

## PRODUCT INFORMATION

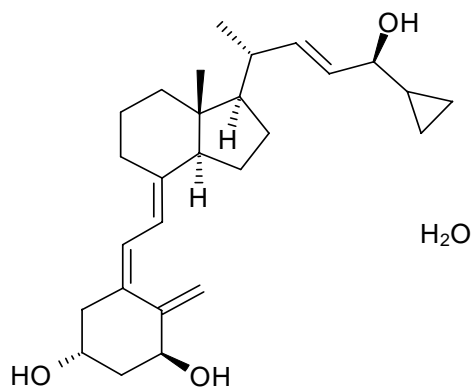
### Daivobet® 50/500 Ointment

Calcipotriol / Betamethasone (as dipropionate)

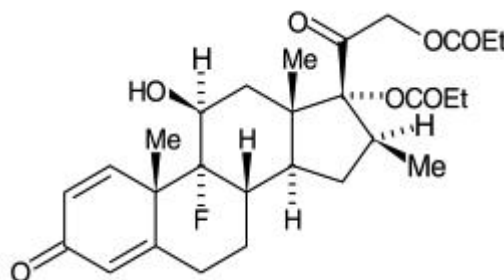
AUST R 98773

#### NAME OF THE MEDICINE:

Daivobet® 50/500 ointment



Calcipotriol



Betamethasone dipropionate

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.

Betamethasone dipropionate is 9-fluoro-11 $\beta$ , 17, 21-trihydroxy-16 $\beta$ -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.

#### DESCRIPTION

Daivobet® ointment is off-white to yellow and contains 50 microgram/g calcipotriol and 500 microgram/g betamethasone (as dipropionate).

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  $\mu$ g/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 is a white or almost white, crystalline powder, practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in alcohol.

Daivobet® ointment also contains paraffin-liquid, PPG-15 stearyl ether, alpha-tocopherol, and paraffin (soft, white).

## PHARMACOLOGY

### Pharmacodynamics:

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.

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). The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.

### Pharmacokinetics:

Clinical studies with radiolabelled ointment demonstrated less than 1% (95% CI: -0.1% to 0.3%) of calcipotriol and betamethasone from the applied dose (2.5 g) was systemically absorbed when applied to normal skin ( $625 \text{ cm}^2$ ) for 12 hours. When the skin is 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.

## 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 one 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 1: 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 ± SD)	Combination OD: -71.3 ± 25.7 Calcipotriol OD: -46.1 ± 30.9 Betamethasone OD: -57.2 ± 29.8 Vehicle OD: -22.7 ± 33.4	Combination OD: -68.6 ± 23.6 Combination TD: -73.8 ± 21.0 calcipotriol TD: -58.8 ± 28.6 Vehicle TD: -26.6 ± 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

## INDICATIONS

Daivobet<sup>®</sup> ointment is indicated for the once daily topical treatment of plaque-type psoriasis vulgaris amenable to topical therapy.

## CONTRAINDICATIONS

- i Allergic sensitisation to any constituent of Daivobet<sup>®</sup> ointment.
- ii Patients with known disorders of calcium metabolism.
- iii Due to the corticosteroid content: viral lesions of the skin (eg 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, ulceration, wounds, perianal and genital pruritus.
- iv Erythrodermic, exfoliative and pustular psoriasis.
- v Patients with severe renal insufficiency or severe hepatic disorders.
- vi NOT FOR OPHTHALMIC USE.

## PRECAUTIONS

### FOR EXTERNAL USE ONLY

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. Daivobet<sup>®</sup> ointment is not recommended for use on the face since it may give rise to itching and erythema of the facial skin. **Treatment of more than 30% of the body surface should be avoided. Patients should be instructed to wash their hands after using Daivobet<sup>®</sup> ointment, to avoid inadvertent transfer of ointment to the face from other body areas.**

In view of the risk of hypercalcaemia secondary to excessive absorption of calcipotriol when there is extensive skin involvement, Daivobet<sup>®</sup> 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 dosage of 100 g ointment per week should not be exceeded.

Treatment with Daivobet<sup>®</sup> 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<sup>®</sup> ointment.** If the serum calcium level is elevated, treatment with Daivobet<sup>®</sup> 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.

As Daivobet<sup>®</sup> ointment contains a potent corticosteroid (classified as WHO group III steroid), concurrent treatment with other steroids should be avoided. Adverse effects found in connection with systemic corticosteroid treatment, such as adrenocortical suppression or impact on the metabolic control of diabetes mellitus, may occur also during topical corticosteroid treatment due to its systemic absorption.

