

NEW ZEALAND DATA SHEET

1 DAIVOBET® 50/500 GEL

Daivobet® 50/500 calcipotriol 50 microgram/g and betamethasone 500 microgram/g present as dipropionate gel.

2 QUANTITATIVE AND QUALITATIVE COMPOSITION

One gram of gel contains 50 micrograms of calcipotriol (as monohydrate) and 500 micrograms of betamethasone (as dipropionate).

Excipients with known effect: hydrogenated castor oil*, butylated hydroxytoluene (E321)

*Hydrogenated castor oil contains peanut products

3 PHARMACEUTICAL FORM

Gel

An almost clear, colourless to slightly off-white gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Daivobet® gel is indicated for the topical treatment of scalp psoriasis.

Daivobet® gel is indicated for the topical treatment of mild to moderate “non scalp” plaque psoriasis vulgaris.

4.2 Dosage and method of administration

Daivobet® gel is FOR TOPICAL USE ONLY. Daivobet® gel is NOT FOR OPHTHALMIC USE.

The phototoxic effects of Daivobet® gel have not been studied in psoriasis patients in Australia. All psoriasis-affected areas treated with Daivobet® gel should be, where possible, protected from direct sunlight and UV-light with items of clothing.

Adults:

Daivobet® gel should be applied to affected areas once daily. The recommended treatment period is for 4 weeks for scalp areas and 8 weeks for non-scalp areas. After this period, Daivobet® gel may be used according to need under medical supervision. There is experience with intermittent courses of Daivobet® gel up to 52 weeks.

When using calcipotriol containing products, the maximum daily dose should not exceed 15 grams and the maximum weekly dose should not exceed 100 grams.

The total body surface area treated with calcipotriol **should not exceed 30%**.

Shake the bottle before use.

In order to achieve optimal effect, it is recommended that the hair and affected areas of the skin are not washed immediately after application of Daivobet® gel. Daivobet® gel should remain on the affected area during the night or during the day.

If used on the scalp: All the affected scalp areas may be treated with Daivobet® gel. Usually an amount between 1 g and 4 g per day is sufficient for treatment of the scalp (4 g corresponds to one teaspoon).

Children:

Daivobet® gel is not recommended for use in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Patients with known disorders of calcium metabolism.

Due to the corticosteroid content: viral lesions of the skin (e.g. herpes or varicella), fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis or syphilis, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, rosacea, ulceration and wounds, and perianal and genital pruritis (see section 4.4)

Guttate, erythrodermic, exfoliative and pustular psoriasis.

Patients with severe renal insufficiency or severe hepatic disorders.

4.4 Special warning and special precautions for useEffects on endocrine system

Impaired glycaemic control of diabetes mellitus, manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, leading to glucocorticosteroid insufficiency, can occur in some individuals as a result of increased systemic absorption of topical steroids. If either of the above are observed, withdraw the drug gradually by reducing the frequency of application, or by substituting a less potent corticosteroid. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency. Risk factors for increased systemic effects are:

- High potency and lipophilic formulation of topical steroid
- Long duration of exposure
- Application to a large surface area
- Use on occluded areas of skin e.g. on intertriginous areas or under occlusive dressings (note: nappies may act as an occlusive dressing)
- Increased hydration of the stratum corneum
- Use on thin skin areas such as the face
- Use on broken skin or other conditions where the skin barrier may be impaired

In a trial in patients with both extensive scalp and extensive body psoriasis using a combination of high doses of Daivobet® gel (scalp application) and high doses of Daivobet® ointment (body application), 5 of 32 patients showed a borderline decrease in cortisol response to adrenocorticotrophic hormone (ACTH) challenge after 4 weeks of treatment.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroid.

Effects on calcium metabolism

Treatment of more than 30% of the body surface should be avoided (see section 4.2).

Due to the content of calcipotriol, hypercalcaemia may occur if the maximum daily dose (15 g) or the maximum weekly dose (100 g) is exceeded. Serum calcium is, however, normalised when treatment is discontinued. The risk of hypercalcaemia is minimal when the recommendations relevant to calcipotriol are followed.

