PRODUCT MONOGRAPH

PrDOVOBET® Gel

calcipotriol and betamethasone dipropionate gel

50 mcg/g calcipotriol (as monohydrate) and
0.5 mg/g betamethasone (as dipropionate) gel

Topical Antipsoriatic Agent
Vitamin D Analogue / Corticosteroid

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SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>topical</td>
<td>Gel: 50 mcg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate)</td>
<td>none For a complete listing see Dosage Forms, Composition and Packaging section.</td>
</tr>
</tbody>
</table>

INDICATIONS AND CLINICAL USE

DOVOBET gel (calcipotriol and betamethasone dipropionate gel) is indicated for the topical treatment of:

- moderate to severe scalp psoriasis vulgaris in patients 18 years and older for up to 4 weeks.
- mild to moderate plaque psoriasis vulgaris on the body in patients 18 years and older for up to 8 weeks

CONTRAINDICATIONS

- Known hypersensitivity to DOVOBET gel (calcipotriol and betamethasone dipropionate gel), to any ingredient in the formulation or to components of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Ophthalmic use
- Patients with known disorders of calcium metabolism.
- 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.
- Guttate, erythrodermic, exfoliative and pustular psoriasis.
- Patients with severe renal insufficiency or severe hepatic disorders.
WARNINGS AND PRECAUTIONS

General
DOVOBET gel (calcipotriol and betamethasone dipropionate gel) should not be used on the face, axillae, flexures, groin, or genitals.

Hypercalcemia and hypercalciuria have been observed with the use of DOVOBET gel. Due to the content of calcipotriol, hypercalcemia may occur if the maximum daily dose (15 g) or maximum weekly dose (100 g) is exceeded. The body surface area treated should not exceed 30%. The effects of DOVOBET gel on calcium metabolism following treatment durations of more than 8 weeks have not been evaluated.

If hypercalemia or hypercalciuria develop, treatment should be discontinued until parameters of calcium metabolism have normalized. Serum calcium is quickly normalized when treatment is discontinued. The risk of hypercalcemia is minimal when the recommendations relevant to calcipotriol are followed (see Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION).

Carcinogenesis and Mutagenesis
Calcipotriol when used in combination with ultraviolet radiation (UVR) may enhance the known skin carcinogenic effect of UVR. This potential risk is based on the pre-clinical finding in mice of a reduced time to tumor formation from long term exposure of UVR and topically applied calcipotriol (see TOXICOLOGY, Carcinogenicity).

Patients who apply DOVOBET gel to exposed skin (e.g. a bald scalp) should avoid excessive exposure to both natural and artificial sunlight (e.g. phototherapy, tanning beds, sun lamps, etc.).

Endocrine and Metabolism
DOVOBET gel contains a potent World Health Organization (WHO) group III steroid and concurrent treatment with other corticosteroids must be avoided.
Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticoid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

In a study of 32 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\(^1\) (body application), 5 of 32 patients (15.6\%) showed a borderline decrease in cortisol response to adrenocorticotropic hormone (ACTH) challenge after 4 weeks of treatment. In another study of 43 patients with extensive scalp and body psoriasis treated with DOVOBET gel on the body and scalp, adrenal suppression was identified in 3 of 43 patients (7.0\%) after 4 weeks of treatment and in 0 of 36 patients who provided data after 8 weeks of treatment (see ACTION AND CLINICAL PHARMACOLOGY and Part II: CLINICAL TRIALS, Special Studies).

Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent steroids, use over large surface areas, use over prolonged periods, use under occlusion, use on an altered skin barrier, and use in patients with liver failure. Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure. See also Special Populations, Pediatrics.

Application of topical corticosteroid products including DOVOBET on large areas of broken skin or under occlusive dressings should therefore be avoided. The use of occlusion may increase penetration of the stratum corneum, increasing the risk of adverse events. Manifestations of Cushing’s syndrome, effects on the metabolic control of diabetes mellitus (e.g. hyperglycaemia, glucosuria) and unmasking of latent diabetes mellitus can also be produced in some patients by systemic absorption of topical corticosteroids.

Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression. An ACTH stimulation test may be

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\(^1\) Dovobet® ointment (50 mcg/g calcipotriol and 0.5 mg/g betamethasone, as dipropionate)
helpful in evaluating patients for HPA axis suppression (see Monitoring and Laboratory Tests). If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

**Ophthalmologic**

DOVOBET gel is not for ophthalmic use. DOVOBET gel may cause eye irritation. Avoid contact with the eyes or conjunctiva (see Skin).

**Skin**

DOVOBET gel should not be used on the face, axillae, flexures, groin, or genitals. The patient must be instructed in the correct use of DOVOBET gel (e.g. washing their hands after each application) to avoid accidental transfer or application to these regions or to the mouth, mucous membranes or eyes (see DOSAGE AND ADMINISTRATION).

Facial skin is very sensitive to Vitamin D analogues and corticosteroids. Dermatitis has been observed with the use of DOVOBET gel. Uncommon local adverse reactions (such as eye irritation or irritation of facial skin), were observed when the drug was accidentally administered in the area of the face, or accidentally to the eyes or conjunctiva (see ADVERSE REACTIONS). Should facial dermatitis develop in spite of the precautions above, DOVOBET gel therapy should be discontinued.

Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local adverse reactions may be irreversible. Treatment should be discontinued in the case of corticosteroid adverse effects related to the use of DOVOBET gel.
When treating psoriasis with topical corticosteroid containing products, including DOVOBET gel, it is recommended that treatment be interrupted periodically. There may be a risk of generalised pustular psoriasis or rebound psoriasis when discontinuing corticosteroids after prolonged periods of use. Medical supervision should therefore continue in the post-treatment period.

Concomitant skin infections should be treated with an appropriate antimicrobial agent. If the infection persists, DOVOBET gel should be discontinued until the infection has been adequately treated.

See also Carcinogenesis, Endocrine and Metabolism and, ADVERSE DRUG REACTIONS and Part II Clinical Pharmacology.

**Special Populations**

**Pregnant Women:** The safety of calcipotriol and/or topical corticosteroids for use during pregnancy has not been established. Pregnant women were excluded from the clinical studies conducted with DOVOBET gel. When given systemically, calcipotriol has been shown to be fetotoxic and betamethasone dipropionate has been shown to be teratogenic in animals (see PART II, TOXICOLOGY, Reproduction and Mutagenicity). The use of DOVOBET gel is not recommended in pregnant women.

**Nursing Women:** The safety of calcipotriol and/or topical corticosteroids for use in nursing women has not been established. It is not known whether calcipotriol can be excreted in breast milk. Betamethasone passes into breast milk, but it is not known if topical application of corticosteroid containing products, including DOVOBET gel, can lead to sufficient systemic absorption to produce detectable quantities in breast milk. The use of DOVOBET gel is not recommended in nursing women.

**Pediatrics (<18 years of age):** Since there is no clinical trial experience with the use of DOVOBET gel in children, use is not recommended. Children may demonstrate greater
susceptibility to systemic corticosteroid related adverse effects due to a larger skin surface area to body weight ratio as compared to adults.

**Geriatrics (≥ 65 years of age):** Of the 824 patients treated with DOVOBET gel for psoriasis on the body in controlled Phase II and III clinical studies, 124 were at least 65 years of age, and 36 were at least 75 years of age. Blood parathyroid hormone increased was reported more frequently in subjects 65 years and older. The clinical significance of this is not known. Of the 1,953 patients treated with DOVOBET gel for scalp psoriasis in the controlled clinical studies, 334 were 65 years or older, and 84 were 75 years or older. Overall the adverse event reporting rate for DOVOBET gel was comparable between subjects over 65 years of age and those younger than 65.

**Monitoring and Laboratory Tests**

Treatment with DOVOBET gel in the recommended amounts (See DOSAGE AND ADMINISTRATION) does not generally result in changes in laboratory values. However, in patients at risk of hypercalcaemia it is recommended that baseline serum calcium levels be obtained before starting treatment with subsequent monitoring of serum calcium levels at suitable intervals. If serum calcium becomes elevated, DOVOBET gel administration should be discontinued and serum calcium levels should be measured once weekly until they return to normal.

An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression. If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA Axis function is generally prompt and complete upon discontinuation of topical corticosteroids (see Endocrine and Metabolism and, ACTION AND CLINICAL PHARMACOLOGY).
ADVERSE REACTIONS

Overview

Studies on the Body

In a safety pool of randomized, multi-centre prospective vehicle- and/or active controlled clinical trials in subjects with plaque psoriasis on non-scalp areas, patients applied study product once daily for up to 8 weeks. A total of 824 patients were treated with DOVOBET gel (calcipotriol and betamethasone dipropionate gel) and the mean weekly dose was 29.0g (median 22.6g). Adverse drug reactions were adverse events that the investigators considered at least possibly related to study treatment. Approximately 6% of patients treated with DOVOBET gel experienced an adverse reaction. In this safety pool, the most common adverse reaction in the DOVOBET gel group was pruritus.

In the safety pool of controlled clinical trials, adverse reactions led to discontinuation of treatment with DOVOBET gel in 0.8% of patients. Patients discontinued treatment due to the following adverse reactions: application site pain, pain of skin, skin irritation, dermatitis contact, dry skin, pruritus and psoriasis.

