



ARTWORK

LEO Pharma A/S
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Subject	INS 160 x 400 mm		Date
Colour	Black		23/11/2023
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Preparation Strength Packsize	Daivobet® gel	Place of production	Ireland
Comments: Page 1 of 2 Font size: 7,5 pt			

IIE014-03 - 160 x 400 mm

Calcipotriol Betamethasone

Daivobet®
50 mcg/ 500 mcg per gram Topical Gel
Anti-psoriasis

Product Description
Gel.
Almost clear, colourless to slightly off-white gel.

Formulation
Each g of gel contains:
Calcipotriol (as Monohydrate), Ph. Eur50mcg
Betamethasone (as Dipropionate), Ph. Eur.....500mcg

Pharmacodynamic properties
Calcipotriol is a vitamin D analogue. In vitro data suggest 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. In general, the mechanism of the anti-inflammatory activity of the topical steroids is unclear.

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.

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

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

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

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

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

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

Mean percentage reduction in PASI (SD)	Daivobet® Gel (n=126)	Betamethasone dipropionate (n=68)	Calcipotriol (n=67)	Gel vehicle (n=35)
week 4	50.2 (32.7)	40.8 (33.3) ¹	32.1 (23.6) ¹	17.0 (31.8) ¹
week 8	58.8 (32.4)	51.8 (35.0)	40.8 (31.9) ¹	11.1 (29.5) ¹

1 Statistically significantly less effective than Daivobet® gel (P<0.05)
Another randomised, investigator-blinded clinical study including 312 patients with scalp psoriasis of at least moderate severity according to the IGA investigated use of Daivobet® Gel once daily compared with Daivonex® Scalp solution twice daily for up to 8 weeks. Results for the primary response criterion (absent or very mild disease according to the IGA at week 8) showed that Daivobet® Gel was statistically significantly more effective than Daivonex® Scalp solution.

% of patients with absent or very mild disease	Daivobet® Gel (n=207)	Daivonex® Scalp solution (n=105)
week 8	68.6 %	31.4 % ¹

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

A randomised, double-blind long-term clinical study including 873 patients with scalp psoriasis of at least moderate severity (according to the IGA) investigated the use of Daivobet® Gel compared with calcipotriol in the gel vehicle. Both treatments were applied once daily, intermittently as required, for up to 52 weeks. Adverse events possibly related to long-term use of corticosteroids on the scalp, were identified by an independent, blinded panel of dermatologists. There was no difference in the percentages of patients experiencing such adverse events between the treatment groups (2.6 % in the Daivobet® Gel group and 3.0 % in the calcipotriol group; P=0.73). No cases of skin atrophy were reported.

Paediatric population
Effects on calcium metabolism were investigated in two uncontrolled open 8-week studies including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Daivobet® Gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations, and reversible.

Pharmacokinetic properties
The systemic exposure to calcipotriol and betamethasone dipropionate from topically applied Daivobet® Gel is comparable to Daivobet® Ointment in rats and minipigs. Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Daivobet® Ointment formulation is less than 1% of the dose (2.5 g) when applied to normal skin (625 cm2) for 12 hours. Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids. Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised. The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice). Calcipotriol and betamethasone dipropionate were below the lower limit of quantification in all blood samples of 34 patients treated for 4 or 8 weeks with both Daivobet® Gel and Daivobet® Ointment for extensive psoriasis involving the body and scalp. One metabolite of calcipotriol and one metabolite of betamethasone dipropionate were quantifiable in some of the patients.

Indications
Topical treatment of scalp psoriasis. Topical treatment of mild to moderate "non-scalp" plaque psoriasis vulgaris.

Posology and method of administration
Posology
Daivobet® Gel should be applied to affected areas once daily. The recommended treatment period is 4 weeks for scalp areas and 8 weeks for "non-scalp" areas. If it is necessary to continue or restart treatment after this period, 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%.

