

PRODUCT MONOGRAPH

Pr **DOVOBET®**

calcipotriol and betamethasone dipropionate

Ointment, 50 mcg/g calcipotriol and
0.5 mg/g betamethasone (as dipropionate)

Topical Antipsoriatic Agent
Vitamin D Analogue / Corticosteroid

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Pr DOVOBET®
calcipotriol and betamethasone dipropionate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|--------------------------------|---|--|
| topical | Ointment, 50 mcg/g calcipotriol and 0.5 mg/g betamethasone (as dipropionate) | none <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i> |

INDICATIONS AND CLINICAL USE

DOVOBET (calcipotriol and betamethasone dipropionate) ointment is indicated for the topical treatment of psoriasis vulgaris for up to 4 weeks.

DOVOBET should not be used on the face.

CONTRAINDICATIONS

- Patients who are hypersensitive to DOVOBET (calcipotriol and betamethasone dipropionate), to any ingredient in the formulation or to components of the tube. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Ophthalmic use
- treatment of viral, fungal or bacterial skin infections, tuberculosis of the skin, syphilitic skin infections, chicken pox, eruptions following vaccinations, and in viral diseases such as herpes simplex, varicella and vaccinia.

WARNINGS AND PRECAUTIONS

General

If DOVOBET (calcipotriol and betamethasone dipropionate) is used in excess of the maximum recommended weekly amount of 100 g, it is important to monitor the serum calcium levels at regular intervals due to the risk of hypercalcemia secondary to excessive absorption of calcipotriol. If the serum calcium level becomes elevated, therapy should be discontinued and the serum calcium level monitored until it returns to normal.

Carcinogenesis

Calcipotriol when used in combination with ultraviolet radiation (UVR) may enhance the known skin carcinogenic effect of UVR (see TOXICOLOGY, Carcinogenicity).

Endocrine and Metabolism

Application on large areas of damaged skin, under occlusive dressings, or in skin folds should be avoided since it increases systemic absorption of corticosteroids and the risk of adverse effects such as adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycaemia and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids. Occlusive dressings should not be applied if body temperature is elevated.

All of the adverse effects associated with systemic use of corticosteroids, including adrenal suppression, may also occur following topical administration of corticosteroid containing products such as DOVOBET, especially in children.

Skin

DOVOBET should not be used on the face since this may give rise to itching and erythema of the facial skin. Patients should be instructed to wash their hands after each application of DOVOBET in order to avoid inadvertent transfer to the face. Should facial dermatitis develop in spite of these precautions, DOVOBET therapy should be discontinued.

Prolonged use of corticosteroid-containing preparations may produce striae or atrophy of the skin or subcutaneous tissues. Therefore, it is recommended that corticosteroid treatment be interrupted periodically, and that one area of the body be treated at a time. Topical corticosteroids should be used with caution on lesions of the face, groin and axillae as these areas are more prone to atrophic changes than other areas of the body. If skin atrophy occurs, discontinue treatment. There may be a risk of rebound psoriasis when discontinuing corticosteroids after prolonged periods of use (see ADVERSE REACTIONS).

Special Populations

Pregnant Women: The safety of calcipotriol and/or topical corticosteroids for use during pregnancy has not been established. Although studies in experimental animals have not shown teratogenic effects with calcipotriol, studies with corticosteroids have shown teratogenic effects. The use of DOVOBET 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 or if topical application of corticosteroids can lead to sufficient systemic absorption to produce detectable quantities in breast milk. The use of DOVOBET is not recommended in nursing women.

Pediatrics (<18 years of age): There is no clinical trial experience with the use of DOVOBET in children. Children may demonstrate greater susceptibility to systemic steroid related adverse effects due to a larger skin surface area to body weight ratio as compared to adults.