Studies on the Scalp

The clinical trial programme for DOVOBET gel has included more than 1,900 patients with scalp psoriasis treated with DOVOBET gel. Approximately 8% of patients treated with DOVOBET gel experienced an adverse reaction. Based on data from clinical trials, the most common adverse reaction is pruritus.

Adverse reactions led to discontinuation of treatment with DOVOBET gel in 0.1-0.2% of patients. Patients discontinued treatment due to the following adverse reactions: pruritus, skin pain or irritation, dermatitis, eye irritation, rash, burning sensation, face oedema, folliculitis and dry skin.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should
not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

**Clinical Studies on the Body**

One randomized, double-blind, vehicle-controlled, 8-week pivotal trial (n=1152) was conducted to evaluate the efficacy and safety of DOVOBET gel compared to betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle, calcipotriol 50 mcg/g in the gel vehicle and the gel vehicle-alone administered once daily in subjects with mild to moderate psoriasis vulgaris on non-scalp regions of the body (trunk and/or limbs). Mild to moderate psoriasis vulgaris was determined by the Investigator’s global assessment of disease severity (IGA). The mean baseline extent of psoriasis was similar among the four treatment groups (approximately 11-13% of body surface area). The mean amount of study medication used per week over the course of the study was similar among the DOVOBET gel, betamethasone gel and gel vehicle groups (approximately 28-32 g/week) and greatest in the calcipotriol group (approximately 37g/week).

Adverse drug reactions were adverse events that the investigators considered at least possibly related to study treatment. In the pivotal study, the incidence of withdrawal due to adverse reactions was highest in the calcipotriol gel group (5.2%) vs. 0.6% in the DOVOBET gel group, 0% in the betamethasone gel group and 0% in the vehicle group. Among patients treated with DOVOBET gel, the adverse drug reactions leading to withdrawal were: application site pain, psoriasis, and dermatitis contact. Signs of skin atrophy were assessed visually by the investigator. There were no reports in any treatment group that were related to skin atrophy, striae, telangiectasia, skin hypopigmentation or hypertrichosis.

Table 1 lists adverse drug reactions reported in at least 1% of subjects in any treatment group in the pivotal trial of DOVOBET gel on the body. Overall, adverse drug reactions were reported most frequently in the calcipotriol gel group (5.3%), followed by the DOVOBET gel group (5.0%), the vehicle group (4.2%) and the betamethasone gel group (3.1%).
Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Patients for the Pivotal Body Study: safety analysis set

<table>
<thead>
<tr>
<th>Primary System Organ Class1</th>
<th>Preferred Term1</th>
<th>DOVOBET ® gel (n=482)</th>
<th>Betamethasone gel (n=479)</th>
<th>Calcipotriol gel (n=96)</th>
<th>Gel vehicle (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients</td>
<td>%</td>
<td>Number of Patients</td>
<td>%</td>
<td>Number of Patients</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>General disorders and administration site disorders</td>
<td>Application site pain</td>
<td>2</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Infections and infestations</td>
<td>Candidiasis</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Investigations</td>
<td>Blood parathyroid hormone increased</td>
<td>7</td>
<td>1.5</td>
<td>6</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dermatitis contact</td>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>3</td>
<td>0.6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Rash papular</td>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Skin irritation</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

1) Coded according to MedDRA version 13.0
Clinical Studies on the Scalp

Two pivotal and 4 supporting controlled clinical studies were conducted in scalp psoriasis. For the pivotal scalp studies, adverse drug reactions reported by at least 1% of patients in any treatment group are summarized in Table 2. Overall, the incidence of patients with at least one ADR was lowest in the DOVOBET gel group.
Table 2. Adverse Drug Reactions Occurring in ≥ 1% of Patients for the Pivotal Scalp Studies: safety analysis set

<table>
<thead>
<tr>
<th>Primary System Organ Class¹</th>
<th>DOVOBET® gel (n=1093)</th>
<th>Betamethasone gel (n=1104)</th>
<th>Calcipotriol gel (n=548)</th>
<th>Gel vehicle (n=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>Number of Patients</td>
<td>%</td>
<td>Number of Patients</td>
<td>%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>0.5</td>
<td>11</td>
<td>1.0</td>
</tr>
<tr>
<td>Burning sensation</td>
<td>2</td>
<td>0.2</td>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>25</td>
<td>2.3</td>
<td>18</td>
<td>1.6</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>5</td>
<td>0.5</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4</td>
<td>0.4</td>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>Erythema</td>
<td>4</td>
<td>0.4</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1</td>
<td>0.1</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>0.1</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

¹ Coded according to MedDRA version 6.1.
Less Common Clinical Trial Adverse Drug Reactions (<1%) for Studies on the Body

The following is a list of less common adverse reactions reported in the pivotal trial conducted in body psoriasis. Adverse reactions reported in <1% of patients treated with DOVOBET gel and not otherwise listed in Table 1 above, are included. Adverse reactions are listed by MedDRA SOC.

General Disorders and Administration Site Conditions: Application site pain, feeling of body temperature change.
Infections and Infestations: Cellulitis, folliculitis and sinusitis.
Investigations: Blood phosphorus decreased.
Nervous System Disorder: Dizziness
Skin and Subcutaneous Tissue Disorders: Dermatitis, guttate psoriasis, rash
Vascular Disorders: Flushing

Less Common Clinical Trial Adverse Drug Reactions (<1%) for Studies on the Scalp

From clinical trials conducted in scalp psoriasis, the uncommon adverse reactions are listed by MedDRA SOC from most to least frequent.

Eye Disorders: eye irritation.
Infections: otitis externa.
Investigations: elevated blood calcium.
Skin and Subcutaneous Tissue Disorders: burning sensation of the skin, skin pain or irritation, folliculitis, dermatitis, contact dermatitis, erythema, acne, dry skin, exacerbations of psoriasis, rash and pustular rash, and face oedema.

See also ACTION AND CLINICAL PHARMACOLOGY and Part II: CLINICAL TRIALS, Special Studies.

Other Adverse Drug Reactions
Adverse reactions observed for the individual drug substances calcipotriol and betamethasone dipropionate are described below.
Calcipotriol
Adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, aggravated psoriasis, photosensitivity and hypersensitivity reactions. There have been infrequent reports of angioedema and facial oedema. Isolated cases of hypercalcaemia or hypercalciuria have been reported (see WARNINGS AND PRECAUTIONS).

Betamethasone 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 corticosteroid containing products, including DOVOBET gel in adults occur infrequently but 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. Application of DOVOBET gel under occlusion or for prolonged treatment periods may result in an increased risk of systemic adverse events, and is therefore not recommended (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions
The following serious and unexpected adverse events not previously listed in the clinical trial adverse reactions section of the Product Monograph have been reported. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The list below includes reactions reported in patients using the gel and/or ointment formulations of DOVOBET.
Blood and lymphatic system disorders: lymphadenopathy
Ear and labyrinth disorders: auricular swelling
Eye disorders: glaucoma
General disorders and administration site conditions: drug ineffective, oedema peripheral
Infections and infestations: gastroenteritis, respiratory tract infection, staphylococcal infection, upper respiratory tract infection
Injury, poisoning and procedural complications: overdose
Nervous system disorders: migraine, tension headache
Psychiatric disorders: suicidal ideation
Renal and urinary disorders: nephrolithiasis
Respiratory, thoracic and mediastinal disorders: dyspnoea
Skin and subcutaneous tissue disorders: erythrodermic psoriasis, skin atrophy, skin exfoliation
Surgical and medical procedures: off label use
Vascular disorders: haematoma

DRUG INTERACTIONS

Drug-Drug Interactions
There is no experience of concomitant therapy with other antipsoriatic drugs. No drug interaction studies have been performed.

Drug-Lifestyle Interactions
Patients who apply DOVOBET gel to exposed skin (e.g. a bald scalp) should avoid excessive exposure to both natural and artificial sunlight (e.g. phototherapy, tanning beds, sun lamps, etc.).
(See WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

DOSAGE AND ADMINISTRATION

Dosing Considerations
- DOVOBET gel (calcipotriol and betamethasone dipropionate gel) is not recommended for use in children and adolescents below the age of 18 years.
- DOVOBET gel is FOR TOPICAL USE ONLY and not for ophthalmic use.
**Recommended Dose and Dosage Adjustment**

DOVOBET gel should be applied to affected areas of the body once daily for up to 8 weeks and to affected areas of the scalp once daily for up to 4 weeks. After satisfactory improvement has occurred, the drug can be discontinued. If recurrence takes place after discontinuation, treatment may be reinstituted.

The maximum daily dose including other calcipotriol-containing products on the body should not exceed 15 g and the maximum weekly dose should not exceed 100 g. The total body surface area treated, including scalp and body should not exceed 30%.

**Missed Dose**

If a dose is missed, the patient should apply DOVOBET gel when he/she remembers, but only once on a given day and then continue on as usual.

**Administration**

Application under occlusive dressings should be avoided since it increases systemic absorption of corticosteroids.

