalp psoriasis. All affected scalp areas may be treated with calcipotriol/betamethasone gel; typically 1–4 g (4 g is equivalent to one teaspoon) is adequate. The maximum daily dose should not exceed 15 g, and the maximum weekly dose should not exceed 100 g. The total BSA treated with calcipotriol/betamethasone gel should not exceed 30%, since repeated treatment of large BSAs may be associated with AEs. To attain maximal efficacy in scalp psoriasis, calcipotriol/betamethasone gel should remain on the scalp during the day or night (i.e. the hair should not be washed immediately after calcipotriol/betamethasone gel application).[66]

Calcipotriol/betamethasone gel is not yet registered for use in children and adolescents aged <18 years;[66] however, preliminary studies of efficacy and safety of the FDC gel in adolescents aged 12–17 years have been encouraging.[3,52,72]

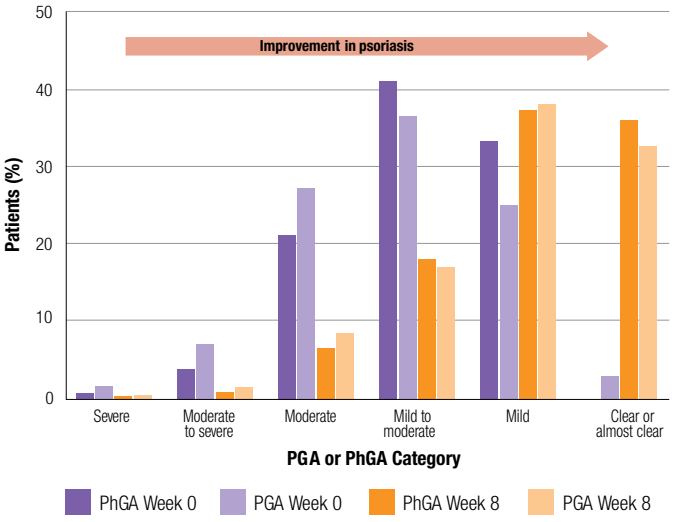


Figure 4. **Calcipotriol/betamethasone significantly improves psoriasis severity, according to PGA and PhGA scores, over 8 weeks.[4]**

Contraindications

The following contraindications to use of calcipotriol/betamethasone gel exist:[66]

- Hypersensitivity to calcipotriol, betamethasone or any of the product excipients.
- Patients with disorders of calcium metabolism.
- Viral skin lesions (e.g. herpes, varicella); bacterial, fungal or parasitic skin infections; dermal manifestations of syphilis or tuberculosis; perioral dermatitis; acne vulgaris; skin atrophy; striae atrophicae; skin-vein fragility; ichthyosis; acne rosacea; rosacea; skin ulceration and wounds; perianal and genital pruritus.
- Guttate, erythrodermic, exfoliative and pustular psoriasis.
- Patients with severe renal insufficiency or severe liver disorders.

Adverse events

The clinical trial database for calcipotriol/betamethasone gel comprises more than 6,000 patients. In body psoriasis, the only AE that occurred in >1% of patients treated with the FDC gel was pruritus: calcipotriol/betamethasone 1.5% of patients; betamethasone 0.4%; calcipotriol 2.9%; gel vehicle 6.6%.[66] In a well-designed, well-controlled study in which 482 patients with body psoriasis applied calcipotriol/betamethasone gel for 8 weeks, no statistically significant difference in AE incidence was noted between calcipotriol/betamethasone gel and gel vehicle.[35,66]

In clinical trials in scalp psoriasis, approximately 8% of patients treated with calcipotriol/betamethasone gel had non-serious AEs considered possibly related to study medication. Pruritus was common (frequency >1/100 to <1/10), and uncommon AEs (>1/1,000 to <1/100) comprised: skin burning, pain or irritation; folliculitis; dermatitis; erythema; acne; dry skin; exacerbation of psoriasis; rash; pustular rash; and eye irritation.[66]

An analysis of pooled safety data from nine clinical trials involving 2,777 patients with body or scalp psoriasis treated with calcipotriol/betamethasone gel revealed that most AEs were mild or moderate in severity.[47] Approximately one-third of patients with body or scalp psoriasis had ≥1 AE; this compared with 24–29% of patients (body psoriasis) or 38–57% of patients (scalp psoriasis) treated with calcipotriol or betamethasone monotherapy. The most frequent AEs (incidence 2–5%) during calcipotriol/betamethasone gel administration were nasopharyngitis, pruritus, and upper respiratory tract infection; only 5% of patients had ≥1 lesional or perilesional AE. The incidence of serious AEs was low (≤1%).[47]