Monitoring and Laboratory Tests

Treatment with DOVOBET in the recommended amounts (See DOSAGE AND ADMINISTRATION) does not generally result in changes in laboratory values. However, in patients at risk for 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 administration should be discontinued and serum calcium levels should be measured once weekly until they return to

normal. Patients with marginally elevated serum calcium may be treated with DOVOBET, provided that serum calcium is monitored at suitable intervals.

ADVERSE REACTIONS

In clinical trials, the most common adverse reaction associated with DOVOBET (calcipotriol and betamethasone dipropionate) was pruritus. Pruritus was usually mild and no patients were withdrawn from treatment.

Calcipotriol is associated with local reactions such as transient lesional and perilesional irritation. Rare cases of hypersensitivity reaction have been reported. Hypercalcemia can develop but is usually related to excessive administration (i.e. greater than the recommended weekly amount of 100 g ointment or 5 mg calcipotriol - See DOSAGE AND ADMINISTRATION).

Topical corticosteroids can cause the same spectrum of adverse effects associated with systemic steroid administration, including adrenal suppression. Adverse effects associated with topical corticosteroids are generally local and include dryness, itching, burning, local irritation, striae, atrophy of the skin or subcutaneous tissues, telangiectasia, hypertrichosis, folliculitis, skin hypopigmentation, allergic contact dermatitis, maceration of the skin, miliaria, or secondary infection. If applied to the face, acne rosacea or perioral dermatitis can occur. In addition, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.

In a randomized, double-blind, parallel group, safety study of psoriasis patients with at least moderate disease severity, DOVOBET ointment was used intermittently on an 'as needed' basis under medical supervision (N=207). Patients were followed for up to 52 weeks. The median amount of study drug used was 15.4 g/week. The effects of DOVOBET ointment on calcium metabolism were not studied and the effects on adrenal suppression were not adequately studied. The following adverse drug reactions were reported in 1% or more of patients: pruritus (5.8%), psoriasis (5.3%), skin atrophy (based on a dermatologist's visual assessment) (1.9%), folliculitis (1.9%), burning sensation (1.4%), skin depigmentation (1.4%), and erythema (1.0%). One case of serious flare-up of psoriasis was reported.

DRUG INTERACTIONS

There is no experience of concomitant therapy with other antipsoriatic drugs.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- DOVOBET (calcipotriol and betamethasone dipropionate) is FOR TOPICAL USE ONLY and not for ophthalmic use.
- There is no clinical trial experience with the use of DOVOBET in children.

Recommended Dose and Dosage Adjustment

DOVOBET should be applied topically to the affected areas 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 reinstated.

The maximum recommended adult dose of DOVOBET ointment is 100 g per week.

Missed Dose

If a dose is missed, the patient should apply DOVOBET as soon as he/she remembers and then continue on as usual.

OVERDOSAGE

Due to the calcipotriol component of DOVOBET (calcipotriol and betamethasone dipropionate), excessive administration (i.e. more than the recommended weekly amount of 100 g) may cause elevated serum calcium, which rapidly subsides when treatment is discontinued. In such cases, it is recommended to monitor serum calcium levels once weekly until they return to normal.

Excessive or prolonged use of topical corticosteroids can suppress pituitary-adrenal function, resulting in secondary adrenal insufficiency and manifestations of hypercorticism, including Cushing's disease. Recovery is usually prompt and complete upon steroid discontinuation. In cases of chronic toxicity, slow withdrawal of corticosteroids is recommended.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

DOVOBET 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 $1,25(\text{OH})_2\text{D}_3$ receptor. Calcipotriol is as potent as $1,25(\text{OH})_2\text{D}_3$, the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than $1,25(\text{OH})_2\text{D}_3$ 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, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity is generally unclear. However, corticosteroids are thought to induce phospholipase A₂ inhibitor proteins, preventing arachidonic acid release and the biosynthesis of potent mediators of inflammation.