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

Special populations
Renal and hepatic impairment
The safety and efficacy of Daivobet® Gel in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

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

Method of administration
Daivobet® Gel should not be applied directly to the face or eyes. In order to achieve optimal effect, it is not recommended to take a shower or bath, or to wash the hair in case of scalp application, immediately after application of Daivobet® Gel. Daivobet® Gel should remain on the skin during the night or during the day.

When using the bottle
Shake the bottle before use and apply Daivobet® Gel to the affected area. The hands should be washed after use.

Contraindications
Hypersensitivity to the active substances or to any of the excipients. Due to the content of calcipotriol, Daivobet® Gel is contraindicated in patients with known disorders of calcium metabolism. Due to the content of corticosteroid, Daivobet® Gel 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, perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers and wounds. Daivobet® Gel 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 adrenocorticotrophic hormone (ACTH) challenge after 4 weeks of treatment.

Effects on calcium metabolism:
Due to the content of calcipotriol, hypercalcaemia may occur if the maximum daily dose (15 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® Gel 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 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.

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New proof requested <input type="checkbox"/>	Sign.: <input type="checkbox"/>	According to: SOP_000647, SOP_000962, SOP_003993 and SOP_008676	According to: SOP_000647, SOP_000962 and SOP_008676
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Comments: Page 2 of 2			

IIE014-03 - 160 x 400 mm

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 for the use of Daivobet® Gel 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 no 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 Daivobet® Gel 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 UVR only if the physician and patient consider that the potential benefits outweigh the potential risks.

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

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

Fertility, pregnancy and lactation
Pregnancy
There are no adequate data from the use of Daivobet® Gel in pregnant women. Studies in animals with glucocorticoids have shown reproductive toxicity, 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® Gel 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® Gel to women who breastfeed. The patient should be instructed not to use Daivobet® Gel 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 ability to drive and use machines
Daivobet® Gel 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 reaction during treatment is pruritus.

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

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)

Infections and infestations	
Uncommon ≥1/1,000 to <1/100	Skin infection* Folliculitis
Immune system disorders	
Rare ≥1/10,000 to <1/1,000	Hypersensitivity
Eye disorders	
Uncommon ≥1/1,000 to <1/100	Eye irritation
Skin and subcutaneous tissue disorders	
Common ≥1/100 to < 1/10	Pruritus
Uncommon ≥1/1,000 to <1/100	Exacerbation of psoriasis Dermatitis Erythema Rash** Acne Skin burning sensation Skin irritation Dry skin
Rare ≥1/10,000 to <1/1,000	Skin striae Skin exfoliation
General disorders and administration site conditions	
Uncommon ≥1/1,000 to <1/100	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 rash erythematous and rash pustular have been reported.

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

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.

Paediatric population
No new adverse events and no new adverse reactions were seen in 109 adolescents aged 12-17 years with scalp psoriasis treated with Daivobet® Gel for 8 weeks. However, due to the size of the studies, no firm conclusion can be drawn as to the safety profile of Daivobet® Gel in adolescents compared to that in adults.

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 were detected. Moreover, reduction in offspring survival, 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 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

In local tolerability studies in rabbits, Daivobet® gel caused mild to moderate skin irritation and a slight transient irritation of the eye.

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 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 (maximum dose 100 g weekly) for 5 months developed Cushing's syndrome and then pustular psoriasis after abruptly stopping treatment.

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Special precautions for storage
Do not refrigerate. Keep the bottle in the outer carton in order to protect from light.
Store at temperatures not exceeding 30°C.
Can be used for 3 months after opening.

Keep out of reach of children.

Dosage Form and Packaging Available
Topical Gel
HDPE Bottle x 15g, 30 g and 60 g
(Box of 1's)

Caution:
Foods, Drugs, and Cosmetics Act prohibits dispensing without prescription.

DR-XY41745

ADR Statement:
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.

This leaflet was last revised in November 2023.

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