Local adverse reactions

Daivobet® gel contains a potent WHO group III steroid and concurrent treatment with other steroids on the same treatment area must be avoided.

Skin of the face and genitals are very sensitive to corticosteroids. Daivobet® gel should not be used in these areas.

Uncommon local adverse reactions (such as eye irritation or irritation of facial skin) were observed when the drug was accidentally administered in the area of face, or accidentally to the eyes or conjunctives (see section 4.8). The patient must be instructed in correct use of the product to avoid application and accidental transfer to the face, mouth and eyes. Hands must be washed after each application to avoid accidental transfer to these areas.

Concomitant skin infections

When lesions become secondarily infected, they should be treated with antimicrobial therapy. However, if infection worsens, treatment with corticosteroids should be stopped.

Discontinuation of treatment

When treating psoriasis vulgaris with topical corticosteroids, there may be a risk of generalised pustular psoriasis or of rebound effects when discontinuing treatment. Medical supervision should therefore continue in the post-treatment period.

Long-term use

The gel should be applied to the affected areas of the scalp once daily for up to 4 weeks, and to other affected areas of the body for up to 8 weeks. After this period, Daivobet® gel may be used according to need under medical supervision.

With long-term use there is an increased risk of local and systemic corticosteroid adverse reactions, including hypothalamic pituitary adrenal (HPA) axis suppression. The treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroid (see section 4.8).

Unevaluated use

There is no experience with the use of Daivobet® gel in guttate psoriasis.

Concurrent treatment and UV exposure

There is no experience with concurrent use of other anti-psoriatic products administered systemically or with phototherapy.

The stability of calcipotriol in sunlight and UV light has not been demonstrated. No clinical trials have been conducted with calcipotriol-containing products in Australia, where there is a particularly high potential to be exposed to high levels of UV radiation. In addition, the phototoxic effects of Daivobet® gel have not been studied in psoriasis patients. Therefore, treated skin areas should be protected from sunlight and UV light (using physical covering and/or sunscreens), particularly where exposure may be considerable for reasons such as occupation. Topical calcipotriol should only be used with UV radiation if the physician and patient consider that the potential benefits outweigh the potential risks

Adverse reactions to excipients

Daivobet[®] gel contains butylated hydroxytoluene (E321) as an excipient, which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Use in children

Daivobet[®] gel is not recommended for use in children and adolescents below 18 years of age as the safety and effectiveness of Daivobet[®] gel in this population has not been established.

Renal impairment

Safety has not been established in patients with renal impairment. Daivobet[®] is contraindicated in patients with severe renal impairment.

Hepatic impairment

Safety has not been established in patients with hepatic impairment. Daivobet[®] is contraindicated in patients with severe hepatic impairment.

Effects on laboratory tests

There are no data available on the effects of Daivobet[®] gel on laboratory tests.

4.5 Interactions with other medicinal products and other forms of interactions

No interaction studies have been performed with Daivobet[®] gel.

There is no experience with concurrent use of other anti-psoriatic products administered systemically or with phototherapy.

4.6 Fertility, pregnancy and lactation

Use in pregnancy (Category B1):

There are no adequate data from the use of Daivobet[®] gel in pregnant women. Daivobet[®] gel should only be used during pregnancy when the potential benefit clearly outweighs the potential risk.

Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations). In reproduction toxicity studies with long-term oral administration of corticosteroids to rats, prolonged gestation and prolonged and difficult labour were detected. Moreover, reduction in offspring survival, body weight and body weight gain was observed. Studies of calcipotriol in animals have shown an increase in the incidence of skeletal variations in rats (wavy ribs, extra ribs, incomplete development of skull bones) at oral doses of 18 µg/kg day and in rabbits (reduced skeletal ossification) at oral doses of 36 µg/kg day. The relevance of these findings for humans is unknown.