Application of Daivobet<sup>®</sup> ointment to large areas of damaged skin, under occlusive dressings, to mucous membranes, or in skin folds should be avoided as these conditions increase the systemic absorption of both corticosteroids and calcipotriol. Elevated systemic absorption of calcipotriol could, as previously mentioned, result in hypercalcaemia in some patients.

Skin of the face and genitals are very sensitive to corticosteroids. Long term treatment of these parts of the body should be avoided. These areas should only be treated with the weaker corticosteroids.

If lesions become secondarily infected, they should be treated with antimicrobial therapy. However, if infection worsens, treatment with topical corticosteroids should be withdrawn.

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

There is no experience of the use of Daivobet<sup>®</sup> ointment on the scalp.

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<sup>®</sup> ointment 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.

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

**The recommended treatment period of Daivobet<sup>®</sup> ointment is 4 weeks under medical supervision, for up to 52 weeks. There is clinical trial experience with intermittent 4 weekly cycles of Daivobet<sup>®</sup> ointment and calcipotriol alone used between treatment cycles (See Adverse Effects and Dosage and Administration).**

With long-term use there is an increased risk of local and systemic corticosteroid adverse effects. Excessive prolonged use of topical corticosteroids may suppress the hypothalamic pituitary adrenal axis (HPA). The treatment should be discontinued in case of adverse effects related to long-term use of corticosteroids as described in the Adverse Effects section.

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

## **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 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. 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).

## **Use in Pregnancy (Category B1):**

There are no adequate data from the use of Daivobet<sup>®</sup> ointment in pregnant women. Daivobet<sup>®</sup> 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 mg/kg/day and in rabbits (reduced skeletal ossification) at oral doses of 36 mg/kg/day. The relevance of these findings for humans is unknown.

## **Impairment of 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 fertility.

## **Use in Lactation:**

Betamethasone is excreted into breast milk. It is unknown if topical application of Daivobet<sup>®</sup> 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 breast-feeding women. Application of Daivobet® ointment to the breast area should be avoided. 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 breast feeding women. After applying Daivobet® ointment to her skin, mothers should wash their hands thoroughly prior to handling her infant child.

#### **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.

#### **Interactions with other drugs:**

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 that enhance the systemic availability of calcium.

No other drug interactions are known.

#### **Effects on Laboratory Tests**

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

## **ADVERSE EFFECTS**

### **Clinical Trials**

Adverse events reported in more than 1% of subjects enrolled in early ~~the~~ 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 2.

Table 2. Adverse events recorded during clinical trials with a frequency of greater than 1%.

<b>Adverse Event</b>	<b>MCB 0003 INT n = 486</b>	<b>MCB 9905 INT n = 151</b>
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 patients with at least moderate psoriasis has investigated repeated courses of Daivobet<sup>®</sup> ointment used once daily as required, either alone or alternating on a four week basis with Daivonex<sup>®</sup> ointment, for up to 52 weeks, compared with Daivonex<sup>®</sup> ointment used alone for 48 weeks after an initial 4 week course of Daivobet<sup>®</sup> ointment. The number of patients who were exposed to intermittent treatment for 52 weeks was 112 in the Daivobet<sup>®</sup> ointment group, 117 in the Daivobet<sup>®</sup> ointment/Daivonex<sup>®</sup> ointment alternating group and 96 in the Daivonex<sup>®</sup> ointment group. Adverse drug reactions were reported by 21.7% of the patients in the Daivobet<sup>®</sup> ointment group, 29.6% in the Daivobet<sup>®</sup> ointment/ Daivonex<sup>®</sup> ointment alternating group and 37.9% in the Daivonex<sup>®</sup> ointment group. Adverse drug reactions reported in 1% or more of the patients are listed in Table 3:

Table 3. Adverse drug reactions reported in the long-term clinical trial with a frequency of 1% or greater

Preferred term	Daivobet <sup>®</sup> ointment 52 weeks		Daivobet <sup>®</sup> ointment/Daivonex <sup>®</sup> ointment alternating 4/4 weeks		Daivobet <sup>®</sup> ointment 4 wks/ Daivonex <sup>®</sup> ointment 48 wks	
	N=207 n	%	N=213 n	%	N=206 n	%
Application site burning	0	0.0	1	0.5	4	1.9
Application site pruritus	0	0.0	3	1.4	1	0.5
Burning sensation	3	1.4	8	3.8	10	4.9
Eczema	0	0.0	3	1.4	2	1.0
Erythema	2	1.0	4	1.9	7	3.4
Folliculitis	4	1.9	3	1.4	3	1.5
Pain of skin	1	0.5	2	0.9	3	1.5
Pruritus	12	5.8	22	10.3	27	13.1
Psoriasis	11	5.3	8	3.8	14	6.8
Skin atrophy	4	1.9	1	0.5	2	1.0
Skin burning sensation	1	0.5	3	1.4	2	1.0
Skin depigmentation	3	1.4	0	0.0	0	0.0
Skin hyperpigmentation	1	0.5	0	0.0	3	1.5
Skin irritation	0	0.0	6	2.8	7	3.4

Adverse effects of concern, possibly related to long-term corticosteroid use were reported by 4.8% of the patients in the Daivobet<sup>®</sup> ointment group, 2.8% in the Daivobet<sup>®</sup> ointment/Daivonex<sup>®</sup> ointment alternating group and 2.9% in the Daivonex<sup>®</sup> ointment group.

