Daivobet® Ointment

Composition
Active Ingredients: Calcipotriol 50 micrograms/g (as hydrate), betamethasone 0.5 mg/g (as dipropionate).
Excipients: Please refer to the list of excipients.

Presentation
Off-white to yellow ointment.
Pack sizes: 15 g, 30 g and 60 g. Not all pack sizes are marketed in the country.

Indications
Initial topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy.

Posology and method of administration
Posology
Daivobet® Ointment should be applied to the affected area once daily. The recommended treatment period is 4 weeks. There is experience with repeated courses of Daivobet® Ointment 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, the maximum weekly dose should not exceed 100 g, and 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 Daivobet® Ointment in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population
The safety and efficacy of Daivobet® Ointment in children below 18 years have not been established. Currently available data in children aged 12 to 17 years are described in section
Undesirable effects and Pharmacodynamics properties but no recommendation on a posology can be made.

Method of Administration
Daivobet® Ointment 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 Daivobet® Ointment.

Contraindications
Hypersensitivity to the active substances or to any of the excipients.
Due to the content of calcipotriol, Daivobet® Ointment is contraindicated in patients with known disorders of calcium metabolism.
Due to the content of corticosteroid Daivobet® Ointment is contraindicated in the following conditions: Viral (e.g. 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, wounds and perianal and genital pruritus.

Daivobet® is contraindicated in erythrodermic, exfoliative and pustular psoriasis.

Special warning and 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. Treatment of more than 30% of the body surface should be avoided.

Local adverse reactions:
Daivobet® Ointment contains a strong 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 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.

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 corticosteroids.

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 adverse reactions. The treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroid.

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

Concurrent treatment and UV exposure:
Daivobet® Ointment 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® Ointment with other anti-psoriatic products at the same treatment area, other anti-psoriatic medicinal products administered systemically or with photo therapy.

During Daivobet® Ointment 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.

Adverse reactions to excipients:
Daivobet® Ointment contains butylhydroxytoluene (E321) as an excipient, which 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® Ointment.

Fertility, Pregnancy and Lactation
Pregnancy:
There are no adequate data from the use of Daivobet® Ointment in pregnant women. Studies in animals with glucocorticoids have shown reproductive toxicity (see Preclinical safety data), 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, Daivobet® Ointment should only be used when the potential benefit justifies the potential risk.

Lactation:
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 Daivobet® Ointment to women who breast-feed. The patient should be instructed not to use Daivobet® Ointment on the breast when breast feeding.

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

Undesirable effects

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 <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

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
Eye Disorders	
Not Known	Vision, blurred****
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
**** See Special Warnings and Precautions for use

Paediatric population:
In an uncontrolled open study, 33 adolescents aged 12-17 years with psoriasis vulgaris were treated with Daivobet® Ointment 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 Daivobet® Ointment 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 with topical corticosteroids, there may be a risk of generalised pustular psoriasis.

Systemic reactions due to topical use of corticosteroids are rare in adults; however, they can be severe. Adrenocortical suppression, cataract, infections, impact on the metabolic control of diabetes mellitus 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
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 pituitary-adrenal 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 Daivobet® Ointment 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 immunosuppressive 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.

The efficacy of once daily use of Daivobet® ointment on psoriasis vulgaris was investigated in a randomised, doubleblind, 4-week clinical study including 1603 randomised patients with psoriasis vulgaris amenable to topical therapy. Comparators were betamethasone dipropionate in the ointment vehicle, calcipotriol in the ointment vehicle and the ointment vehicle alone, all used once daily. Primary response criteria were controlled disease according to the Investigator's Global Assessment of disease severity (IGA) at end of treatment and the percentage reduction in Psoriasis Severity and Area index (PASI) from baseline to end of treatment. For patients who had a baseline disease severity of moderate, severe or very severe,

"controlled disease" is defined as 'absence of disease' or 'very mild disease', whereas for patients who had a baseline disease severity of mild, "controlled disease" is defined as 'absence of disease'.

% of patients with controlled disease	Daivobet® ointment (n=490)	Betamethasone Dipropionate (n=476)	Calcipotriol (n=480)	Ointment vehicle (n=157)
End of treatment, (week 4)	48.0%	26.3%[1]	16.5%[1]	7.6%[1]

[1] Statistically significantly less effective than Daivobet® ointment (P<0.001)

Mean percentage reduction in PASI (SD)	Daivobet® ointment (n=490)	Betamethasone Dipropionate (n=476)	Calcipotriol (n=480)	Ointment vehicle (n=157)
End of treatment, (week 4)	71.3 (25.7)	57.2 (29.8)[1]	46.1 (30.9)[1]	22.7 (33.5)[1]

[1] Statistically significantly less effective than Daivobet® ointment (P<0.001)

A safety study in 634 psoriasis patients has investigated repeated courses of Daivobet® Ointment 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 the Daivobet® Ointment 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 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 treatment related increase in urinary calcium.

Pharmacokinetic properties
Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Daivobet® 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. Absorption through damaged skin is approx 24%. Protein binding is approx 64%. Plasma elimination half-life after intravenous application is 5-6 hours. Due to the formation of a depot in the skin elimination after dermal application is in order of days. Betamethasone is metabolised especially in the liver, but also in the kidneys to glucuronide and sulphate esters. Excretion takes place by urine and faeces.

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, in body weight and body weight gain was observed. There was no impairment of fertility. The relevance for humans is 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 risk of betamethasone dipropionate to humans. No photocarcinogenicity study has been performed with betamethasone dipropionate.

Incompatibilities
Not to be mixed with other medicinal products.

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)

Shelf life
Unopened container: 2 years.
After first opening of container: 12 months.

Special precautions for storage
Do not store above 30°C.
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