

# NEW ZEALAND DATA SHEET

## 1 DAIVOBET® 50/500 OINTMENT

Daivobet® 50/500 calcipotriol 50 microgram/g and betamethasone 500 microgram/g (as dipropionate) ointment

## 2 QUANTITATIVE AND QUALITATIVE COMPOSITION

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

## 3 PHARMACEUTICAL FORM

Ointment

Off-white to yellow ointment.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Daivobet® ointment is indicated for the once daily topical treatment of plaque-type psoriasis vulgaris amenable to topical therapy in adult patients 18 years and older.

### 4.2 Dosage and method of administration

Daivobet® ointment is indicated FOR TOPICAL USE ONLY and NOT FOR OPHTHALMIC USE.

All psoriasis-affected areas treated with Daivobet® should be, where possible, protected from direct sunlight and UV-light with items of clothing. Topical calcipotriol should only be used with UV radiation if the physician and patient consider that the potential benefits outweigh the potential risks. The potential phototoxic effects of Daivobet® over long term exposure have not been fully investigated.

#### Adults:

Daivobet® ointment should be applied topically to the affected area once daily. The maximum daily dose should not exceed 15 grams.

**The maximum recommended weekly dose of Daivobet® ointment is 100 g/week.**

The treated area should not be more than 30% of the body surface.

**The recommended treatment period of Daivobet® ointment is 4 weeks.** At the completion of the treatment period, repeated treatment with Daivobet® ointment can be initiated under medical supervision. There is no clinical experience with Daivobet® Ointment beyond 52 weeks.

#### Children:

Daivobet® ointment is not recommended for use in children and adolescents below the age of 18 years.

### 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 (see section 4.4).

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, wounds, perianal and genital pruritus (see section 4.4).

Erythrodermic, exfoliative and pustular psoriasis.

Patients with severe renal insufficiency or severe hepatic disorders.

NOT FOR OPHTHALMIC USE.

#### **4.4 Special warnings and special precautions for use**

FOR EXTERNAL USE ONLY

##### Effects 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
- 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 vulgaris 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.

Elevated systemic absorption of calcipotriol could result in hypercalcaemia in some patients (see section 4.8).

##### 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

In view of the risk of hypercalcaemia secondary to excessive absorption of calcipotriol when there is extensive skin involvement, Daivobet® ointment should not be used on more than 30% of the body surface area.

The risk of hypercalcaemia is minimal when the recommendations relevant to calcipotriol are observed. In adults, the maximum daily dose of 15 g or the maximum weekly dose of 100g ointment should not be exceeded.

Treatment with Daivobet® ointment in adults in the recommended amounts up to 100 g per week does

not generally result in changes in laboratory values. **Serum calcium and renal function should be monitored at 3 monthly intervals during periods of usage of topical calcipotriol, including that in Daivobet® ointment.** If the serum calcium level is elevated, treatment with Daivobet® ointment should be discontinued and the condition should be treated appropriately. The levels of serum calcium should be measured once weekly until the serum calcium levels return to normal values.

#### Local adverse reactions

As Daivobet® contains potent corticosteroid (classified as WHO group III steroid), 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® ointment is not recommended for use on the face since it may give rise to itching and erythema of the facial skin. Daivobet® ointment is not recommended for use on genitals.

The patient must be instructed on correct use of the product to avoid application and/or accidental transfer to the scalp, face, mouth or eyes. **Patients should be instructed to wash their hands after using Daivobet® ointment to avoid inadvertent transfer of ointment to the face from other body areas.**

#### Concomitant skin infections

If lesions become secondarily infected, they should be treated with antimicrobial therapy. However, if infection worsens, treatment with topical corticosteroids should be stopped (see section 4.3)

#### Other

When treating psoriasis with topical corticosteroids there may be a risk of generalised pustular psoriasis.

#### Concurrent treatment and UV exposure

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® ointment have not been extensively studied in the clinic.

Treated skin areas should be protected from sunlight and UV light (using physical coverings 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.

#### Long-term use

With long-term use there is an increased risk of local and systemic corticosteroid adverse reactions. The treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroids (see section 4.8).