Use in lactation

Betamethasone is excreted into breast milk. It is unknown if topical application of Daivobet[®] gel could result in sufficient systemic absorption to produce significant quantities of this corticosteroid in human breast milk. There are no data on the excretion of calcipotriol in breast milk.

Caution should be exercised when prescribing Daivobet[®] gel to breastfeeding women. Application of Daivobet[®] gel to the breast area should be avoided. Daivobet[®] gel should only be used during lactation if the potential benefits clearly outweigh the potential risks.

NOTE: After applying Daivobet[®] gel, mothers should wash their hands thoroughly prior to handling their child.

Effects on fertility

Possible effects of betamethasone in combination with calcipotriol on fertility have not been investigated in animals. Studies of the oral administration of calcipotriol in rats have shown no impairment of male and female fertility.

4.7 Effects on ability to drive and use machines

Daivobet® gel has no or negligible influence on the ability to drive and to use machines.

4.8 Undesirable effects

Clinical Trials

The clinical trial programme for Daivobet® gel has so far included more than 4,700 patients of whom more than 2,100 were treated with Daivobet® gel.

Definition of frequency of adverse events:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very Rare	<1/10,000

Approximately 8% of patients treated with Daivobet® gel experienced a non-serious adverse drug reaction (possibly related to study medication).

Based on the above frequency definition, data from clinical trials show that the only common adverse drug reaction is pruritus. The uncommon adverse events are burning sensation of the skin, skin pain or irritation, folliculitis, dermatitis, erythema, acne, dry skin, exacerbation of psoriasis, rash, pustular rash and eye irritation. These adverse events were all non-serious local reactions.

Post-Marketing Use

The estimation of the frequency of adverse reactions is based on a pooled analysis of data from clinical trials including post-marketing safety studies and spontaneous reporting.

The most frequently reported adverse reaction during treatment is pruritus.

Adverse reactions are listed by MedDRA SOC and the individual adverse reactions are listed starting with the most frequently reported. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very Rare	<1/10,000

Table 2: Adverse reactions listed by MedDRA SOC based on pooled data from clinical trials including post-marketing safety studies and spontaneous reporting

Infections and infestations	
Uncommon $\geq 1/1,000$ and $< 1/100$	Skin infection* Folliculitis
Immune system disorders	
Rare $\geq 1/10,000$ and $< 1/1,000$	Hypersensitivity
Eye disorders	
Uncommon $\geq 1/1,000$ and $< 1/100$	Eye irritation
Skin and subcutaneous tissue disorders	
Common $\geq 1/100$ and $< 1/10$	Pruritus
Uncommon $\geq 1/1,000$ and $< 1/100$	Exacerbation of psoriasis Dermatitis Erythema Rash** Acne Skin burning sensation Skin irritation Dry skin
Rare $\geq 1/10,000$ and $< 1/1,000$	Skin striae Skin exfoliation
General disorders and administration site conditions	
Uncommon $\geq 1/1,000$ and $< 1/100$	Application site pain***
Rare $\geq 1/10,000$ and $< 1/1,000$	Rebound effect

*Skin infections including bacterial, fungal and viral skin infections have been reported.

**Various types of rash reactions such as exfoliative rash, rash popular and rash pustular have been reported.

***Application site burning is included in application site pain.

Adverse reactions associated with the pharmacological classes

The following adverse reactions are considered to be related to the pharmacological classes of calcipotriol and betamethasone, respectively:

Calcipotriol

Potential adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, psoriasis aggravated, photosensitivity, transient changes in skin pigmentation, allergic and hypersensitivity reactions including very rare cases of angioedema and facial oedema.

Systemic effects after topical use may appear very rarely causing hypercalcaemia or hypercalciuria.

Betamethasone (as dipropionate)

This product contains a potent corticosteroid.

Local reactions can occur after topical corticosteroid use, especially during prolonged application,

including skin atrophy, telangiectasia, striae, skin wrinkling, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, urticaria, depigmentation, alopecia, trichorrhexis, and colloid milia.