Clinical Pharmacology

A large multicentre, randomized, double-blind clinical trial has shown DOVOBET ointment (50 mcg/g calcipotriol plus 0.5 mg/g betamethasone (as dipropionate)) administered twice daily to be more efficacious and to provide faster onset of action than either of the individual components alone (calcipotriol or betamethasone dipropionate) for the treatment of plaque psoriasis. These findings were supported by a second large, multicentre, randomised, double-blind trial comparing DOVOBET twice daily to calcipotriol and betamethasone dipropionate, each in their currently marketed formulations. A third large, multicentre, randomised, double-blind trial found DOVOBET once daily to be more efficacious than vehicle alone and calcipotriol twice daily (betamethasone alone was not evaluated). It was also demonstrated that

once daily DOVOBET was similar to twice daily DOVOBET for most of the efficacy measures. In all three studies, DOVOBET was effective in terms of reducing PASI (Psoriasis Area and Severity Index) score and thickness of target lesions. Furthermore, a significant proportion of patients on DOVOBET achieved marked improvement or clearance at the end of 4 weeks of treatment. Clinical improvement occurred rapidly and a significant improvement was evident within 1 week of treatment. DOVOBET was well tolerated with the most common adverse reaction being mild pruritus. In one additional study, patients were treated with DOVOBET once daily for 8 weeks. Optimal population results in this study were seen between 4 and 5 weeks of treatment. The therapeutic goal envisioned with DOVOBET is to provide an effective, rapid acting topical agent for initial treatment of psoriasis and/or for treatment of flare-ups of psoriasis.

Pharmacokinetics

A pharmacokinetic study of calcipotriol ointment demonstrated that the apparent systemic absorption over 12 hours is approximately 5.5% of the dose in normal subjects and in psoriatic patients. Topical application of corticosteroids to normal skin results in minimal absorption. Only small amounts of drug reach the dermis and are then absorbed into the systemic circulation. However, absorption may be greater when corticosteroids are applied to certain areas of the body (such as the axilla and scrotum) or if the epidermis is damaged by disease or inflammation. Continued absorption of corticosteroids may occur, even after washing, due to retention of the drug in the stratum corneum. The individual pharmacokinetics of calcipotriol and betamethasone dipropionate, are not affected by their combined presence in DOVOBET ointment. Under normal conditions of use, systemic absorption of calcipotriol and/or betamethasone from DOVOBET is not expected to have any effects.

STORAGE AND STABILITY

Store at 5 to 25°C. Use within 12 months of first opening the tube.

For easy application do not refrigerate, this is to prevent pulling of delicate skin.

LEO®

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

Ointment (faintly translucent white to yellowish ointment)

Composition

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

Non-medicinal ingredients: white soft paraffin, liquid paraffin, polyoxypropylene-15-stearyl ether and α -tocopherol.

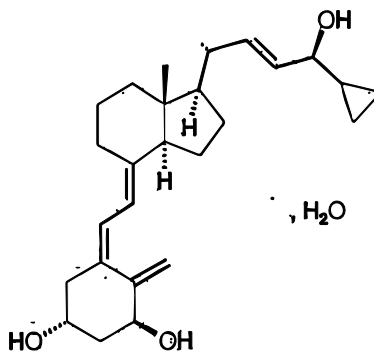
Packaging

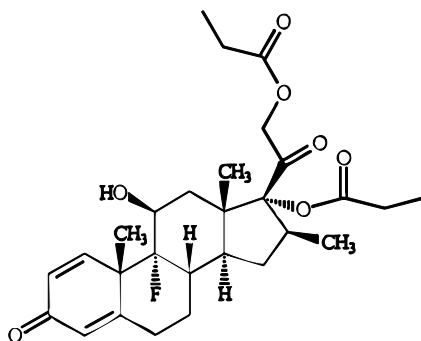
Available in 30 g, 60 g, and 120 g lacquered aluminium tubes (equipped with an aluminium membrane).