#### Discontinuation of treatment

There may be a risk of generalised pustular psoriasis or rebound effects when discontinuing a long-term treatment with corticosteroids. Medical supervision should therefore continue in the post-treatment period.

#### Unevaluated use

There is no experience with the use of Daivobet® ointment on the scalp or in guttate psoriasis.

#### Adverse reactions to excipients

Daivobet® ointment contains butylated hydroxytoluene (E321) (an excipient within the excipient polyoxypropylene stearyl ether), which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

#### Use in Children

Daivobet® ointment is not recommended for use in children and adolescents below 18 years of age as

the safety and effectiveness of Daivobet® ointment in this population has not been established.

#### Renal Impairment

Safety has not been established in patients with renal impairment.

#### Hepatic Impairment

Safety has not been established in patients with hepatic impairment.

#### Effects on Laboratory Tests

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

### **4.5 Interaction with other medicinal products and other forms of interactions**

There is no experience with concurrent use of Daivobet® ointment and other anti-psoriatic products applied locally or systemically or with phototherapy.

Daivobet® ointment should not be used concurrently with calcium or vitamin D supplements, or with drugs, which enhance the systemic availability of calcium.

No interactions trials have been performed with Daivobet® ointment.

### **4.6 Fertility, pregnancy and lactation**

#### Use in pregnancy (Category B1):

There are no adequate data from the use of Daivobet® ointment in pregnant women. Daivobet® ointment 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). Long-term oral administration of corticosteroids in rats has been shown to prolong gestation and make labour more difficult and prolonged. A reduction in postnatal survival and growth was observed in the offspring of these rats.

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.

#### 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.

#### Use in Lactation

Betamethasone is excreted into breast milk. It is unknown if topical application of Daivobet® ointment 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® ointment to breastfeeding women. Application of Daivobet® ointment to the breast area should be avoided when breastfeeding. Daivobet® ointment should only be used during lactation if the potential benefits clearly outweigh the potential risks.

NOTE: In order to avoid possible direct ingestion by infants, Daivobet® ointment should not be applied to the chest area of breastfeeding women. After applying Daivobet® ointment to her skin, mothers should wash their hands thoroughly prior to handling her infant child.

### **4.7 Effects on ability to drive and use machines**

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

## 4.8 Undesirable effects

### Clinical Trials

Adverse events reported in more than 1% of subjects enrolled in the early clinical trials with Daivobet® ointment (in total 912 patients exposed to twice daily applications and 1286 patients exposed to once daily applications) are listed in Table 1.

Table 1. Adverse events recorded during clinical trials with a frequency of greater than 1%.

Adverse Event	MCB 0003 INT n = 486	MCB 9905 INT n = 151
Pruritus NOS	17	4
Rash scaly	-	4
Back pain	-	2
Blood calcium increase	-	2
Ecchymosis	-	2
Headache NOS	16	2
Nasopharyngitis	11	4
Psoriasis	-	2
Upper respiratory tract infection NOS	6	-

A safety study in 634 psoriasis patients has investigated repeated courses of Daivobet® ointment used once daily as required, either alone or alternating on a four week basis with Daivonex® ointment, for up to 52 weeks, compared with Daivonex® ointment used alone for 48 weeks after an initial 4 week course of Daivobet® ointment. Adverse drug reactions were reported by 21.7% of the patients in the Daivobet® ointment group, 29.6% in the Daivobet® ointment/ Daivonex® ointment alternating group and 37.9% in the Daivonex® ointment group. The adverse drug reactions that were reported by more than 2% of the patients in the Daivobet® ointment group were pruritus (5.8%) and psoriasis (5.3%). Adverse effects of concern, possibly related to long-term corticosteroid use were reported by 4.8% of the patients in the Daivobet® ointment group, 2.8% in the Daivobet® ointment/Daivonex® ointment alternating group and 2.9% in the Daivonex® ointment group.

In total, the clinical trial programme for Daivobet® ointment has so far included more than 2 500 patients, and has shown that approximately 10% of patients can be expected to experience a non-serious adverse effect (see Post Marketing Use section for more details).

### Post-Marketing Use

The estimation of the frequency of adverse reactions is based on data from clinical trials and post-market (spontaneous) reporting.

