IIE007-01 - 175 x 280 mm

175 mm

280 mm

Calcipotriol Betamethasone

Daivobet® Ointment 50 mcg/500 mcg per gram

ANTIPSORIATIC

Product Description
Daivobet® ointment contains the drug substances calcipotriol (50 mcg/g) as monohydrate and betamethasone (0.5 mg/g) as dipropionate. The drug product appears as an off white to yellow ointment.

Formulation:
Each g of ointment contains:
Calcipotriol (as Monohydrate), Ph. Eur ..... 50 mcg
Betamethasone (as Dipropionate), Ph. Eur ..... 500 mcg

Indications
For the management of psoriasis vulgaris.

Posology and Method of Administration
Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) should be applied to the affected area once daily. There is experience with repeated courses of Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) up to 52 weeks. If it is necessary to continue or restart treatment after 4 weeks, treatment should be continued after medical review and under regular medical supervision.

When using calcipotriol containing medicinal products, the maximum daily dose should not exceed 15 g and the maximum weekly dose should not exceed 100 g.
The body surface area treated with calcipotriol containing medicinal products should not exceed 30%.

Special populations
Renal and hepatic impairment
The safety and efficacy of Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population
The safety and efficacy of Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) in children below 18 years have not been established.
Currently available data in children aged 12 to 17 years are described in section 4.8 and 5.1 but no recommendation on a posology can be made.

Method of administration
Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) should be applied to the affected area. In order to achieve optimal effect, it is not recommended to take a shower or bath immediately after application of Calcipotriol hydrate and betamethasone dipropionate (Daivobet®).

Contraindications
Hypersensitivity to the active substances or to any of the excipients.

Due to the content of calcipotriol, calcipotriol hydrate and betamethasone dipropionate (Daivobet®) is contraindicated in patients with known disorders of calcium metabolism.

Due to the content of corticosteroid, Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) is contraindicated in the following conditions:
Viral (eg. herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis, rosacea, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, ulcers and wounds.

Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) is contraindicated in erythrodermic, exfoliative and pustular psoriasis.

Special Warnings and Special Precautions for Use

Effects on endocrine system
Adverse reactions 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 systemic absorption.

Application under occlusive dressings should be avoided since it increases the systemic absorption of corticosteroids. Application on large areas of damaged skin, or on mucous membranes or in skin folds should be avoided since it increases the systemic absorption of corticosteroids.

In a study 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 adrenocorticotropic hormone (ACTH) challenge after 4 weeks of treatment.

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

Local adverse reactions
Daivobet contains a potent 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.
The medicinal product should not be used in these areas.
The patient must be instructed in correct use of the medicinal 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 antimicrobiological therapy. However, if infection worsens, treatment with corticosteroids should be stopped.

Discontinuation of treatment
When treating psoriasis 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
With long-term use there is an increased risk of local and systemic corticosteroid undesirable effects.
The treatment should be discontinued in case of undesirable effects' related to long-term use of corticosteroid.

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

Concurrent treatment and UV exposure
Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) for body psoriasis lesions has been used in combination with Daivobet® gel for scalp psoriasis lesions, but there is limited experience of combination of Daivobet® with other topical anti-psoriatic products at the same treatment area, other anti-psoriatic medicinal products administered systemically or with phototherapy.

During Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) treatment, physicians are recommended to advise patients to limit or avoid excessive exposure to either natural or artificial sunlight. Topical calcipotriol should be used with UV radiation only if the physician and patient consider that the potential benefits outweigh the potential risks.

Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) contains butylhydroxytoluene (E321) as an excipient. This may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed with Daivobet®.

Fertility, Pregnancy and Lactation
Pregnancy:
There are no adequate data from the use of Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) in pregnant women.
Studies in animals with glucocorticoids have shown reproductive toxicity (see section 5.3), but a number of epidemiological studies (less than 300 pregnancy outcomes) have not revealed congenital anomalies among infants born to women treated with corticosteroids during pregnancy.
The potential risk for humans is uncertain. Therefore, during pregnancy, Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) should only be used when the potential benefit justifies the potential risk.