PART II: SCIENTIFIC INFORMATION**PHARMACEUTICAL INFORMATION****Drug Substance**

| | | |
|----------------------------|--|---|
| Proper name (I.N.N.): | <u>Calcipotriol hydrate</u> | <u>Betamethasone dipropionate</u> |
| Chemical name: | 9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-(1 α ,3 β ,5Z,7E,22E,24S) | 9-fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate |
| Alternative chemical name: | 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 | Pregna-1,4-diene-3,20-dione,9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-(11 β ,16 β) |
| Laboratory code name: | MC 903 or MC 903-000 | 433 or 433/M |
| Molecular formula: | C ₂₇ H ₄₀ O ₃ , H ₂ O | C ₂₈ H ₃₇ FO ₇ |
| Molecular mass: | 430.6 | 504.59 |
| Chirality: | The calcipotriol molecular 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. | |

Structural formula:
Calcipotriol hydrate



Betamethasone dipropionate

Physicochemical properties:

*Physical Form:**Solubility at room temperature:**Melting point:**Polymorphism:**Other characteristics:*Calcipotriol hydrate

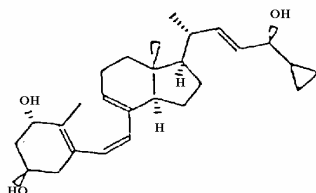
White or almost white crystalline substance.

Freely soluble in ethanol, soluble in chloroform and propylene glycol, practically insoluble in liquid paraffin. Solubility in water is 0.6 mcg/ml.

166-168/C

So far no signs have indicated the existence of polymorphic forms.

Calcipotriol is a vitamin D derivative. It is well-known that vitamin D in solution forms a reversible temperature dependent equilibrium between vitamin D and pre-vitamin D (described in (i.e.) J Pharm Sci 1968; 57:1326). In the same way, solutions of calcipotriol establish an equilibrium with “pre-calcipotriol”. The structural formula of “pre-calcipotriol” is shown below.

Betamethasone dipropionate

White or almost white odourless powder.

Freely soluble in acetone, in dioxane, in dichloromethane and in chloroform; soluble in methanol; sparingly soluble in alcohol; slightly soluble in ether; insoluble in water and in hexane.

176-180/C

CLINICAL TRIALS

A large multicentre, randomized, double-blind clinical trial has shown DOVOBET ointment (50 mcg/g calcipotriol plus 0.5 mg/g betamethasone (as dipropionate)) administered twice daily to be more efficacious and to provide faster onset of action than either of the individual components alone (calcipotriol or betamethasone dipropionate) for the treatment of plaque psoriasis. These findings were supported by a second large, multicentre, randomised, double-blind trial comparing DOVOBET twice daily to calcipotriol and betamethasone dipropionate, each in their currently marketed formulations. A third large, multicentre, randomised, double-blind trial found DOVOBET once daily to be more efficacious than vehicle alone and calcipotriol twice daily (betamethasone alone was not evaluated). It was also demonstrated that once daily DOVOBET was similar to twice daily DOVOBET for most of the efficacy measures. In all three studies, DOVOBET was effective in terms of reducing PASI (Psoriasis Area and Severity Index) score and thickness of target lesions. Furthermore, a significant proportion of patients on DOVOBET achieved marked improvement or clearance at the end of 4 weeks of treatment. Clinical improvement occurred rapidly and a significant improvement was evident within 1 week of treatment. DOVOBET was well tolerated with the most common adverse reaction being mild pruritus. In one additional study, patients were treated with DOVOBET once daily for 8 weeks. Optimal population results in this study were seen between 4 and 5 weeks of treatment. The therapeutic goal envisioned with DOVOBET is to provide an effective, rapid acting topical agent for initial treatment of psoriasis and/or for treatment of flare-ups of psoriasis.