The bottle should be shaken before use and DOVOBET gel applied to the affected area. DOVOBET gel should not be applied directly to the face or eyes (see WARNINGS AND PRECAUTIONS, Ophthalmologic, Skin). 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 DOVOBET gel. DOVOBET gel should remain on the skin during the night or during the day. Patients should be advised that DOVOBET gel should not be applied to the scalp 12 hours before or after colouring, perming or any chemical hair treatments.

**OVERDOSAGE**

Use of DOVOBET gel (calcipotriol and betamethasone dipropionate gel) above the recommended dose may cause elevated serum calcium which should rapidly subside when treatment is discontinued. In such cases, it is recommended to monitor serum calcium levels.
once weekly until they return to normal. Excessive prolonged use of topical corticosteroid containing products, including DOVOBET gel, may suppress the pituitary-adrenal functions, resulting in secondary adrenal insufficiency which is usually reversible. If this occurs, symptomatic treatment is indicated. In cases of chronic toxicity, treatment with DOVOBET gel must be discontinued gradually. It has been reported that due to misuse one patient treated with 240 g of DOVOBET ointment (50 mcg/g calcipotriol and 0.5 mg/g betamethasone, as dipropionate) 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

DOVOBET gel is a combination of the vitamin D analogue calcipotriol and the corticosteroid betamethasone dipropionate.

Calcipotriol is a non-steroidal antipsoriatic agent, derived from the naturally occurring vitamin D. Calcipotriol exhibits a vitamin D-like effect by competing for the 1,25(OH)2D3 receptor. Calcipotriol is as potent as 1,25(OH)2D3, the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than 1,25(OH)2D3 in its effect on calcium metabolism. Calcipotriol induces differentiation and suppresses proliferation of keratinocytes (without any evidence of a cytotoxic effect), thus reversing the abnormal keratinocyte changes in psoriasis. The therapeutic goal envisaged with calcipotriol is thus a normalization of epidermal growth.

Topical corticosteroids such as betamethasone dipropionate have anti-inflammatory, anti-pruritic, vasoconstrictive and immunosuppressive properties. In general, the mechanism of the anti-inflammatory activity of topical corticosteroids is unclear. Corticosteroids are thought to
induce phospholipase A\textsubscript{2} inhibitor proteins, preventing arachidonic acid release and the biosynthesis of potent mediators of inflammation.

**Pharmacodynamics**

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 (on the scalp) and DOVOBET ointment (on the body) (study A). 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.

In addition, HPA axis suppression was evaluated in adult patients (n=43) with extensive psoriasis involving 15-30% of the body surface area (including the scalp) (study B). Treatment consisted of once daily application of DOVOBET gel on the body and the scalp for up to 8 weeks. Adrenal suppression, as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL, was observed in 3 of 43 patients (7%) after 4 weeks of treatment and in 0 of the 36 patients who provided data after 8 weeks treatment.

A study was conducted to evaluate the atrophogenic potential of betamethasone dipropionate in DOVOBET gel compared with marketed betamethasone dipropionate ointment and gel vehicle. The study was conducted as an intra-individual comparison of once daily application for 4 weeks in 48 healthy volunteers. Skin thickness was measured by sonography performed before treatment, weekly during the 4-week treatment period and 2 weeks after the end of treatment. DOVOBET gel induced reversible skin thinning, which was similar to that induced by betamethasone dipropionate ointment.

**Pharmacokinetics**

**Absorption:** 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 dipropionate from the DOVOBET 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.

Calcipotriol and betamethasone dipropionate were below the lower limit of quantification in all blood samples of 34 patients with extensive psoriasis involving the scalp and body and treated for 4 or 8 weeks with DOVOBET gel on the scalp and DOVOBET ointment on the body. One metabolite of calcipotriol and one metabolite of betamethasone dipropionate were quantifiable in some of the patients. While the biological activity of the calcipotriol metabolite is less than that of calcipotriol, the activity of the betamethasone dipropionate metabolite cannot be distinguished from the activity of the parent compound.

The serum levels of calcipotriol and betamethasone dipropionate and their major metabolites were measured after 4 weeks of once daily application of DOVOBET gel to 15-30% of the body surface area (body and scalp areas). Calcipotriol and its major metabolite were below the lower limit of quantification in all serum samples and betamethasone dipropionate was quantifiable in 1 of the samples in 5 of 43 (11.6%) patients. The primary metabolite of betamethasone dipropionate was quantifiable in 16 of 43 (37.2%) patients.

**Metabolism:** Calcipotriol metabolism following systemic uptake is rapid and occurs in the liver. Calcipotriol is metabolized to MC1046 (the α,β-unsaturated ketone analog of calcipotriol), which is metabolized further to MC1080 (a saturated ketone analog). MC1080 is the major metabolite in plasma. MC1080 is slowly metabolized to calcitroic acid.

Betamethasone dipropionate is metabolized to betamethasone 17-propionate and betamethasone, including the 6β-hydroxy derivatives of those compounds by hydrolysis. Betamethasone 17-propionate (B17P) is the primary metabolite.
STORAGE AND STABILITY
Store at 15°C - 30°C. Do not refrigerate. Shake before use. Protect from light, keep the bottle in the outer carton. Use within 6 months of first opening the bottle. Keep out of reach of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form
Gel: almost clear, colourless to slightly off-white lipophilic gel.

Composition
50 mcg/g calcipotriol (as monohydrate) plus 0.5 mg/g betamethasone (as dipropionate)

Non-medicinal ingredients: liquid paraffin, polyoxypropylene-11-stearyl ether (contains butylhydroxytoluene), hydrogenated castor oil, and α-tocopherol.

Packaging
Available in 30 g, 60 g, and 2 x 60 g polyethylene bottles.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

<table>
<thead>
<tr>
<th>Proper name (I.N.N.)</th>
<th>Calcipotriol monohydrate</th>
<th>Betamethasone dipropionate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical name:</td>
<td>9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-, monohydrate, (1α,3β,5Z,7E,22E,24S)</td>
<td>Pregna-1,4-diene-3,20-dione,9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxoproxy)-(11β,16β)</td>
</tr>
<tr>
<td>Alternative chemical name:</td>
<td>20(R)-(3'S)-Cyclopropyl-3'-hydroxyprop-1'(E)-enyl-1(S),3(R)-dihydroxy-9-10-secopregna-5(Z),7(E),10(19)-triene, hydrate</td>
<td>9-fluoro-11β,17,21-tri hydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate</td>
</tr>
<tr>
<td>Laboratory code name:</td>
<td>MC 903 monohydrate</td>
<td>433 or 433/M</td>
</tr>
<tr>
<td></td>
<td>MC 903, H₂O</td>
<td></td>
</tr>
<tr>
<td>Molecular formula:</td>
<td>C₂₇H₄₀O₃, H₂O</td>
<td>C₂₈H₃₇FO₇</td>
</tr>
<tr>
<td>Molecular mass:</td>
<td>430.6</td>
<td>504.6</td>
</tr>
<tr>
<td>Chirality:</td>
<td>The calcipotriol molecule is one single stereoisomer. The absolute configuration of the chiral centres at carbon atoms nos. 1, 3, 13, 14, 17, 20 and 24 is indicated in the structural formula below.</td>
<td></td>
</tr>
</tbody>
</table>

Structural formula:
Calcipotriol monohydrate
Betamethasone dipropionate

Physicochemical properties:

<table>
<thead>
<tr>
<th>Physical form:</th>
<th>Calcipotriol monohydrate</th>
<th>Betamethasone dipropionate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White or almost white</td>
<td>White or almost white</td>
</tr>
<tr>
<td></td>
<td>crystalline substance.</td>
<td>crystalline powder.</td>
</tr>
<tr>
<td>Solubility at room</td>
<td>Freely soluble in ethanol,</td>
<td>Freely soluble in acetone,</td>
</tr>
<tr>
<td>temperature:</td>
<td>soluble in chloroform and</td>
<td>in dioxane, in dichloromethane</td>
</tr>
<tr>
<td></td>
<td>propylene glycol, practically</td>
<td>and in chloroform; soluble in</td>
</tr>
<tr>
<td></td>
<td>insoluble in liquid paraffin.</td>
<td>methanol; sparingly soluble in</td>
</tr>
<tr>
<td></td>
<td>Solubility in water is 0.6</td>
<td>alcohol; slightly soluble in</td>
</tr>
<tr>
<td></td>
<td>mcg/ml.</td>
<td>ether; insoluble in water and in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hexane.</td>
</tr>
<tr>
<td>Melting point:</td>
<td>166-168 °C</td>
<td>176-180 °C</td>
</tr>
<tr>
<td>Polymorphism:</td>
<td>So far no signs have indicated</td>
<td>the existence of polymorphic</td>
</tr>
<tr>
<td></td>
<td>the existence of polymorphic</td>
<td>forms.</td>
</tr>
<tr>
<td>Other characteristics:</td>
<td>Calcipotriol is a vitamin D derivative. It is well-known that vitamin</td>
<td>D in solution forms a reversible temperature dependent equilibrium</td>
</tr>
<tr>
<td></td>
<td>D in solution forms a reversible temperature dependent equilibrium</td>
<td>between vitamin D and pre-vitamin D (described in (i.e.) J Pharm</td>
</tr>
<tr>
<td></td>
<td>between vitamin D and pre-vitamin D (described in (i.e.) J Pharm</td>
<td>Sci 1968; 57:1326). In the same way, solutions of calcipotriol</td>
</tr>
<tr>
<td></td>
<td>Sci 1968; 57:1326). In the same way, solutions of calcipotriol</td>
<td>establish an equilibrium with “pre-calcipotriol”. The structural</td>
</tr>
<tr>
<td></td>
<td>establish an equilibrium with “pre-calcipotriol”. The structural</td>
<td>formula of “pre-calcipotriol” is shown below.</td>
</tr>
</tbody>
</table>
**CLINICAL TRIALS**