It is difficult during postmarketing surveillance to define frequency and establish a causal link between AEs and medication, since events are reported voluntarily from populations of uncertain size.[66] Nonetheless, in more than 5 years' postmarketing surveillance in various countries, calcipotriol/betamethasone gel has been generally well tolerated: steroid-related AEs and skin irritation were rarely reported, screening for laboratory parameters was usually not requested, and metabolic alterations were not identified.[34] The frequency of AEs in the real-life setting appeared to be lower than that in clinical trials, and when AEs occurred it was typically because the gel was not used as advised, or patients were not given clear instructions about how to use the gel. After stopping treatment with the gel, a rebound effect — potentially due to the calcipotriol constituent — did not occur.[34]

Summary

In summary, calcipotriol/betamethasone gel has an especially encouraging clinical profile. It is easy and convenient to use, and preferred by patients and prescribers (i.e. physicians only have one rather than several prescriptions to write for the treatment of body and scalp psoriasis together). In Australia, therefore, the FDC gel formulation is now likely to consolidate and extend its already well-established place in the antipsoriatic armamentarium. In Europe and America, psoriasis treatment guidelines already advocate calcipotriol/betamethasone as a first-line intervention for management of mild-to-moderate plaque psoriasis of the body and scalp.[12] Daudén and colleagues[34] concur that *'… the fixed combination of calcipotriol and betamethasone dipropionate gel advances topical psoriasis treatment. It is a highly effective first-line topical treatment for mild-to-moderate psoriasis that is preferred …'*. However, in Australia, to obtain calcipotriol/betamethasone gel on authority prescription, patients must already have failed monotherapy with a topical corticosteroid or calcipotriol.

Take home messages

- The prevalence of psoriasis in Australia ranges from 2.5–6.5% of the population. Most patients have limited disease (<5% BSA affected) and typically respond well to topical agents such as corticosteroids, vitamin D analogues, tar products and moisturisers.
- Numerous potential advantages exist for combining a potent topical steroid with a vitamin D analogue in one formulation for the treatment of both body and scalp psoriasis: e.g. complementary, dual mechanism of action; reduced application time; time savings for prescribers; improved efficacy and tolerability; cost savings; and improved patient convenience, acceptability, satisfaction and adherence to treatment.
- The FDC of calcipotriol/betamethasone gel is a simple, once-daily solution specifically designed to treat psoriasis of the body and scalp. It is fast and easy to use, and provides faster and greater symptom relief than a potent steroid used alone. The FDC has been associated with improvements in efficacy and tolerability, QoL, patient convenience, acceptability and adherence, patient and dermatologist preference, and cost savings.
- Overall, the gel formulation of calcipotriol/betamethasone advances the topical treatment of psoriasis, and provides a particularly effective and markedly preferred first-line option for the treatment of mild-to-moderate plaque psoriasis of both the body and scalp.

EXPERT'S SUMMARY COMMENT

This detailed review of the evidence of efficacy and safety for the topical FDC of calcipotriol/betamethasone for several forms of psoriasis means that medical practitioners should feel confident in prescribing this therapy early on in the management of patients with psoriasis. As the current listing in Australia only allows subsidy of the FDC preparation after an inadequate response to topical steroids or a vitamin D analogue alone, these agents are normally tried first. However, some patients may then become despondent because of potentially lower response rates attained after weeks on steroid monotherapy. Hence, after starting treatment in newly presenting patients with psoriasis, it is important to see the patients sooner, such as at 4 weeks, to assess response and modify treatment if rapid enough clearance has not been achieved. Studies have shown that compliance with topical therapies in psoriasis, even in patients involved in clinical trials, is poor. Therefore, having a once-daily combination treatment with improved efficacy is desirable.

Studies have demonstrated that the presence of calcipotriol can mitigate some of the atrophogenic side effects of the steroid, so it also makes sense from a safety standpoint to use the combination preparation. For scalp psoriasis in particular, the gel formulation is easy to use compared with sticky ointments and creams and runny liquids, which are often used in combination with keratolytic shampoos. As most chronic plaque psoriasis affects extensor aspects of the body, such as trauma-prone sites on the elbows, knees and shins, the topical FDC calcipotriol/betamethasone gel is an ideal treatment for many patients. Thinner, more sensitive parts of the skin, such as the face, neck, genital and submammary areas, may occasionally be irritated by use of this potent preparation and respond to lower strength topical therapies, such as hydrocortisone 1% or topical calcineurin inhibitors, which also have less propensity towards skin thinning or acne induction. Patients with refractory psoriasis require referral to a dermatologist to start second-line treatments, such as ultraviolet or systemic therapy, after consideration of compliance issues.

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