The effects of Daivobet<sup>®</sup> ointment on calcium metabolism and HPA function with long term use in psoriasis patients were not adequately studied.

In total, the clinical trial programme for Daivobet<sup>®</sup> 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

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

Based on the above frequency definition, data from clinical trials and post market use show that the common adverse events, in the order of most frequently reported, are pruritus, rash and burning sensation of the skin. Additional uncommon adverse events, in the order of most frequently reported include skin pain or irritation, dermatitis, erythema, exacerbation of psoriasis, folliculitis and application site pigmentation changes. Pustular psoriasis and photosensitivity are rare undesirable effects.

Single cases of serious and life threatening undesirable effects including adrenal suppression and pustular psoriasis have been reported after prolonged use (2 years or more).

Adverse events observed for calcipotriol and betamethasone are provided below.

#### *Calcipotriol:*

Potential adverse events include application site reactions, pruritis, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, and aggravation of psoriasis, transient photosensitivity, transient changes in skin pigmentation and allergic and hypersensitivity reactions including very rare cases of angioedema and facial oedema. After topical use, systemic effects, causing hypercalcaemia or hypercalciuria may appear very rarely.

#### *Betamethasone:*

This product contains a potent corticosteroid.

Local reactions can occur after topical corticosteroid use, especially during prolonged application, including skin atrophy, telangiectasia, striae, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation and colloid milia. When used for the treatment of psoriasis, there may be the risk of generalised pustular psoriasis. There may be a risk of rebound when discontinuing long term treatment with corticosteroids.

Systemic effects due to corticosteroids are rare, in adults, however, they can be severe. HPA suppression, hypercalcaemia, cataract, infections and increase in intra-ocular pressure can occur, especially after long term treatment. Systemic effects occur more frequently when applied under occlusion, when applied on large areas or during long treatment.

## **DOSAGE AND ADMINISTRATION**

Daivobet<sup>®</sup> ointment is indicated FOR TOPICAL USE ONLY. Daivobet<sup>®</sup> ointment is NOT FOR OPHTHALMIC USE.

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

#### **Adults:**

Daivobet<sup>®</sup> 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<sup>®</sup> ointment is 100 grams/week.**

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

**The use of Daivobet<sup>®</sup> 50/500 ointment should be intermittent for up to one year under close medical supervision. Treatment should be limited to four week periods with calcipotriol used alone for one month between periods of use of Daivobet<sup>®</sup> 50/500 Ointment as needed.**

**Children:**

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

**OVERDOSAGE**

Use at more than the recommended dose may cause elevated serum calcium, which rapidly subsides when treatment is discontinued. 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.

It has been reported that due to misuse one patient with extensive erythrodermic psoriasis treated with 240 g of Daivobet<sup>®</sup> ointment per week (maximum recommended dose is 100 g per week) for 5 months developed Cushing's syndrome and after abruptly stopping treatment, developed pustular psoriasis.

Contact the Poisons Information Centre on 131 126 for further advice on overdose management.

**PRESENTATION AND STORAGE CONDITIONS**

Daivobet<sup>®</sup> ointment contains 50 micrograms calcipotriol per gram and 500 micrograms betamethasone (as dipropionate) per gram in an off-white to yellow ointment base. It is available in tubes of 3 grams, 15 grams and 30 grams.

**Storage:** Store below 25°C.  
Shelf life: Unopened container: 2 years  
After first opening of container: 3 months

Do not use beyond the expiry date on the package.

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

**NAME AND ADDRESS OF SPONSOR**

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**MANUFACTURER**

LEO Pharmaceutical Products A/S  
Ballerup DENMARK

**POISON SCHEDULE OF MEDICINE**

S4

**DATE OF APPROVAL**

**Initial Date of Approval:** 11 August 2004

**Safety Related Notification change:** August 2006

**Date of Approval:** 3 December 2007

Daivobet<sup>®</sup> is a registered trademark of LEO Pharmaceutical Products Ltd A/S, Denmark