**Clinical Studies on the Body**

One randomized, double-blind, vehicle-controlled, 8-week pivotal trial (n=1152) was conducted to evaluate the efficacy and safety of DOVOBET gel (calcipotriol and betamethasone dipropionate gel) compared to betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle, calcipotriol 50 mcg/g in the gel vehicle and the gel vehicle-alone administered once daily in patients with mild to moderate psoriasis vulgaris on non-scalp regions of the body (trunk and/or limbs, including neck, hands, buttocks and feet). The scalp, face, flexures and genitals were not treated and were not assessed as part of the efficacy analysis. Patients had mild to moderate psoriasis vulgaris at baseline, as determined by the Investigator’s Global Assessment of disease severity (IGA). Patients were also to have a minimum modified Psoriasis Area and Severity Index (PASI) score for extent of 2 in at least one body region (i.e. psoriasis affecting at least 10% of arms and/or 10% of trunk, and/or 10% of legs).

Seventy-eight (78%) percent of patients had disease of moderate severity at baseline. The mean baseline extend of psoriasis was similar among the four treatment groups (approximately 11-13% of body surface area). The average amount of study medication used per week over the course of the study was similar among the DOVOBET gel, betamethasone gel and gel vehicle groups (approximately 28-32 g/week) and greatest in the calcipotriol group (approximately 37g/week). The mean age was 48.6 years (range 18-88 years) and approximately 60% of patients were male. The majority of patients were White (89.1%), 6.2% were Black or African American and 2.6% were Asian.

Results for the co-primary response criterion [percentage of patients who achieved “controlled disease” according to the IGA at weeks 4 and 8] showed that DOVOBET gel was statistically significantly more effective than each of the individual components alone at Week 8. At Week 4, although statistical significance was not achieved for the comparison with betamethasone in gel vehicle, DOVOBET gel was statistically significantly more effective than calcipotriol in gel vehicle (see table below).
Clinical Studies on the Scalp
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 1,000 DOVOBET gel treated patients with scalp psoriasis of at least moderate severity according to the IGA. The number of patients with mild scalp psoriasis included in the studies was small making estimates of efficacy less reliable in this subgroup. 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 (see table below). The majority of patients who responded achieved satisfactory improvement before 4 weeks of treatment. Further increases in efficacy beyond 4 weeks were minimal. Results for speed of onset based on data at week 2 also showed DOVOBET gel to be statistically significantly more effective than the comparators.

<table>
<thead>
<tr>
<th>% of Patients with controlled disease (clear or almost clear)*</th>
<th>DOVOBET gel (n = 482)</th>
<th>Betamethasone Dipropionate in gel vehicle (n = 479)</th>
<th>Calcipotriol in gel vehicle (n = 96)</th>
<th>Gel vehicle (n= 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 4</td>
<td>13.3%</td>
<td>12.5%</td>
<td>5.2%†</td>
<td>2.1%‡</td>
</tr>
<tr>
<td>week 8</td>
<td>29.0%</td>
<td>21.5%†</td>
<td>14.6%‡</td>
<td>6.3%§</td>
</tr>
</tbody>
</table>

* Patients with mild disease at baseline were required to be “Clear” to be considered controlled. Patients with moderate disease at baseline were required to be “Clear” or “Almost clear”.
† DOVOBET gel statistically significantly more effective than comparator treatment gel (p<0.05)
§ DOVOBET gel statistically significantly more effective than comparator treatment gel (p<0.01)

<table>
<thead>
<tr>
<th>% of Patients with absent or very mild disease</th>
<th>DOVOBET gel (n=1,108)*</th>
<th>Betamethasone dipropionate (n=1,118)*</th>
<th>Calcipotriol (n=558)*</th>
<th>Gel vehicle (n=136)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 2</td>
<td>53.2%</td>
<td>42.8%†</td>
<td>17.2%†</td>
<td>11.8%†</td>
</tr>
<tr>
<td>week 4</td>
<td>60.7%</td>
<td>52.9%†</td>
<td>24.7%†</td>
<td>14.7%†</td>
</tr>
<tr>
<td>week 8</td>
<td>69.8%</td>
<td>62.5%†</td>
<td>40.1%†</td>
<td>22.8%†</td>
</tr>
</tbody>
</table>

† DOVOBET gel statistically significantly more effective than comparator treatment gel (p<0.001)
* including patients graded as mild at baseline
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 (see table below).

<table>
<thead>
<tr>
<th>% of Patients with absent or very mild disease</th>
<th>DOVOBET gel (n=207)</th>
<th>DOVONEX® scalp solution (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 4</td>
<td>55.1%†</td>
<td>18.1%</td>
</tr>
<tr>
<td>week 8</td>
<td>68.6%†</td>
<td>31.4%</td>
</tr>
</tbody>
</table>

† statistically significantly more effective than DOVONEX® scalp solution (p<0.001)

**Special Studies**

A randomised, double-blind, study of 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. The average amount of study drug used was 10.6 g/week. Adverse events possibly related to prolonged use of corticosteroids on the scalp, were identified by an independent, blinded panel of dermatologists. There was no difference between the treatment groups (2.6% in the DOVOBET gel group and 3.0% in the calcipotriol group; p<0.73) in the percentages of patients experiencing such adverse events. No cases of skin atrophy (based on a dermatologist’s visual assessment) were reported.

Effects on adrenal function and calcium metabolism were investigated in an open-label study in 35 patients with extensive psoriasis on both scalp (at least 30% of scalp area) and body (15-30% of body surface area). Patients used an average of 23.7 g/week DOVOBET gel on the scalp and an average of 40.2 g/week DOVOBET ointment on the body. Adrenal response to ACTH was determined by measuring serum cortisol levels 30 and 60 minutes after ACTH challenge. A borderline decrease in cortisol response at 30 minutes post ACTH challenge was seen in 5 of the
32 evaluable 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 a change in calcium metabolism observed in these patients.

Effects on adrenal function and calcium metabolism were also investigated using only DOVOBET gel in an open-label study in 43 adult patients with extensive psoriasis involving 15-30% of the body surface area (including the scalp). Treatment consisted of once daily application of DOVOBET gel on the body and the scalp for up to 8 weeks. Adrenal response to ACTH was determined by measuring serum cortisol levels 30 and 60 minutes after ACTH challenge. The mean baseline extent of psoriasis was 20.6% of body surface area. The mean amount of study drug used over the total treatment period was 52.3 g/week (range 7.6 g/week to 92.9 g/week).

Three (7.0%) subjects had a serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test at week 4. None of the 36 subjects who continued to week 8 and had samples with data had a 30 minute serum cortisol ≤18 mcg/dL. The adrenal suppression was considered borderline in two of these subjects because the 30 minute value was only slightly below the defined cut off level and the 60 minute value showed adequate response. One subject showed clear signs of adrenal suppression with a cortisol level lower than the cut off level at both 30 and 60 minutes.—There were no clinically relevant changes in mean serum or urinary calcium levels. Elevated urinary calcium levels outside the normal range were observed in 2 patients (1 at 4 weeks and 1 at 8 weeks).
## SUMMARY OF CLINICAL TRIALS

**Clinical Studies on the Body**

<table>
<thead>
<tr>
<th>STUDY CODE</th>
<th>STUDY TYPE / DURATION</th>
<th>STUDY DESIGN</th>
<th>DOSAGE / ROUTE</th>
<th>TREATMENT / PATIENT NO.</th>
<th>RESULTS</th>
</tr>
</thead>
</table>
| LEO80185-G23    | Efficacy, safety study in patients with psoriasis vulgaris on the body       | Multi-centre, prospective, randomised, double-blind, active- and vehicle-controlled, parallel group study | 1. DOVOBET gel (50 mcg/g calcipotriol, as monohydrate + 0.5 mg/g betamethasone, as dipropionate) | DOVOBET gel, n=482;  
Betamethasone, n=479;  
Calcipotriol, n=96;  
Gel vehicle, n=95 | There was no significant difference between DOVOBET gel and betamethasone in gel vehicle in the percentage of patients who achieved controlled disease at week 4. DOVOBET gel (29%) was statistically significantly more effective than betamethasone in the gel vehicle (21.5%, p=0.008), calcipotriol in the gel vehicle (14.6%, p=0.002) and the gel vehicle (6.3%, p<0.001) at achieving controlled disease at week 8.  
Adverse Events (AEs) were reported for 26.0% patients treated with DOVOBET gel vs. 20.0% betamethasone in gel vehicle, 23.2% calcipotriol in gel vehicle and 23.2% gel vehicle.  
AEs in the treatment area occurred in 2.7% of patients in the DOVOBET gel group vs. 2.3% in the betamethasone gel group, 4.2% in the calcipotriol gel group and 4.2% in the gel vehicle group. |

