Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dovobet 50 microgram/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 with known effect
Butylhydroxytoluene (E321) 160 micrograms/g gel

For the 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
Dovobet 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 Dovobet 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 Dovobet gel in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population
The safety and efficacy of Dovobet gel 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
Dovobet 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 Dovobet gel. Dovobet gel should remain on the skin during the night or during the day.

When using the Applicator
Prior to the first use of the Applicator the cartridge and the applicator head must be assembled.
After priming, each full actuation delivers 0.05 g of Dovobet gel.

Dovobet gel is applied to the affected area by using the Applicator.
The hands should be washed after use if Dovobet gel gets on the fingers.
Dovobet gel Applicator is accompanied by the package leaflet with detailed instructions for use.

When using the bottle
The bottle should be shaken before use and Dovobet gel applied to the affected area.
The hands should be washed after use.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Dovobet is contraindicated in erythrodermic, exfoliative and pustular psoriasis.

Due to the content of calcipotriol, Dovobet is contraindicated in patients with known disorders of calcium metabolism (see section 4.4).

Due to the content of corticosteroid, Dovobet 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 (see section 4.4).

4.4 Special warnings and precautions for use

Effects on endocrine system
Dovobet 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 Dovobet gel (scalp application) and high doses of Dovobet 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).

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 a 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.

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. Treatment of more than 30% of the body surface should be avoided (see section 4.2).

Local adverse reactions
Dovobet 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 the 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 (see section 4.3).

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 use
There is no experience with the use of Dovobet in guttate psoriasis.

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

During Dovobet 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
Dovobet gel contains butylhydroxytoluene (E321) as an excipient, 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 interactions

No interaction studies have been performed with Dovobet.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Dovobet 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, Dovobet should only be used when the potential benefit justifies the potential risk.

Breast-feeding
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 Dovobet to women who breast-feed. The patient should be instructed not to use Dovobet 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Dovobet has no or negligible influence on the ability to drive and use machines.

4.8 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 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)
Very rare (<1/10,000)
Not known (cannot be estimated from available data)

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
Not known	Vision, blurred**
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
Not known	Hair colour changes****
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.
**See section 4.4.
***Various types of rash reactions such as rash erythematous and rash pustular have been reported.
****Transient discolouration of the hair at scalp application site, to a yellowish colour in white or grey hair, has 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 (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 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 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).

Paediatric population
No clinically relevant differences between the safety profiles in adult and adolescent populations have been observed.
A total of 216 adolescent subjects were treated in three open label clinical trials.
See section 5.1 for further details regarding the trials.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Use above the recommended dose may cause elevated serum calcium which subsides when treatment is discontinued. The symptoms of hypercalcaemia 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 Dovobet 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.

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 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 Dovobet gel and Dovobet 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 Dovobet gel and ointment may have a weak effect on the HPA axis.

The efficacy of once daily use of Dovobet 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 Dovobet gel was statistically significantly more effective than the comparators. Results for speed of onset based on similar data at week 2 also showed Dovobet gel to be statistically significantly more effective than the comparators.

% of patients with absent or very mild disease	Dovobet 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 Dovobet® gel (P<0.001)

The efficacy of once daily use of Dovobet 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	Dovobet 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 Dovobet® gel (P<0.05)

Mean percentage reduction in PASI (SD)	Dovobet 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 Dovobet® 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 Dovobet gel once daily compared with Dovonex 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 Dovobet gel was statistically significantly more effective than Dovonex Scalp solution.

% of patients with absent or very mild disease	Dovobet gel (n=207)	Dovonex Scalp solution (n=105)
week 8	68.6%	31.4%[1]

[1] Statistically significantly less effective than Dovobet® 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 Dovobet 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 Dovobet gel group and 3.0% in the calcipotriol group; P=0.73). No cases of skin atrophy were reported.

Paediatric population

Scalp

Effects on calcium metabolism were investigated in two uncontrolled open 8-week trials including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Dovobet 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.

Scalp and body

Effects on calcium metabolism were investigated in one uncontrolled open 8-week trial in 107 adolescents aged 12-17 years with scalp and body psoriasis who used up to 114.2 g per week of Dovobet gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 31 patients; five patients showed a decrease in cortisol response to ACTH challenge where 2 of the 5 patients showed only borderline decreases. Four of the patients showed decrease after 4 weeks of treatment and 2 showed decrease after 8 weeks including 1 patient showing a decrease at both periods. These events were mild, without clinical manifestations, and reversible.

5.2 Pharmacokinetic properties

The systemic exposure to calcipotriol and betamethasone dipropionate from topically applied Dovobet gel is comparable to Dovobet ointment in rats and minipigs. Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Dovobetointment 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 sulfate 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 Dovobet gel and Dovobet 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 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.

In local tolerability studies in rabbits, Dovobet 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 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

3 years.

Bottle: After first opening: 6 months.

Applicator: After first opening: 6 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Bottles: High-density polyethylene bottles with a low-density polyethylene nozzle and a high-density polyethylene screw cap. The bottles are placed in cartons.
Pack sizes: 15 g, 30 g, 60 g, 80 g, 2 x 60 g, 2 x 80 g and 3 x 60 g.

Applicator: The Applicator consists of a polypropylene cartridge (with a high-density polyethylene plunger and screw cap), an applicator head (polypropylene outer casing, polyoxymethylene lever and thermoplastic elastomer nozzle) and polypropylene cover. The cartridge, applicator head and cover are assembled prior to use. The cartridge(s), applicator head(s) and cover(s) are placed in a carton.
Pack sizes: 60 g (equivalent to 68 ml) and 2 x 60 g (equivalent to 2 x 68 ml)

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

PA1025/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th September 2008
Date of last renewal: 1st October 2015

10 DATE OF REVISION OF THE TEXT

November 2019