When treating psoriasis with topical corticosteroids, there may be the risk of generalised pustular psoriasis. There may be a risk of rebound when discontinuing long term treatment with corticosteroids.

Systemic reactions due to topical corticosteroids are rare in adults, however, they can be severe. Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushingoid features (e.g. moon face, central obesity), increased weight/obesity, decreased endogenous cortisol levels, osteoporosis, hypercalcaemia, glaucoma, cataract, infections, impact on the metabolic control of diabetes mellitus, (e.g hyperglycaemia/glucoosuria), hypertension, and infections. Systemic reactions occur more frequently when applied under occlusion (for example, plastic, skin folds), when applied on large areas or during long treatment (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/> .

4.9 Overdose

Use at more than the recommended dose may cause elevated serum calcium, which subsides when treatment is discontinued. The symptoms of hypercalcaemia include polyuria, constipation, muscle weakness, confusion and coma.

Excessive prolonged use of topical corticosteroids may suppress the HPA, resulting in secondary adrenal insufficiency, which is usually reversible. In such cases symptomatic treatment is indicated.

In case of chronic toxicity the topical corticosteroid treatment must be withdrawn gradually.

In a reported case of misuse, one patient with extensive erythrodermic psoriasis treated for 5 months with 240 g of Daivobet[®] ointment per week (maximum recommended dose is 100 g per week) and received a corresponding daily dose of approximately 34 g, which is above the maximum dose of 15 g daily. The patient developed Cushing's syndrome during treatment and then pustular psoriasis after abruptly stopping treatment.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsoriatics. Other antipsoriatics for topical use, calcipotriol, combinations. ATC Code: D05AX52

Mechanism of action

Daivobet[®] gel combines the pharmacological effects of calcipotriol hydrate as a synthetic vitamin D3 analogue and betamethasone dipropionate as a synthetic corticosteroid.

Calcipotriol is a non-steroidal antipsoriatic agent, derived from vitamin D. Calcipotriol exhibits a vitamin D-like effect by competing for the 1, 25(OH)₂D₃ receptor. Calcipotriol is as potent as 1,25(OH)₂D₃, the naturally occurring active form of vitamin D, in regulating cell proliferation and cell

differentiation, but much less active than 1,25(OH)₂D₃ in its effect on calcium metabolism. Calcipotriol induces differentiation and suppresses proliferation (without any evidence of a cytotoxic effect) of keratinocytes, thus reversing the abnormal keratinocyte changes in psoriasis. The therapeutic goal envisaged with calcipotriol is thus a normalisation of epidermal growth.

In vitro vitamin D has a normalising effect on human keratinocytes, arresting growth and enhancing differentiation in inappropriately proliferating cells and stimulating normal growth in quiescent cells. The underlying antiproliferative mechanism of vitamin D in keratinocytes is incompletely understood but is known to involve the induction of the growth inhibitory factor transforming growth factor- β and of cyclin-dependent kinase inhibitors, with subsequent growth arrest in the G1 phase of the cell cycle plus down-regulation of the two proliferation factors early growth response-1 and polo-like kinase-2.

In addition, vitamin D has an immunomodulatory effect, suppressing activation and differentiation of Th17/Th1 cells while inducing a Th2/Treg response.

Betamethasone dipropionate is a potent topically-active corticosteroid producing prompt, marked and prolonged anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties, without curing the underlying condition. These effects can be enhanced under occlusive conditions due to increased penetration of stratum corneum (by approximately a factor of 10).

In psoriasis vulgaris, corticosteroids suppress the immune system, particularly proinflammatory cytokines and chemokines, thereby inhibiting T-cell activation. At the molecular level, corticosteroids act via the intracellular glucocorticoid receptor and the anti-inflammatory function is due to transrepression of pro-inflammatory transcription factors such as nuclear factor κ B, activator protein-1, and interferon regulatory factor-3.

In combination, calcipotriol monohydrate and betamethasone dipropionate promote greater anti-inflammatory and anti-proliferative effects than either component alone.