- **LEO®**
## SUMMARY OF CLINICAL TRIALS (continued)

### Clinical Studies on the Scalp

<table>
<thead>
<tr>
<th>STUDY CODE</th>
<th>STUDY TYPE / DURATION</th>
<th>STUDY DESIGN</th>
<th>DOSAGE / ROUTE</th>
<th>TREATMENT / PATIENT NO.</th>
<th>RESULTS</th>
</tr>
</thead>
</table>
| MBL 0405 INT | Efficacy, safety study in patients with scalp psoriasis 8 weeks  | Multi-centre, randomised, double-blind, active- and vehicle-controlled, parallel group study  
Primary endpoint: % of patients with controlled disease at week 8  | 1. DOVOBET gel (50 mcg/g calcipotriol, as monohydrate + 0.5 mg/g betamethasone, as dipropionate)  
2. Betamethasone in the gel vehicle (0.5 mg/g, as dipropionate)  
3. Calcipotriol in the gel vehicle (50 mcg/g)  
4. Gel vehicle  
Once daily; topical  | DOVOBET gel, n=541;  
Betamethasone, n=556;  
Calcipotriol, n=272;  
Gel vehicle, n=136  | Total 1505 randomized  
DOVOBET gel (71.2%) was statistically significantly more effective than betamethasone in the gel vehicle (64.0%, p=0.011), calcipotriol in the gel vehicle (36.8%, p<0.001 and the gel vehicle (22.8%, p<0.001) at achieving controlled disease at wk 8.  
AEs for DOVOBET gel and betamethasone in the gel vehicle were similar and favourable (34.5% vs. 34.9%, respectively) compared with calcipotriol in the gel vehicle (46.2%) and the gel vehicle (40%).  
Lesional/perilesional AEs occurred in: 4.7% DOVOBET gel, 5.3% betamethasone in the gel vehicle versus 13.2% calcipotriol in the gel vehicle and 13.3% the gel vehicle.  
DOVOBET gel was more effective in treating scalp psoriasis and the incidence of lesional/perilesional AEs was low. |
### SUMMARY OF CLINICAL TRIALS (continued)

#### Clinical Studies on the Scalp (continued)

<table>
<thead>
<tr>
<th>STUDY CODE</th>
<th>STUDY TYPE / DURATION</th>
<th>STUDY DESIGN</th>
<th>DOSAGE / ROUTE</th>
<th>TREATMENT / PATIENT NO.</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBL 0406 INT</td>
<td>Efficacy, safety study in patients with scalp psoriasis 8 weeks</td>
<td>Multi-centre, randomised, double-blind, active-controlled, parallel group study</td>
<td>1. DOVOBET gel 2. Betamethasone in the gel vehicle (0.5 mg/g, as dipropionate) 3. Calcipotriol in the gel vehicle (50 mcg/g)</td>
<td>DOVOBET gel, n=568; Betamethasone, n=563; Calcipotriol, n=286 Total 1417 randomized</td>
<td>DOVOBET gel (68.4%) was statistically significantly more effective than betamethasone in the gel vehicle (61.0%, p=0.008) and calcipotriol in the gel vehicle (43.4%, p&lt;0.001) at achieving controlled disease at wk 8. AEs for DOVOBET gel and betamethasone in the gel vehicle were similar and favourable (38.7% vs. 41.0%, respectively) compared with calcipotriol in the gel vehicle (46.1%). Lesional/perilesional AEs occurred in: 6.2% DOVOBET gel and 5.8% betamethasone in the gel vehicle versus 12.8% calcipotriol in the gel vehicle. DOVOBET gel was more effective in treating scalp psoriasis and the incidence of lesional/perilesional AEs was low.</td>
</tr>
<tr>
<td>MBL 0503 INT</td>
<td>Efficacy, safety, relapse and rebound study in patients with scalp psoriasis 8 weeks treatment + 8 weeks observation period (treatment–free)</td>
<td>Multi-centre, randomised, investigator-blinded, active-controlled, parallel group study</td>
<td>1. DOVOBET gel (50 mcg/g calcipotriol, as monohydrate + 0.5 mg/g betamethasone, as dipropionate) 2. Dovonex® scalp solution (50 mcg/g calcipotriol)</td>
<td>DOVOBET gel, n=207; Dovonex® scalp solution, n=105 Total 312 randomized</td>
<td>DOVOBET gel (68.6%) was statistically significantly more effective than Dovonex® scalp solution (31.4%, p&lt;0.001) at achieving controlled disease at wk 8. QoL measures favoured DOVOBET gel. Frequency of AEs in the DOVOBET gel group (34.5%) were significantly lower (p&lt;0.001) than in the Dovonex® scalp solution group (56.7%). Lesional/perilesional AEs in the DOVOBET gel group (3.4%) were significantly lower (p&lt;0.001) than in the Dovonex® scalp solution group (19.2%). DOVOBET gel was more effective than Dovonex® scalp solution in treating scalp psoriasis.</td>
</tr>
</tbody>
</table>
DETAILED PHARMACOLOGY

Preclinical Pharmacology

Animal Pharmacodynamic Studies with Calcipotriol: The pharmacodynamic studies performed with calcipotriol have been aimed at establishing the activity of the compound as a regulator of cell differentiation and proliferation in cells possessing the receptor for the active form of vitamin D₃, 1,25(OH)₂D₃. These studies are relevant for the intended clinical use in patients with psoriasis, due to the characteristic findings of epidermal hyperproliferation and incomplete keratinocyte differentiation in this disease.

Other current therapeutic agents act mainly through non-specific cytostatic/cytotoxic effects on the proliferating cells or suppression of underlying inflammatory and immunological reactions. In contrast, calcipotriol was shown to induce differentiation of low-differentiated human histiocytic lymphoma cells, of skin cells from newborn mice and of human keratinocytes. At the same time, proliferation was inhibited without evidence of any cytotoxic effect. The therapeutic goal envisaged with calcipotriol is thus a normalization of epidermal growth.

Calcipotriol was also found to inhibit cell proliferation induced by interleukin-1 but not by other related cellular mediators. Interleukin-1 is produced both by keratinocytes in the epidermis and by activated macrophages in the dermis. It is thought to play a pathogenetic role in psoriasis by activating both keratinocytes and immunological cells. Inhibition of interleukin-1 mediated effects in psoriatic skin by calcipotriol may therefore provide a way of regulating epidermal/dermal interactions in affected skin areas.

The pharmacodynamic studies performed in-vitro have shown that the activity of calcipotriol is very similar, both qualitatively and quantitatively, to that of 1,25(OH)₂D₃. This is not surprising given the structural analogy of the two compounds and the ability of calcipotriol to bind to the cellular 1,25(OH)₂D₃ receptor with the same affinity as 1,25(OH)₂D₃ itself. In-vivo however, the effects of calcipotriol were significantly different from those of 1,25(OH)₂D₃. The active form of vitamin D₃, 1,25(OH)₂D₃, had potent effects on calcium metabolism and overdosage resulted in hypercalcemia and hypercalciuria.
From studies performed in rats, it was shown that the effect of calcipotriol on calcium metabolism was at least 100 to 200 times lower than that of 1,25(OH)$_2$D$_3$. This low activity on calcium metabolism might be an intrinsic property of the calcipotriol molecule. However, the pharmacokinetic studies performed with calcipotriol suggested that the low activity on calcium metabolism was associated with a rapid metabolic degradation of the active compound.

**Animal Pharmacokinetic Studies with Calcipotriol:** Pharmacokinetic studies with $^3$H-calcipotriol have been performed in rats and minipigs.

**In vivo:** Oral absorption of calcipotriol was approximately 60% in rats and 40% in minipigs. The half-life of calcipotriol was 12 minutes in rats and 60 minutes in minipigs. The major metabolite of calcipotriol MC1080 was present in the first plasma sample at 5 minutes; its half-life was 54 minutes in rats and 1.8 hours in minipigs. Drug-related radioactivity was excreted in urine and faeces and clearance was considered to be almost exclusively metabolic, as less than 5% of the administered radioactivity was excreted at the time of disappearance of all calcipotriol from plasma. Determination of the tissue distribution of calcipotriol was complicated by the appearance of $^3$H-H$_2$O from the metabolic degradation of $^3$H-calcipotriol. Autoradiography studies performed in rats, however, established that calcipotriol concentrations were highest in the liver, kidney and intestine. No drug-related radioactivity was present 24 hours after administration of $^3$H-calcipotriol.