Breastfeeding:
Betamethasone passes into breast milk, but risk of an adverse effect on the infant seems unlikely with therapeutic doses. There are no data on the excretion of calcipotriol in breast milk.

Caution should be exercised when prescribing Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) to women who breastfeed.
The patient should be instructed not to use Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) on the breast when breastfeeding.

Fertility:
Studies in rats with oral doses of calcipotriol or betamethasone dipropionate demonstrated no impairment of male and female fertility.

Effects on the ability to drive and use machines
Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) has no or negligible influence on the ability to drive and use machines.

Adverse Drug Reaction
The estimation of the frequency of adverse reactions is based on a pooled analysis of data from clinical studies including post-authorisation safety studies and spontaneous reporting.
The most frequently reported adverse reactions during treatment are various skin reactions, like pruritus, and skin exfoliation.
Pustular psoriasis and hypercalcaemia have been reported.
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 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1000)
Very rare (<1/10,000)

Infections and infestations	
Uncommon ≥1/1,000 to <1/100	Skin infection* Folliculitis
Rare ≥1/10,000 to <1/1,000	Furuncle
Immune system disorders	
Rare ≥1/10,000 to <1/1,000	Hypersensitivity
Metabolism and nutrition disorders	
Rare ≥1/10,000 and to <1/1,000	Hypercalcaemia

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Metabolism and nutrition disorders	
Rare ≥1/10,000 and to <1/1,000	Hypercalcaemia
Skin and subcutaneous tissue disorders	
Common ≥1/100 to < 1/10	Skin exfoliation Pruritus
Uncommon ≥1/1,000 to <1/100	Skin atrophy Exacerbation of psoriasis Dermatitis Erythema Rash** Purpura or ecchymosis Skin burning sensation Skin irritation
Rare ≥1/10,000 to <1/1,000	Pustular psoriasis Skin striae Photosensitivity reaction Acne Dry skin
General disorders and administration site conditions	
Uncommon ≥1/1,000 to <1/100	Application site pigmentation changes Application site pain***
Rare ≥1/10,000 to <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

Paediatric population:
In an uncontrolled open study, 33 adolescents aged 12-17 years with psoriasis vulgaris were treated with Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) for 4 weeks to a maximum of 56 g per week.
No new adverse events were observed and no concerns regarding systemic corticosteroid effect were identified. The size of this study does however not allow firm conclusions regarding the safety profile of Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) in children and adolescents.

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

Betamethasone (as dipropionate):
Local reactions can occur after topical use, especially during prolonged application, including skin atrophy, telangiectasia, striae, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation and colloid milia.
When treating psoriasis there may be a risk of generalised pustular psoriasis.
Systemic effects due to topical use of corticosteroids are rare in adults, however they can be severe.
Adrenocortical suppression, cataract, infections and increase of intra-ocular pressure can occur, especially after long term treatment. Systemic effects occur more frequently when applied under occlusion (plastic, skin folds), when applied on large areas and during long term treatment.

Overdose and Treatment
Use above the recommended dose may cause elevated serum calcium which subsides when treatment is discontinued. The symptoms of hypercalcemia include polyuria, constipation, muscle weakness, confusion and coma.
Excessive prolonged use of topical corticosteroids may suppress the pituitaryadrenal functions, resulting in secondary adrenal insufficiency which is usually reversible. In such cases, symptomatic treatment is indicated.
In case of chronic toxicity the corticosteroid treatment must be discontinued gradually.
It has been reported that due to misuse one patient with extensive erythrodermic psoriasis treated with 240 g of Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) weekly (corresponding to a daily dose of approximately 34 g) for 5 months (maximum recommended dose 15 g daily) developed Cushing's syndrome during treatment and then pustular psoriasis after abruptly stopping treatment.