The most frequently reported adverse reactions during treatment are various skin reactions including pruritus and skin exfoliation.

Pustular psoriasis and hypercalcaemia have been reported rarely.

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 data from clinical trials and post-market (spontaneous) reporting

<b>Infections and infestations</b>	
Uncommon ≥1/1,000 and <1/100	Skin infection* Folliculitis
Rare ≥1/10,000 and <1/1,000	Furuncle
<b>Immune system disorders</b>	
Rare ≥1/10,000 and <1/1,000	Hypersensitivity
<b>Metabolism and nutrition disorders</b>	
Rare ≥1/10,000 and <1/1,000	Hypercalcaemia
<b>Skin and subcutaneous tissue disorders</b>	
Common ≥1/100 and <1/10	Skin exfoliation Pruritus
Uncommon ≥1/1,000 and <1/100	Skin atrophy Exacerbation of psoriasis Dermatitis Erythema Rash** Purpura or ecchymosis Skin burning sensation Skin irritation
Rare ≥1/10,000 and <1/1,000	Pustular psoriasis Skin striae Photosensitivity reaction Acne Dry skin
<b>General disorders and administration site conditions</b>	
Uncommon ≥1/1,000 and <1/100	Application site pigmentation changes Application site pain***
Rare ≥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 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 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 (see section 4.4).

### *Betamethasone (as dipropionate):*

This product contains a potent corticosteroid.

Local reactions can occur after topical 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.

Systemic reactions due to topical use of 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, impaired glycaemic control of diabetes mellitus (e.g. hyperglycaemia/glycosuria), 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. In such cases, the monitoring of serum calcium levels once weekly until the serum calcium returns to normal levels is recommended.

Excessive prolonged use of topical corticosteroids may suppress the hypothalamic pituitary adrenal axis (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 was 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 recommended 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: DO5AX52.

#### Mechanism of action

Daivobet® ointment combines the pharmacological effects of calcipotriol (as monohydrate) 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  $1,25(\text{OH})_2\text{D}_3$  receptor. Calcipotriol is as potent as  $1,25(\text{OH})_2\text{D}_3$ , the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than  $1,25(\text{OH})_2\text{D}_3$  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- $\beta$  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  $\kappa$  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<sup>®</sup> gel and Daivobet<sup>®</sup> 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<sup>®</sup> gel and ointment may have a weak effect on the HPA axis.

#### Clinical Trials

The pivotal clinical trials with Daivobet<sup>®</sup> ointment undertaken in adults are summarised below.

#### **Topical treatment of psoriasis in adults using combination of calcipotriol 50 microgram/g plus betamethasone (as dipropionate) 500 microgram/g ointment regimen.**

Two double-blind, multicentre, randomised, vehicle-controlled studies assessed the efficacy and safety of the combination calcipotriol 50 microgram/g plus betamethasone (as dipropionate) 500 microgram/g ointment once daily vs calcipotriol ointment 50 microgram/g or betamethasone (as dipropionate) 500 microgram/g ointment alone once daily in patients with psoriasis. The study duration was 4 weeks. The primary efficacy endpoint was the percentage reduction of the Psoriasis Area & Severity Index (PASI)

score. In both studies (MCB 0003 INT, MCB 9905 INT) there was a statistically significant difference ( $p < 0.001$ ) favouring combination group administered once daily. There was no significant difference ( $p = 0.052$ ) when combination therapy was used once daily compared to twice daily after 4 weeks of treatment (MCB 9905 INT).