**In vitro:** Two main metabolites of calcipotriol were observed in incubations of calcipotriol with rat liver homogenate supernatants. The two metabolites, MC1046 and MC1080, were isolated, identified and synthesized. Both metabolites were also present in supernatants from minipig, rabbit and human liver homogenates and in plasma samples from rats and minipigs. Although the necessity of using very high dosages of calcipotriol precludes the study of calcipotriol metabolism in humans, the present evidence strongly suggests that calcipotriol metabolism is qualitatively similar in rats, minipigs, rabbits and humans. In addition, both metabolites had lost most of the biological activity associated with calcipotriol thus constituting a deactivation pathway for the drug.
**Animal Pharmacokinetic Studies with Calcipotriol and Betamethasone:** Studies were conducted in rats and minipigs to determine the extent of absorption and excretion of $[^3]$H-calcipotriol plus betamethasone and $[^3]$H-betamethasone plus calcipotriol after single dermal administration of the drug combination in gel and ointment formulations. In minipigs, absorption of calcipotriol and betamethasone dipropionate from the gel and ointment formulations was similar. In the rat, calcipotriol from the gel was significantly less absorbed than calcipotriol from the ointment. The main route of excretion for the gel and ointment was via the faeces for both calcipotriol and betamethasone.
### IN VIVO PHARMACOKINETIC STUDIES WITH CALCIPOTRIOL AND BETAMETHASONE

<table>
<thead>
<tr>
<th>TYPE OF STUDY</th>
<th>STUDY DESIGN</th>
<th>MAJOR RESULTS</th>
</tr>
</thead>
</table>
| Absorption and Excretion study in albino SD rats | Single dose of calcipotriol and betamethasone in a gel formulation compared an ointment formulation  
6M, 6F rats per dose group (fed)  
Dermal application to 10cm² patch on the back  
1) [³H]-calcipotriol (50 μg/g) + betamethasone (500 μg/g)  
2) Calcipotriol (50 μg/g) + [³H]-betamethasone (500 μg/g)  
Sampling at 0, 6, 24, 48, 72, 96, 120, 144, 168 h  
Cumulative excretion of total (% of dose applied) radioactivity in urine, faeces, liver, serum, whole blood, dosed skin, carcass, cage wash | 1) Transdermal absorption of calcipotriol: gel 10% (M9.0%, F11.6%), ointment 19% (male 15.8%, female 21.3%)  
Highest level found in faeces (gel, ointment), dosed skin (gel, ointment), and carcass (gel, ointment)  
2) Transdermal absorption of betamethasone: gel 8% (M8.1%, F7.7%), ointment 9% (M9.3%, F8.9%)  
Highest level found in faeces (gel, ointment) and urine (gel, ointment)  
Absorption of betamethasone from the gel and ointment was similar. However, absorption of calcipotriol from the gel was significantly less than from the ointment. The main route of excretion was via the faeces for both calcipotriol and betamethasone. |
| Absorption and Excretion study in minipigs | Single dose of calcipotriol and betamethasone in a gel formulation compared to an ointment formulation  
4F minipigs per dose group (fasted)  
Dermal application to 2x150cm² patch on the upper flanks  
1) [³H]-calcipotriol (50 μg/g) + betamethasone (500 μg/g)  
2) Calcipotriol (50 μg/g) + [³H]-betamethasone (500 μg/g)  
Sampling at 0, 6, 24, 48, 72, 96, 120, 144, 168 h  
Cumulative excretion of total (% of dose applied) radioactivity in urine, faeces, liver, serum, whole blood, dosed skin, cage wash | 1) Transdermal absorption of calcipotriol: gel 2.4%, ointment 3.5%  
Highest level found in cage wash (gel) and faeces (ointment)  
2) Transdermal absorption of betamethasone: gel 2.6%, ointment 3.5%  
Highest level found in faeces (gel, ointment) and cage wash (ointment)  
Absorption of calcipotriol and betamethasone from DOVOBET gel and DOVOBET ointment was similar. The main route of excretion was via the faeces for both calcipotriol and betamethasone. |
Clinical Pharmacology

The atrophogenic potential and dermal tolerance of DOVOBET gel (calcipotriol and betamethasone dipropionate gel) was compared with that of Diprosone* (Schering Plough Ltd.) ointment, containing 0.5 mg/g betamethasone (as dipropionate) and the DOVOBET gel vehicle in a randomized, controlled right/left comparison on the forearm of healthy subjects. Sonography showed a similar reversible decrease in skin thickness for DOVOBET gel (10.6%) and Diprosone* ointment (11.1%) when applied once daily for 4 weeks. However, a statistically significant skin thinning effect was seen with DOVOBET gel compared to the gel vehicle. This effect was reversible at the end of treatment. There were no clinical signs of skin atrophy, telangiectasia or erythema.

The vasoconstrictive effects of DOVOBET gel were compared to Diprosone*, a potent WHO group III steroid. DOVOBET gel was not bioequivalent to Diprosone* ointment as the 90% CI for the colorimetric skin blanching response ratio was 0.64 to 0.95, i.e. outside the pre-defined interval of 0.80 to 1.25. The vasoconstrictive effect of DOVOBET gel was lower than that of Diprosone* ointment. Based on the results of this study, the potency of betamethasone dipropionate in DOVOBET gel is not expected to exceed that of a potent WHO group III steroid.

TOXICOLOGY

Toxicologic studies are summarized briefly here and in more detail by species in tabular form following this section.

Acute and Long-term Toxicity

Calcipotriol: Despite the intended topical use of calcipotriol in the treatment of psoriasis, most of the toxicological studies were performed using the oral route of administration. This was done to assure maximum exposure to the compound. From these studies it was evident that toxicity associated with the administration of pharmacologically excessive doses of calcipotriol was due to the calcitropic activity of the compound. The maximum doses were 54 mcg/kg/day in rats, 18 mcg/kg/day in minipigs and 3.6 mcg/kg/day in dogs. In the acute, subacute and
chronic toxicity studies the main signs of toxicity were loss of bodyweight, increases in plasma
or serum calcium, creatinine and urea, renal toxicity and soft tissue calcifications. These
changes resulted from the exaggerated absorption of calcium and phosphorous from the intestine
and are characteristic of vitamin D overdosage. The kidney was the main target organ of toxicity
and tubular lesions and calcifications were apparent after prolonged hypercalcemia in all species
investigated.

Calcipotriol and Betamethasone Dipropionate: Two dermal studies of 4-week and 9-month
duration respectively were conducted in minipigs to assess local and systemic toxicity. In both
studies, minipigs received daily topical administration of calcipotriol/betamethasone ointment at
doses of 2/20, 10/100 and 50/500 mcg/g. The main observation was erythema of varying
severity seen primarily in the high dose group. There were no systemic effects after 4 weeks,
however after 9 months systemic absorption resulted in dermal atrophy of non-treated skin.

Local Tolerance

Calcipotriol: Dermal tolerability of calcipotriol was limited to a slight-to-moderate skin irritative
effect. The studies performed with calcipotriol ointment showed that the incidence and severity
of skin irritation was slightly less in the calcipotriol-treated group than in the placebo ointment
group. The formulation of the ointment base is analogous to that employed for a number of
corticosteroids available for the treatment of psoriasis. Skin thinning, as seen with corticosteroid
application, was not observed with the calcipotriol ointment.

Calcipotriol and Betamethasone Dipropionate: Two dermal tolerability studies with
calcipotriol and betamethasone ointment were conducted in rabbits. In the first study, no skin
irritation was observed and only slight irritation attributed primarily to calcipotriol was observed
in the second study. A gradual reduction in skin thickness was observed over 6 weeks which
was attributed to betamethasone. However, the stratum corneum of rabbit skin is much thinner
than that of humans and rabbits are very sensitive to skin irritants. Similar results were obtained
for two dermal tolerability studies in rabbits using a gel formulation of calcipotriol and
betamethasone. In addition, an eye irritation study was conducted in rabbits using a single ocular
application (approx. 100 mg) of calcipotriol and betamethasone gel. There was a temporary pink discolouration of the orbital ring and ptosis observed which cleared within 6 hrs.

**Reproduction and Mutagenicity**

Animal reproduction studies have not been conducted with DOVOBET gel.

*Calcipotriol:* Reproduction studies have shown that calcipotriol has no effect on fertility in male and female rats nor on their F1 generation progeny. Teratogenicity studies were performed by the oral route in rats and rabbits. In rats, a few minor deviations occurred in pregnant rats given calcipotriol at doses up to 54 mcg/kg/day during days 6-15 of gestation, attributable to the pharmacological effects of calcipotriol on calcium metabolism. No teratogenic effects were observed. In rabbits, at 36 mcg/kg/day of calcipotriol from day 6-18 of gestation, maternal toxicity was observed, characterized by deaths, body weight losses, reduced food intake, increased post-implantation loss, reduced mean fetal weight and increased minor ossification changes. At 12 mcg/kg/day slight signs of maternal toxicity (body weight loss, reduced food intake, maternal death or abortion in 2/18 animals) and reduced mean fetal weight were seen. Peri- and post-natal development studies indicated that calcipotriol had no toxic effects on the F1 or F2 generation. There was also no evidence for a mutagenic or clastogenic potential with calcipotriol.

*Betamethasone:* Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations). In reproduction 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.