In a randomized, double-blind, parallel group, safety study, patients with at least moderate disease severity were given DOVOBET ointment intermittently on an 'as needed' basis under medical supervision (N=207). Patients were followed for up to 52 weeks. The median amount of study drug used was 15.4 g/week. **The effects of DOVOBET ointment on calcium metabolism were not studied and the effects on adrenal suppression were not adequately studied.** The following adverse drug reactions were reported in 1% or more of patients: pruritus (5.8%), psoriasis (5.3%), skin atrophy (based on a dermatologist's visual assessment) (1.9%), folliculitis (1.9%), burning sensation (1.4%), skin depigmentation (1.4%), and erythema (1.0%). One case of serious flare-up of psoriasis was reported.

SUMMARY OF CLINICAL TRIALS

| STUDY CODE | STUDY DESIGN | EVALUATION CRITERIA AND RESULTS |
|-------------|---|---|
| MCB 9903 DE | <p><u>Design:</u> Randomised, double-blind, right/left comparison on the forearm.</p> <p><u>Inclusion Criteria:</u> Healthy volunteers.</p> <p><u>Treatment Period:</u> Twice daily topical application for 4 weeks (28 days).</p> <p><u>Treatment Groups:</u> Phase I: (1) Dovobet ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate); (2) Betamethasone dipropionate ointment (0.5 mg/g). (n=30) Phase II: (1) Dovobet ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate); (2) Placebo ointment. (n=15)</p> | <p><u>Evaluation Criteria:</u> Sonography was performed on day 1. Sonography and clinical assessments of atrophy, telangiectasia and erythema) were performed on days 8, 15, 22 and 29. Skin biopsies were taken from 10 subjects on day 29 for morphometric determination of epidermal and dermal thickness and epidermal cell layers. Sonography and clinical assessments were repeated 2 weeks after treatment (day 43) in subjects who did not have a biopsy taken.</p> <p><u>Results:</u> There were no clinical signs of atrophy, telangiectasia or irritation (erythema). Sonography demonstrated skin thinning with Dovobet relative to placebo ointment but similar to betamethasone (12.3% and 13.2% respectively) after 4 weeks of treatment. There were no histological differences in epidermal or dermal thickness between Dovobet and betamethasone.</p> |

SUMMARY OF CLINICAL TRIALS (continued)

| STUDY CODE | STUDY DESIGN | EVALUATION CRITERIA AND RESULTS |
|-------------|--|---|
| MCB 9902 FR | <p><u>Design:</u> Single centre, randomised, double-blind, bioequivalence study according to FDA guideline for vasoconstrictor assays.</p> <p><u>Inclusion Criteria:</u> Healthy volunteers.</p> <p><u>Treatment Period:</u> Pilot Phase: Single 10 mcl application on the ventral forearm for 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 hours followed up to 24 hours.</p> <p>Pivotal Phase: (1) Single 10 mcl application of Dovobet and betamethasone dipropionate ointment (Diprosone*) at a dose-duration corresponding to ED₅₀ (1h04min) on two sites each per forearm. (2) Betamethasone was also applied on two sites per forearm at dose-durations corresponding to 0.5 times ED₅₀ (32 min.) and 2 times ED₅₀ (2h08min.)</p> <p><u>Treatment:</u> Pilot Phase: Diprosone* (0.5 mg/g betamethasone as dipropionate). (n=12) Pivotal Phase: (1) Dovobet (50 mcg/g calcipotriol plus 0.5 mg/g betamethasone as dipropionate) ointment; (2) Diprosone* (0.5 mg/g betamethasone as dipropionate). (n=90)</p> | <p><u>Evaluation Criteria:</u> Skin blanching (vasoconstrictor) assessed using the chromametric a value and visual scoring.</p> <p><u>Results:</u> Pilot Part: Betamethasone dipropionate ointment (Diprosone*) produced a dose-duration dependent vasoconstriction with an ED₅₀ (half maximal response) of 1h04min., D₁ (0.5 times ED₅₀) of 32 min and D₂ (2 times ED₅₀) of 2h08 min. 67% of the included subjects were 'detectors' (AUC at D₁ was at least 1.25 time the AUC at D₂).</p> <p>Pivotal Part: Betamethasone dipropionate in Dovobet ointment is bioequivalent to the reference product, Diprosone* ointment, as the 90% confidence interval for the skin blanching response ratio (test to reference) is [0.81 ; 1.04] and within the interval [0.80 ; 1.25] as defined by the applicable FDA guideline.</p> <p>* registered trademark of Schering-Plough Ltd.</p> |