Pharmacodynamic effects

Adrenal response to ACTH was determined by measuring serum cortisol levels in patients with both extensive scalp and body psoriasis vulgaris, using up to 106 g per week combined Daivobet® gel and Daivobet® ointment. A borderline decrease in cortisol response at 30 minutes post ACTH challenge was seen in 5 of 32 patients (15.6 %) after 4 weeks of treatment and in 2 of 11 patients (18.2 %) who continued treatment until 8 weeks. In all cases, the serum cortisol levels were normal at 60 minutes post ACTH challenge. There was no evidence of change of calcium metabolism observed in these patients. With regard to HPA suppression, therefore, this trial shows some evidence that very high doses of Daivobet® gel and ointment may have a weak effect on the HPA axis.

Clinical efficacy and safety

Efficacy

The efficacy of once daily use of Daivobet® gel was investigated in two randomised, double-blind, 8-week clinical studies including a total of more than 2,900 patients with scalp psoriasis of at least mild severity according to the Investigator's Global Assessment of disease severity (IGA). Comparators were betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and (in one of the studies) the gel vehicle alone, all used once daily. Results for the primary response criterion (absent or very mild disease according to the IGA at week 8) showed that Daivobet® gel was statistically significantly more effective than the comparators. Results for speed of onset based on similar data at week 2 also showed Daivobet® gel to be statistically significantly more effective than the comparators.

Table 2- Efficacy of once daily use of Daivobet® gel in adults compared to the individual active components in the same gel formulation.

% of patients with absent or very mild disease	Daivobet® gel (n=1, 108)	Betamethasone dipropionate (n=1, 118)	Calcipotriol (n=558)	Gel vehicle (n=136)
week 2	53.2%	42.8% ¹	17.2% ¹	11.8% ¹
week 8	69.8%	62.5% ¹	40.1% ¹	22.8% ¹

¹ Statistically significantly less effective than Daivobet® gel (P<0.001)

The efficacy of once daily use of Daivobet® gel on non-scalp regions of the body was investigated in a randomised, double-blind, 8-week clinical study including 296 patients with psoriasis vulgaris of mild or moderate severity according to the IGA. Comparators were betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle alone, all used once daily. Primary response criteria were controlled disease according to the IGA at week 4 and week 8. Controlled disease was defined as 'clear' or 'minimal disease' for patients with moderate disease at baseline or 'clear' for patients with mild disease at baseline. The percentage change in Psoriasis Severity and Area Index (PASI) from baseline to week 4 and week 8 were secondary response criteria.

Table 3- Efficacy of once daily use of Daivobet® gel in adults compared to the individual active components in the same gel formulation.

% of patients with controlled disease	Daivobet® gel (n=126)	Betamethasone dipropionate (n=68)	Calcipotriol (n=67)	Gel vehicle (n=35)
week 4	20.6%	10.3% ¹	4.5% ¹	2.9% ¹
week 8	31.7%	19.1% ¹	13.4% ¹	0.0% ¹

¹ Statistically significantly less effective than Daivobet® gel (P<0.05)

Table 4- Efficacy of once daily use of Daivobet® gel in adults compared to the individual active components in the same gel formulation

Mean % reduction in PASI (SD)	Daivobet® gel (n=126)	Betamethasone dipropionate (n=68)	Calcipotriol (n=67)	Gel vehicle (n=35)
week 4	50.2% (32.7)	40.8% (33.1) ¹	32.1% (23.6) ¹	17.0% (31.8) ¹
week 8	58.8% (32.4)	51.8% (35.0) ¹	40.8% (31.9) ¹	11.1% (29.5) ¹

¹ Statistically significantly less effective than Daivobet® gel (P<0.05)

Another randomised, investigator-blinded clinical study including 312 patients with scalp psoriasis of at least moderate severity according to the IGA investigated use of Daivobet® gel once daily compared with Daivonex® Scalp solution twice daily for up to 8 weeks. Results for the primary response criterion (clear or minimal disease according to the IGA at week 8) showed that Daivobet® gel was statistically significantly more effective than Daivonex® Scalp solution.