**Carcinogenicity**

*Calcipotriol:* A dermal carcinogenicity study in mice showed no indications of increased carcinogenic risks. Calcipotriol solution was applied topically for up to 24 months at doses of 3, 10 and 30 mcg/kg/day (corresponding to 9, 30 and 90 mcg/m²/day). The high-dose was considered to be the Maximum Tolerated Dose for dermal treatment of mice with calcipotriol.
Survival was decreased at 10 and 30 mcg/kg/day; particularly in the males. The reduced survival was associated with an increased incidence of obstructive uropathy, most probably caused by treatment-related changes in the urinary composition. This is an expectable effect of treatment with high doses of calcipotriol or other vitamin D analogues. There were no dermal effects and no dermal or systemic carcinogenicity.

**Betamethasone:** No carcinogenicity studies have been performed.

**Photo(co)carcinogenicity**

**Calcipotriol:** In a study where albino hairless mice were repeatedly exposed to both ultraviolet radiation (UVR) and topically applied calcipotriol for 40 weeks at the same dose levels as in the dermal carcinogenicity study (see above), a reduction in the time required for UVR light to induce the formation of skin tumours was observed (statistically significant in males only), suggesting that calcipotriol may enhance the effect of UVR to induce skin tumours.

**Betamethasone:** No photocarcinogenicity studies have been performed with betamethasone dipropionate alone.

**Calcipotriol and Betamethasone Dipropionate:** Albino hairless mice were treated repeatedly with either calcipotriol solution or calcipotriol and betamethasone gel, followed by irradiation with UVR. The study showed a similar enhancing effect of calcipotriol alone on the photobiological response of the skin but indicated no effect of the calcipotriol and betamethasone combination.
LONG-TERM TOXICITY OF CALCIPOTRIOL AND BETAMETHASONE DIPROPIONATE

<table>
<thead>
<tr>
<th>STUDY TYPE</th>
<th>ANIMAL / STRAIN</th>
<th>DOSE / ROUTE / DURATION</th>
<th>IMPORTANT FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat-dose</td>
<td>Minipigs (Göttingen) 3M/3F per group</td>
<td>Calcipotriol/betamethasone ointment: 0, 2/20, 10/100, 50/500 mcg/g</td>
<td>Dose-dependent irritant effect on the skin at 50/500 mcg/g with no signs of systemic toxicity. NOAEL: 10/100 mcg/g calcipotriol/betamethasone. Very slight erythema in the 10/100 mcg/g group; slight to moderate erythema in the 50/500 mcg/g group.</td>
</tr>
<tr>
<td>Repeat-dose</td>
<td>Minipigs (Göttingen) 5M/5F per group</td>
<td>Calcipotriol/betamethasone ointment: 0, 2/20, 10/100, 50/500 mcg/g</td>
<td>Moderate to severe persistent erythema in the 10/100 and 50/500 mcg/g groups, respectively. Tendency towards treatment-related elevated urinary Ca and PO4 (calcipotriol effect) and decreased adrenal organ weight and dermal atrophy (betamethasone effect). NOAEL: 2/20 mcg/g calcipotriol/betamethasone.</td>
</tr>
<tr>
<td>Dose-range finding</td>
<td>Mice (albino hairless) 10F per group</td>
<td>1) Untreated 2) Calcipotriol solution: 0, 3, 10, 30 mcg/mL 3) Calcipotriol and betamethasone gel: 0/0, 3/30, 10/100 mcg/g</td>
<td>Skin reactions (30 mcg/mL and 30/300 mcg/g) including erythema, oedema, flaking, wrinkling and thickening and body weight losses (30/300 mcg/g) that resulted in termination of these groups after 6 d of administration. Dose-dependent skin thinning and reduction in body weight in the calcipotriol and betamethasone gel formulation groups. Clinical findings (supported by histopathological evaluation) of dose-dependent skin inflammation for both formulations, including modification of the calcipotriol effects by the addition of betamethasone.</td>
</tr>
</tbody>
</table>
## OTHER TOXICITY OF CALCIPOTRIOL AND BETAMETHASONE DIPROPIONATE

<table>
<thead>
<tr>
<th>STUDY TYPE</th>
<th>ANIMAL / STRAIN</th>
<th>DOSE / ROUTE / DURATION</th>
<th>IMPORTANT FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photosafety</td>
<td>Mice (albino hairless) 24F per group</td>
<td>1) Untreated (UVR dose:0, 1, 2)  2) Calcipotriol solution: 0 (vehicle), 1, 3, 10 mcg/mL (UVR dose:1)  3) Calcipotriol and betamethasone gel: 0/0 (vehicle), 1/10, 3/30, 10/100 mcg/g (UVR dose:1)  4) Triamcinolone gel: 5000 mcg/g (UVR dose:1)  Once daily dermal application for 4 weeks  UVR dose 1 MED = 2 standard erythema doses</td>
<td><strong>Calcipotriol solution vehicle:</strong> no UVR-induced histopathological changes.  <strong>Calcipotriol solution (1-10 mcg/mL):</strong> elicited skin irritation and changes in histopathological markers indicating possible enhancement of photocarcinogenesis.  <strong>Calcipotriol/betamethasone gel vehicle:</strong> elicited cutaneous gross and histopathological changes indicative of irritation.  <strong>Calcipotriol/betamethasone gel (1/10-10/100 mcg/g):</strong> no UVR-induced histopathological changes.  Gross reactions and microscopic findings in the skin of these mice were similar to mice given triamcinolone (shown in published data to not enhance photo-carcinogenesis).</td>
</tr>
<tr>
<td>Photosafety</td>
<td>Mice (albino hairless) 12F per group</td>
<td>1) Untreated  2) Calcipotriol solution: 0 (vehicle) 1, 3, 10 mcg/mL  3) Calcipotriol and betamethasone gel: 0/0 (vehicle), 1/10, 3/30, 10/100 mcg/g  4) Triamcinolone gel: 5000 mcg/g  Once daily dermal application for 4 weeks  All mice exposed to a series of 6 UVR doses.  UVR dose: 0.5, 0.7, 1.0, 1.4, 2.0, 2.8 MEDₜ</td>
<td>Repeated administration of Calcipotriol solution (up to 100 mcg/mL) or calcipotriol betamethasone gel (up to 10/100 mcg/mL) followed by a single series of UVR exposures, had no adverse effect on the observational minimal erythema dose (MEDₜ).  Skin reactions, clinical observations and body weight effects were consistent with the known effects of these test formulations in this test system. The MEDₜ skin reaction and clinical observations for the 10/100 mcg/g calcipotriol/betamethasone group were similar to the group given 5000 mcg/g triamcinolone.  Hence, there was no evidence of UVR-induced cutaneous inflammation from repeated topical administration of calcipotriol solution or calcipotriol and betamethasone gel.</td>
</tr>
</tbody>
</table>
### LOCAL TOLERANCE OF CALCIPOTRIOL AND BETAMETHASONE DIPROPIONATE

<table>
<thead>
<tr>
<th>STUDY TYPE</th>
<th>ANIMAL</th>
<th>DOSE / ROUTE / DURATION</th>
<th>IMPORTANT FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal tolerability</td>
<td>Rabbit (n=6)</td>
<td>Once daily application of 100 mg calcipotriol and betamethasone dipropionate ointment (DOVOBET® ointment) and 100 mg vehicle ointment on separate skin areas for 6 weeks.</td>
<td>No skin irritation was observed. Histopathological changes consisting of squamous metaplasia of pilosebaceous tissue and comedogenic activity attributable to the ointment vehicle were observed.</td>
</tr>
<tr>
<td>Dermal tolerability</td>
<td>Rabbit (n=6)</td>
<td>Once daily application of 100 mg of calcipotriol and betamethasone dipropionate ointment (DOVOBET® ointment), calcipotriol (50 mcg/g), betamethasone (as dipropionate) (0.5 mg/g), and vehicle ointment on separate skin areas for 6 weeks.</td>
<td>Slight skin irritation attributed primarily to calcipotriol was observed. Histopathological changes consisting of squamous metaplasia of pilosebaceous tissue and comedogenic activity attributable primarily to the ointment vehicle were observed.</td>
</tr>
<tr>
<td>Dermal tolerability (non-occlusive)</td>
<td>Rabbit (NZW) (6M per group)</td>
<td>Once daily topical application of 100 mg of calcipotriol and betamethasone dipropionate gel (DOVOBET® gel) and gel vehicle for 3 weeks.</td>
<td>Mild to moderate skin irritation. Mean score for erythema (max=4) on day 18 was gel vehicle 1.0 and DOVOBET® gel 0.67. Irritation was ascribed to the vehicle. DOVOBET® gel treated rabbits showed decreased weight gain and smaller adrenal glands.</td>
</tr>
<tr>
<td>Dermal tolerability (non-occlusive)</td>
<td>Rabbit (NZW) (6M per group)</td>
<td>Once daily topical application of 100 mg of calcipotriol and betamethasone dipropionate gel (DOVOBET® gel) and gel vehicle for 4 weeks.</td>
<td>Mild to moderate skin irritation. Mean score for erythema (max=4) on day 28 was gel vehicle 1.0 and DOVOBET® gel 1.5. Irritation was ascribed to one or both active components and the vehicle. Treated and untreated areas showed a marked decrease in skin fold thickness (betamethasone effect). A temporary weight loss due to betamethasone was seen in the first 2 weeks of the study.</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Rabbit (NZW) (5M)</td>
<td>Single ocular application of 2 drops (approx. 100 mg) of calcipotriol and betamethasone dipropionate gel (DOVOBET® gel)</td>
<td>The mean score of ocular lesions (max) based on 24, 48 and 72 hr assessments: cornea opacity 0 (4); iris lesion 0(2); conjunctiva erythema 0(3); conjunctivae chemosis 0(4). The only effects observed were ptosis and slight pink discolouration of the orbital ring at 1 hr after treatment but these effects disappeared within 6 hrs.</td>
</tr>
</tbody>
</table>
REFERENCES


5. BMS-181161 (calcipotriol): Dermal carcinogenicity study in mice (Study no. CTOX0101), data on file at LEO Pharma Inc., Thornhill, ON, L3T 7W8.