SUMMARY OF CLINICAL TRIALS (continued)

| STUDY CODE | STUDY DESIGN | EVALUATION CRITERIA AND RESULTS |
|-------------|--|---|
| MCB 9801 NL | <p><u>Design:</u> Single centre, open, randomised, multiple (2 application sites on the thigh) topical absorption study.</p> <p><u>Inclusion Criteria:</u> Healthy volunteers.</p> <p><u>Treatment Period:</u> Single 12 hour application.</p> <p><u>Treatment:</u> Dovobet (50 mcg/g calcipotriol plus 0.5 mg/g betamethasone (as dipropionate)) ointment containing ³H-labelled calcipotriol. (n=4)</p> | <p><u>Evaluation Criteria:</u> Pharmacokinetic parameters: Recovery of ³H-radioactivity from gauzes, gloves, swabs and shorts; excretion of ³H-radioactivity in urine and faeces; ³H-radioactivity levels in serum. Safety parameters: adverse events, local tolerability results, vital signs, ECG parameters and clinical laboratory parameters.</p> <p><u>Results:</u> Excretion and recovery data suggest that there is only minimal systemic absorption of calcipotriol. The ointment was well tolerated.</p> |

SUMMARY OF CLINICAL TRIALS (continued)

| STUDY CODE | STUDY DESIGN | EVALUATION CRITERIA AND RESULTS |
|-------------|---|--|
| MCB 9901 NL | <p><u>Design:</u> Single centre, open, randomised, multiple (2 application sites on the thigh) topical absorption study.</p> <p><u>Inclusion Criteria:</u> Healthy volunteers.</p> <p><u>Treatment Period:</u> Single 12 hour application of ³H labelled ointment and single 12 hour application after 4 weeks of twice daily topical application of unlabelled ointment.</p> <p><u>Treatment Groups:</u> Group I: Single 12 hour application of 2.5 g Dovonex (50 mcg/g calcipotriol) ointment containing ³H labelled calcipotriol. Four weeks (28 days) of twice daily treatment with unlabelled Dovonex. On day 36, another single 12 hour application of Dovonex containing ³H labelled calcipotriol. (n=6)</p> <p>Group II: Single 12 hour application of 2.5 g Dovobet (50 mcg/g calcipotriol plus 0.5 mg/g betamethasone dipropionate) ointment containing ³H labelled calcipotriol. Four weeks (28 days) of twice daily treatment with unlabelled Dovobet. On day 36, another single 12 hour application of Dovobet containing ³H labelled calcipotriol. (n=6)</p> <p>Group III: Single 12 hour application of 2.5 g Dovobet ointment vehicle containing ³H labelled calcipotriol.</p> <p>Group IV: Single 12 hour application of 2.5 g Dovobet ointment containing ³H labelled betamethasone.</p> <p>Group V: Single 12 hour application of 2.5 g Dovobet ointment vehicle containing ³H labelled betamethasone.</p> | <p><u>Evaluation Criteria:</u> Pharmacokinetic parameters: Recovery of ³H radioactivity from gauzes, gloves, swabs and shorts; excretion of ³H radioactivity in urine and faeces; ³H radioactivity levels in serum. Safety parameters: adverse events, local tolerability results, vital signs, ECG parameters and clinical laboratory parameters.</p> <p><u>Results:</u> The absorption of calcipotriol after a single application of Dovobet is similar to absorption after application of the other marketed formulation of calcipotriol (i.e. Dovonex®; 50 mcg/g calcipotriol). Thus, the safety profile of Dovonex is applicable to Dovobet. Betamethasone dipropionate in Dovobet does not influence the absorption rate of calcipotriol and vice versa calcipotriol does not affect the absorption of betamethasone. Absorption of calcipotriol is similar after 4 weeks of treatment with Dovobet as it is after a single application.</p> |