Pharmacodynamic Properties
Calcipotriol is a vitamin D analogue. In vitro data suggests that calcipotriol induces differentiation and suppresses proliferation of keratinocytes. This is the proposed basis for its effect in psoriasis.
Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic, vasoconstrictive and immunosuppresive properties, however, without curing the underlying condition.
Through occlusion the effect can be enhanced due to increased penetration of the stratum corneum. The incidence of adverse events will increase because of this. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.

A safety study in 634 psoriasis patients has investigated repeated courses of Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) used once daily as required, either alone or alternating with Daivonex®, for up to 52 weeks, compared with Daivonex® used alone for 48 weeks after an initial course of Daivobet ointment. Adverse drug reactions were reported by 21.7 % of the patients in Calcipotriol hydrate and betamethasone dipropionate (Daivobet®) group, 29.6 % in the Daivobet® ointment/Daivonex® alternating group and 37.9 % in the Daivonex® 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 events of concern possibly related to long-term corticosteroid use (e.g. skin atrophy, folliculitis, depigmentation, furuncle and purpura) were reported by 4.8 % of the patients in the Daivobet® ointment group, 2.8 % in the Daivobet® ointment/Daivonex® alternating group and 2.9 % in the Daivonex® group. 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. With regard to HPA suppression, therefore, this study shows some evidence that very high doses of Daivobet® gel and ointment may have a weak effect on the HPA axis.

Paediatric population
The adrenal response to ACTH challenge was measured in an uncontrolled 4-week study in 33 adolescents aged 12-17 years with body psoriasis who used up to 56 g per week of Daivobet® ointment. No cases of HPA axis suppression were reported. No hypercalcaemia was reported but one patient had a possible treatmentrelated increase in urinary calcium.

Pharmacokinetic Properties
The human transdermal absorption of calcipotriol and betamethasone respectively has been shown to be less than 1% of the administered dose for both substances. The systemic absorption under normal conditions of use is not expected to have any influence on systemic parameters.
The pharma - cokinetic behaviour of the two active constituents is not influenced by the presence of each other.

Preclinical Safety Data
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 was detected. Moreover, reduction in offspring survival, body weight and body weight gain were observed. There was no impairment of fertility. The relevance for humans in unknown.
A dermal carcinogenicity study with calcipotriol in mice and an oral carcinogenicity study in rats revealed no special risk to humans.
Photo(co)carcinogenicity studies in mice suggest that calcipotriol may enhance the effect of UVR to induce skin tumours.
A dermal carcinogenicity study in mice and an oral carcinogenicity study in rats revealed no special hazard risk of betamethasone dipropionate to humans. No photocarcinogenicity study has been performed with betamethasone dipropionate.

Storage Conditions
Store at temperatures not exceeding 30°C.
Shelf-life: 24 months
Can be used for 12 months after opening.

Dosage Forms and Packaging Available (pack size)
Ointment
Aluminum tube
Pack sizes: 15 g and 30 g (Box of 1's)

List of excipients
Liquid paraffin (contains all-rac-α-tocopherol as an antioxidant)
Polyoxypropylene stearyl ether (contains butylhydroxytoluene (E321) as an antioxidant)
All-rac-α-tocopherol
White soft paraffin (contains all-rac-α-tocopherol as an antioxidant)

Special Precautions for Handling and Disposal
No special requirements.

Name and Address of Marketing Authorization Holder
Imported and Distributed by:
DKSH Market Expansion Services Philippines, Inc.
3rd Floor Science Hub Tower 2 Campus Avenue, McKinley Hill Cyberpark, Pinagsama, Taguig City, Metro Manila

Name and Address of Manufacturer
Manufactured by:
LEO Laboratories Ltd.
285 Cashel Road, Crumlin, Dublin 12
D12 E923, Ireland

For:
LEO Pharma A/S
Industriparken 55,
Ballerup, 2750, Denmark

Caution Statement:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph and to the DKSH Market Expansion Services Philippines, Inc. Pharmacovigilance at pharmacovigilance.ph@dksh.com or hotline +63998-965-4158. The patient should seek medical attention immediately at the first sign of any adverse drug reaction.

Registration Number:
DR-XY28706

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