Table 5 – Efficacy of Daivobet® gel in adults compared to Daivonex® Scalp Solution

% of patients with clear or minimal disease	Daivobet® gel (n=126)	Daivonex® Scalp solution (n=105)

week 8	68.6%	31.4% ¹
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¹ Statistically significantly less effective than Daivobet® gel (P<0.001)

Safety

A randomised, double-blind long-term clinical study including 869 patients with scalp psoriasis of at least moderate severity (according to the IGA) investigated the use of Daivobet® gel compared with calcipotriol in the gel vehicle. Both treatments were applied once daily, intermittently as required, for up to 52 weeks.

Adverse events possibly related to long-term use of corticosteroids on the scalp, were identified by an independent, blinded panel of dermatologists. There was no difference in the percentages of patients experiencing such adverse events between the treatment groups (2.6% in the Daivobet® gel group and 3.0% in the calcipotriol group; P=0.73). No cases of skin atrophy were reported.

Adrenal response to ACTH was determined by measuring serum cortisol levels in patients with both extensive scalp and body psoriasis, using up to 106 g per week combined Daivobet® gel and Daivobet® ointment. A borderline decrease in cortisol response at 30 minutes post ACTH challenge was seen in 5 of 32 patients (15.6%) after 4 weeks of treatment and in 2 of 11 patients (18.2%) who continued treatment until 8 weeks. In all cases, the serum cortisol levels were normal at 60 minutes post ACTH challenge. There was no evidence of change of calcium metabolism observed in these patients.

5.2 Pharmacokinetic properties

Absorption

The systemic exposure to calcipotriol and betamethasone dipropionate from topically applied Daivobet® gel is 13 – 45% less than Daivobet® ointment in rats and minipigs. Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Daivobet® ointment formulation is less than 1% of the dose (2.5 g) when applied to normal skin (625 cm²) for 12 hours. Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids.

Calcipotriol and betamethasone dipropionate were below the lower limit of quantification in all blood samples of 34 patients treated for 4 or 8 weeks with both Daivobet® gel and Daivobet® ointment for extensive psoriasis involving the body and scalp. One metabolite of calcipotriol and one metabolite of betamethasone dipropionate were quantifiable in some of the patients.

Distribution

In rats, tissue distribution studies with radiolabelled calcipotriol and betamethasone dipropionate, respectively, showed that the kidney and liver had the highest level of radioactivity.

Metabolism

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised.

Excretion

The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice).

5.3 Preclinical safety data

Carcinogenicity

A dermal carcinogenicity study with calcipotriol in mice showed no indications of increased carcinogenic risks. Calcipotriol solution was applied topically for up to 24 months at doses of 3, 10 and 30 µg/kg/day (corresponding to 9, 30 and 90 µg/m²/day). The high-dose was considered to be the Maximum Tolerated Dose for dermal treatment of mice with calcipotriol. Survival was decreased at 10 and 30 µg/kg/day, particularly in the males. The reduced survival was associated with an increased incidence of renal lesions. This is an expected effect of treatment with high doses of calcipotriol or other vitamin D analogues. There were no dermal effects and no dermal or systemic carcinogenicity.

In a study where albino hairless mice were repeatedly exposed to both ultraviolet (UV) radiation and topically applied calcipotriol for 40 weeks at the same dose levels as in the dermal calcipotriol carcinogenicity study, a reduction in the time required for UV radiation to induce the formation of skin tumours was observed (statistically significant in males only), suggesting that calcipotriol may enhance the effect of UV radiation to induce skin tumours. In a supplementary study, mice of the same strain were treated repeatedly with either calcipotriol solution or calcipotriol/betamethasone gel, followed by irradiation with UVR and measurement of recognised cellular indicators of skin photocarcinogenicity. This study showed a similar enhancing effect of calcipotriol alone on the photobiological response of the skin. Calcipotriol/betamethasone gel increased cellular proliferation but did not increase other markers indicative of enhancement of photocarcinogenesis. The clinical relevance of these findings is unknown.