6. BMS-181161 (calcipotriol) solution: 12-month photocarcinogenesis study with ultraviolet radiation in hairless mice (Study no. CTOX0102), data on file at LEO Pharma Inc., Thornhill, ON, L3T 7W8.


34. Ristow HJ. A major factor contributing to epidermal proliferation in inflammatory skin diseases appears to be interleukin 1 or a related protein. Proc Natl Acad Sci USA 1987;84:1940-4.


43. Clinical trial and adverse event data (including children) on file at LEO Pharma Inc., Thornhill, ON, L3T 7W8.
PART III: CONSUMER INFORMATION

**DOVOBET® Gel**
calcipotriol and betamethasone dipropionate gel

This leaflet is part III of a three-part "Product Monograph" published when Dovobet® gel was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Dovobet® gel. Contact your doctor or pharmacist if you have any questions about this drug.

ABOUT THIS MEDICATION

**What the medication is used for:**
Dovobet® gel is used topically in the treatment of patients 18 years and older with:
- Moderate to severe psoriasis on the scalp for up to 4 weeks, and
- Mild to moderate psoriasis plaques on the body for up to 8 weeks.

**What it does:**
Dovobet® gel contains two active ingredients in one product; calcipotriol (a vitamin D-like substance) and betamethasone (a corticosteroid) that work together to control psoriasis.

Psoriasis lesions are areas of inflamed skin where the production of skin cells is too rapid. This creates red, scaly, thick patches (plaques) of skin. Treatment is targeted at reducing signs of redness and scaling and symptoms such as itching.

Calcipotriol helps to bring the rate of skin cell growth back to normal. Betamethasone works to reduce inflammation (redness, swelling and itching).

**When it should not be used:**
**Do not use Dovobet® gel:**
- if you are allergic to any of the ingredients or the container (polyethylene) of Dovobet® gel
- if you have problems with high calcium levels in your body
- if you have skin infections caused by viruses (e.g. cold sores, chicken pox), a fungus (e.g. athlete’s foot, ringworm), bacteria, parasites (e.g. scabies)
- if you have tuberculosis or syphilis
- if you have perioral dermatitis (red mouth rash), ichthyosis (dry, scaly skin), acne (pimples), rosacea (flushed facial skin), ulcers or broken skin
- if you have thin skin, easily damaged veins, stretch marks
- if you have other types of psoriasis
- if you have severe liver disease
- if you have severe kidney disease

Dovobet® gel is not for use in the eyes or on itchy skin of the genital or anal area.

**What the medicinal ingredients are:**
Each gram of gel contains 50 mcg calcipotriol (as monohydrate) and 0.5 mg betamethasone (as dipropionate)

**What the nonmedicinal ingredients are:**
Paraffin liquid, hydrogenated castor oil, polyoxypropylene-11-stearyl ether (contains butylhydroxytoluene) and α-tocopherol.

**What dosage forms it comes in:**
Dovobet® gel is an almost clear, colourless to slightly off-white gel. Available in 30 g, 60 g and 2x 60 g bottles.

WARNINGS AND PRECAUTIONS

BEFORE you use Dovobet® gel talk to your doctor or pharmacist if you:
- have diabetes
- have skin infections
- use other medicines that contain corticosteroids
- are pregnant or planning to get pregnant
- are breast feeding

Dovobet® gel is not recommended in children and adolescents under 18 years of age.

Calcipotriol in Dovobet® gel may increase the risk of developing skin cancer caused by ultraviolet radiation (UVR).

While using Dovobet® gel, you should avoid exposure to natural or artificial sunlight (UVR) such as phototherapy, tanning beds, sunlamps, etc.

Do not use Dovobet® gel on your face, skin folds (e.g. groin, armpit, under the breast or in the creases of the buttocks), or on broken skin. Do not use Dovobet® gel in or near the eyes. Dovobet® gel may cause eye irritation and irritation of facial skin.

Do not bandage, cover or wrap the treated skin area after applying Dovobet® gel on your body.

If used on the scalp, do not cover your scalp with a shower cap, bandages or dressings after applying Dovobet® gel.

The maximum daily dose is 15 g per day, or 100 g per week, in total of all products containing calcipotriol.

Talk to your doctor about the maximum amount of skin area that should be treated with Dovobet® gel.

If required, your doctor may recommend a blood test to check your calcium level or the functioning of your adrenal gland.
INTERACTIONS WITH THIS MEDICATION

Before using Dovobet® gel tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those you can buy without a prescription, especially medicines that contain a corticosteroid and/or calcipotriol.

PROPER USE OF THIS MEDICATION

Always use Dovobet® gel exactly as your doctor has told you. Shake the bottle well before use.

Usual dose:
Apply Dovobet® gel once a day to the affected areas. Treatment on the body may be continued for up to 8 weeks. Treatment on the scalp may be continued for up to 4 weeks. The maximum daily dose is 15 g per day, or 100 g per week, in total of all products containing calcipotriol.

Before Applying Dovobet® gel:
- Use only on areas of your skin affected by psoriasis and not on skin that does not have psoriasis.
- If you accidentally get Dovobet® gel on your face wipe it off.
- If applying to your scalp, you don’t need to wash your hair before applying Dovobet® gel.

Using Dovobet® gel on the body:
Apply a sufficient amount of gel on affected area to cover plaque with an even layer. Massage gently until gel has been absorbed into skin.

Using Dovobet® gel on the scalp:

1. Comb dry hair first to remove loose psoriasis scales.
2. For long hair, gently part your hair to reveal affected scalp area.
3. Apply gel to affected scalp areas that have visible psoriasis.
4. For a larger area of plaque or for very thick hair, you may need to re-part hair to expose neighbouring psoriasis area. Repeat until the entire affected area (or plaque) is covered with an even layer of gel.

After applying Dovobet® Gel:
- Wash your hands well after applying Dovobet® Gel.
- It is important to leave treatment areas uncovered. Do not bandage, cover or wrap the skin or scalp.
- Do not wash your body/hair immediately after application. Dovobet® Gel should be left on body/scalp until absorbed.
- Dovobet® gel should not be applied 12 hours before or after colouring, perming or any chemical hair treatments. To help avoid irritation, always ask your doctor about using any hair treatments with scalp psoriasis.

Overdose:
In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use Dovobet® gel use it as soon as you remember. Next time, follow your regular application routine. It’s important not to use Dovobet® gel more than once a day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effect with use of Dovobet® gel on the scalp as well as on the body is itching. Other less common effects reported for Dovobet® gel include: burning sensation of the skin, skin pain or irritation, inflammation of hair root, hair loss, rash (with or without pustules), skin infection, eye irritation, redness, acne, dizziness, dry skin, headache, facial swelling, flushing, migraine, outer ear infection, sinus infection, increased blood calcium level, increased blood parathyroid hormone and decreased blood phosphorus level.

Side effects caused by long term use of corticosteroids such as betamethasone include: thinning of the skin, stretch marks or surface veins, changes in hair growth, red mouth rash, skin rash with inflammation, small white spots, lightening of skin colour.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist</th>
<th>Stop taking drug and call your doctor or pharmacist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: Worsening of psoriasis (red, scaly, thick patches of skin)</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Rare: Pustular psoriasis (red area with yellowish pustules, headache, fever, chills, arthralgia, malaise, anorexia, nausea)</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

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</tr>
</thead>
<tbody>
<tr>
<td>Rare: Adrenal effects (weakness, increased urination/thirst, fatigue, weight loss, cataracts, infections)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Very Rare: Allergic reaction (rash, itching, swelling, trouble breathing, dizziness)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Very Rare: High blood calcium (fatigue, depression, mental confusion, anorexia, nausea, vomiting, constipation, increased urination/thirst)</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

This is not a complete list of side effects. For any unexpected effects while taking Dovobet® gel, contact your doctor or pharmacist.

**HOW TO STORE IT**

Store at 15-30 °C. Do not refrigerate. Protect from light by keeping the bottle in the carton between applications.

- Keep Dovobet® gel out of the reach and sight of children and pets.
- Use the medicine within 6 months of first opening the bottle.
- Do not use Dovobet® gel after the expiry date on the label (EXP).

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at: [www.leo-pharma.ca](http://www.leo-pharma.ca) or by contacting the sponsor, LEO Pharma Inc., at: 1-800-668-7234.

This leaflet was prepared by LEO Pharma Inc.

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