Table 3: Administration of combination calcipotriol 50 microgram/g plus betamethasone (as dipropionate) 500 microgram/g ointment in adults

Study	MCB 0003 INT	MCB 9905 INT
Treatment administered:	Combination OD: n = 490 Calcipotriol OD: n = 480 Betamethasone OD: n = 476 Vehicle OD: n = 157	Combination OD: n = 150 Combination TD: n = 234 Calcipotriol TD: n = 227 Vehicle TD: n = 207
Results: Percentage reduction in PASI (Mean $\pm$ SD)	Combination OD: $-71.3 \pm 25.7$ Calcipotriol OD: $-46.1 \pm 30.9$ Betamethasone OD: $-57.2 \pm 29.8$ Vehicle OD: $-22.7 \pm 33.4$	Combination OD: $-68.6 \pm 23.6$ Combination TD: $-73.8 \pm 21.0$ Calcipotriol TD: $-58.8 \pm 28.6$ Vehicle TD: $-26.6 \pm 31.3$
Statistical analysis of percentage reduction (mean (95% CI))	Combination OD vs calcipotriol OD: $-25.3$ ( $-28.7$ to $-21.9$ )* Combination OD vs Betamethasone OD: $-14.2$ ( $-17.6$ to $-10.8$ )* Combination OD vs Vehicle OD: $-48.3$ ( $-53.2$ to $-43.4$ )*  * $p < 0.001$	Combination OD vs Combination TD: $-5.4$ ( $-10.8$ to $0.1$ )# Combination OD vs calcipotriol TD: $-9.8$ ( $-15.2$ to $-4.3$ )* Combination OD vs Vehicle TD: $-42.0$ ( $-47.5$ to $-36.4$ )*  * $p < 0.001$ # $p = 0.052$

OD = Once daily:  
TD = Twice daily

## 5.2 Pharmacokinetic properties

### Absorption

Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Daivobet<sup>®</sup> ointment is less than 1% (95% CI: 0.1% to 0.3%) of the dose (2.5 g ointment) when applied to normal skin (625 cm<sup>2</sup>) for 12 hours. When the skin was damaged absorption was increased (~24% of applied dose). Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids. Approximately 64% of the absorbed dose is protein bound. Plasma elimination half-life after intravenous administration is 5 to 6 hours. Elimination after dermal application is in order of days due to the formation of a depot in the skin.

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<sup>®</sup> gel and Daivobet<sup>®</sup> 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 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 and mutagenicity

The carcinogenic or mutagenic potential of topical corticosteroids has not been investigated in animal studies.

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/m<sup>2</sup>/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 obstructive uropathy, most probably caused by treatment-related changes in the urinary composition. 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 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. The clinical relevance of these findings is unknown.

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

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).

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Liquid paraffin  
Polyoxypropylene stearyl ether (which contains butylated hydroxytoluene)  
Alpha-tocopherol  
White soft paraffin

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

2 years.  
After first opening of container: 1 year.

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**

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Store below 25°C.

## 6.5 Nature and contents of container

Aluminium tube with polyethylene screw cap.

Pack sizes: 3 g (sample), 15 g, 30 g, 60 g, 100 g, 120 g

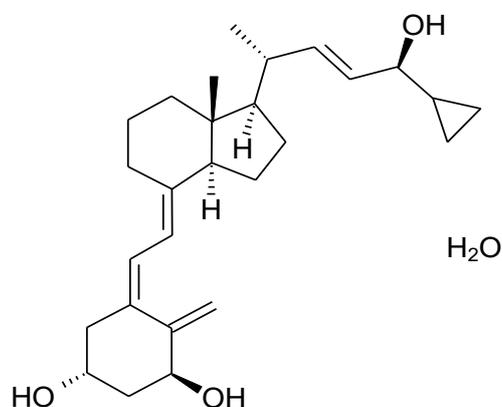
Marketed pack size: 30 g

## 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

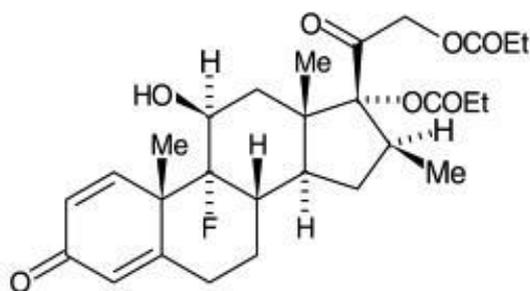
### *Calcipotriol (as monohydrate)*



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 – 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-11β, 17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20 -dione 17,21-dipropionate (CAS No. 5593-20-4). The empirical formula is C<sub>28</sub>H<sub>37</sub>FO<sub>7</sub>. 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

21 April 2005

## 10 DATE OF REVISION OF 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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