SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Daivobet® 50 micrograms/g + 0.5 mg/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of gel contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).

Excipient: 160 micrograms butylated hydroxytoluene/g gel

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.
An almost clear, colourless to slightly off-white gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment of scalp psoriasis in adults. Topical treatment of mild to moderate “non-scalp” plaque psoriasis vulgaris in adults.

4.2 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. The body surface area treated with calcipotriol containing medicinal products should not exceed 30 % (see section 4.4).

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. No data are available.

Method of administration
The bottle should be shaken before use and Daivobet gel applied to the affected area. Daivobet gel should not be applied directly to the face or eyes. The hands should be washed after use. 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.

4.3 Contraindications

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

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

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 or syphilis, perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers, wounds, perianal and genital pruritus.

4.4 Special warnings and precautions for use

Effects on endocrine system
Daivobet gel contains a potent group III steroid and concurrent treatment with other steroids must be avoided. 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 (see section 4.8).

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 (see section 5.1).

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, however, quickly 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 (see section 4.2).

Local adverse reactions
Skin of the face and genitals are very sensitive to corticosteroids. The medicinal product should not be used in these areas. Uncommon local adverse reactions (such as eye irritation or irritation of facial skin) were observed, when the medicinal product was accidentally administered in the area of face, or accidentally to the eyes or conjunctives (see sections 4.8 and 5.1).

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 adverse reactions. The treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroid (see section 4.8).

Unevaluated uses
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 (see section 5.3).

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 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 (see section 5.3), but a number of epidemiological studies 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.

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 Daivobet gel to women who breast-feed. The patient should be instructed not to use Daivobet 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.

4.7 Effects on ability to drive and use machines

Daivobet gel has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The clinical trial programme for Daivobet gel has so far included more than 4,700 patients of whom more than 2,100 were treated with Daivobet gel. Approximately 8 % of patients treated with Daivobet gel experienced a non-serious adverse reaction.
These reactions are usually mild and cover mainly various skin reactions with pruritus being the most common.

Based on data from clinical trials and postmarket use the following adverse reactions are listed for Daivobet gel.
The adverse reactions are listed by MedDRA System Organ Class, and the individual adverse reactions are listed starting with the most frequently reported. Within each frequency grouping, the adverse reactions are listed in order of decreasing seriousness.
The following terminologies have been used in order to classify the frequencies of adverse reactions:

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)

Eye disorders	
Uncommon	Eye irritation
Skin and subcutaneous tissue disorders	
Common	Pruritus
Uncommon	Exacerbation of psoriasis Burning sensation of skin Skin pain or irritation Folliculitis Dermatitis Erythema Acne Dry skin Rash Pustular rash

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 (see section 4.4).

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 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 reactions occur more frequently when applied under occlusion (plastic, skin folds), when applied on large areas and during long term treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Bulgarian drug agency
8 Damyan Gruev Str.
1303 Sofia
Tel.: +359 2 8903417
website: www.bda.bg

4.9 Overdose

Use above the recommended dose may cause elevated serum calcium which should rapidly subside when treatment is discontinued.
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 and pustular psoriasis after abruptly stopping treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsoriatics. Other antipsoriatics for topical use, Calcipotriol, combinations. ATC Code: D05AX52

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 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. 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.

5.2 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 cm^2) 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 %.

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised. 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. The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice). In rats, tissue distribution studies with radiolabelled calcipotriol and betamethasone dipropionate, respectively, showed that the kidney and liver had the highest level of radioactivity.

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.

5.3 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 hazard to humans.

Photo(co)carcinogenicity studies in mice suggest that calcipotriol may enhance the effect of UVR to induce skin tumours.

No carcinogenicity or photocarcinogenicity studies have 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Paraffin, liquid
Polyoxypropylene-11 stearyl ether
Castor oil, hydrogenated
Butylhydroxytoluene (E321)
All-rac-α-tocopherol

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

After first opening: 3 months.

6.4 Special precautions for storage

Do not refrigerate. Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

High-density polyethylene bottles with low-density polyethylene nozzle and a high-density polyethylene screw cap. The bottles are placed in cartons.
Pack sizes: 15, 30, 60 and 2 x 60 g and 3 x 60 g.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

20120168

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22.03.2012

10. DATE OF REVISION OF THE TEXT

06/2013

Detailed information on this medicinal product is available on the website of Bulgarian drug agency