No carcinogenicity or photocarcinogenicity studies have been performed with betamethasone dipropionate.

Genotoxicity

Calcipotriol was not genotoxic in assays for gene mutations (Ames test and mouse lymphoma TK locus assay) or chromosomal damage (human lymphocyte chromosomal aberration or mouse micronucleus test). Betamethasone dipropionate was not genotoxic in the Ames mutagenicity assay, the mouse lymphoma TK locus assay or in the rat micronucleus test.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid paraffin
Polyoxypropylene stearyl ether
Hydrogenated castor oil*
Butylated hydroxytoluene (E321)
Alpha tocopherol

*Hydrogenated castor oil contains peanut products

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf life: 3 years from date of manufacture
Use within 6 months of opening.

Do not use beyond the expiry date on the package.

Do not use if the pack shows signs of damage or tampering.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate.

Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Registered pack sizes: 15, 30, 60 and 2 x 60 g.
Not all pack sizes may be marketed.

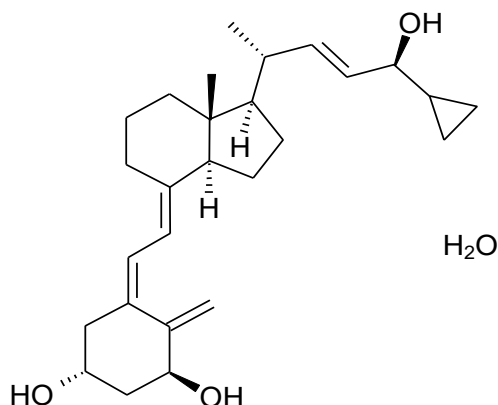
The bottle consists of a high-density polyethylene multi-dose bottle with a low-density polyethylene nozzle and a high-density polyethylene screw cap. The bottle is placed in a carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

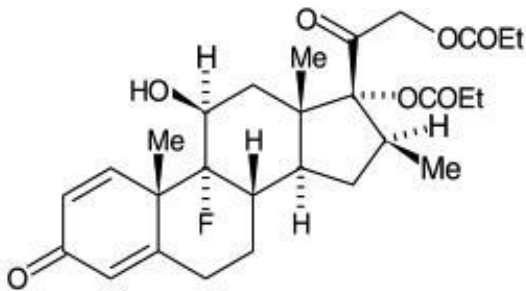
Calcipotriol (as monohydrate)



Calcipotriol is (1S, 3R, 5Z, 7E, 22E, 24S) -24-Cyclopropyl-9, 10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol (CAS no.: 112828-00-9). The molecular weight of calcipotriol hydrate is 430.6.

Calcipotriol is a white or almost white crystalline substance. It is freely soluble in ethanol, soluble in chloroform and propylene glycol, particularly insoluble in liquid paraffin. Solubility in water is 0.6 µg/mL and the melting point is 166 to 168°C. Calcipotriol is a vitamin D derivative and behaves in a similar manner to vitamin D, forming a reversible temperature-dependent equilibrium between calcipotriol and pre-calcipotriol.

Betamethasone dipropionate



Betamethasone dipropionate is 9-fluoro-11 β , 17, 21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate (CAS no.: 5593-20-4). The empirical formula is C₂₈H₃₇FO₇. The molecular weight of betamethasone dipropionate is 504.6.

Betamethasone dipropionate is a white or almost white, crystalline powder, practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in alcohol.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

LEO Pharma Ltd
Auckland
New Zealand

Toll Free No. 0800 497 456

9 DATE OF FIRST APPROVAL

14 July 2011

10 DATE OF REVISION OF THE TEXT

15 May 2023

Summary Table of Changes

Section changed	Summary of new information
4.4	Updated HPA axis suppression under Section 4.4
4.8	Updated HPA axis suppression under Section 4.8

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