SUMMARY OF CLINICAL TRIALS (continued)

| STUDY CODE | STUDY DESIGN | EVALUATION CRITERIA AND RESULTS |
|-----------------|---|---|
| MCB 9802 INT | <p><u>Design:</u> Multi-centre, randomised, double-blind, vehicle-controlled, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Plaque psoriasis amenable to topical treatment.</p> <p><u>Treatment Period:</u> Twice daily topical application for 4 weeks of active treatment.</p> <p><u>Treatment Groups:</u> (1) Combination ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate; Dovobet), (n=301); (2) Calcipotriol ointment (50 mcg/g), (n=308); (3) Betamethasone dipropionate ointment (0.5 mg/g), (n=313); (4) Ointment vehicle, (n=108)</p> | <p><u>Evaluation Criteria:</u> Change in PASI score after 4 weeks of treatment, speed of response (change in PASI score after 1 week of treatment), change in plaque thickness of a target lesion, investigators' overall assessment of treatment response (clearance or marked improvement) at the end of treatment, patient assessment of overall treatment response, patient assessment of treatment acceptability, adverse events, and serum biochemistry.</p> <p><u>Results:</u> Dovobet combination treatment was effective and provided a more rapid onset of action than either of the individual components (calcipotriol or betamethasone dipropionate). At the end of 4 weeks treatment, PASI score was reduced by 73% with Dovobet, 49% with calcipotriol, 63% with betamethasone and 29% with vehicle (p<0.001). After 1 week of treatment PASI score was reduced by 48% with Dovobet, 28% with calcipotriol, 41% with betamethasone and 22% with vehicle (p<0.001). The greatest reduction in target lesion thickness was observed with Dovobet. Plaque thickness was reduced by 79% with Dovobet compared to 54% with calcipotriol, 67% with betamethasone and 27% with vehicle (p<0.001). The greatest treatment response according to the investigators' overall assessment was also observed in the Dovobet group. With Dovobet combination treatment 76% of patients achieved clearance or marked improvement compared to 33% with calcipotriol, 56% with betamethasone and 8% with vehicle (p<0.001). Adverse reactions associated with Dovobet were similar to reactions with betamethasone. Mild pruritus was the most common adverse reaction.</p> |

SUMMARY OF CLINICAL TRIALS (continued)

| STUDY CODE | STUDY DESIGN | EVALUATION CRITERIA AND RESULTS |
|--------------|---|---|
| MCB 9904 INT | <p><u>Design:</u> Multi-centre, randomised, double-blind, vehicle-controlled, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Plaque psoriasis amenable to topical treatment.</p> <p><u>Treatment Period:</u> Phase 1: Twice daily topical application of active treatment (double-blind) for 4 weeks. Phase 2: twice daily maintenance therapy with Dovonex® (open-label) for 4 weeks.</p> <p><u>Treatment Groups:</u> Phase 1: (1) Dovobet ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate), (n=369); (2) Dovonex® ointment (50 mcg/g calcipotriol, Leo Pharmaceutical Products), (n=365); (3) Diprosone* ointment (0.5 mg/g betamethasone dipropionate, Schering-Plough Ltd.), (n=363)</p> <p>Phase 2: Patients from each of the above groups (n=344, 332, and 344, respectively) transferred to Dovonex® ointment.</p> | <p><u>Evaluation Criteria:</u> Phase 1: Change in PASI score after 4 weeks of treatment, speed of response (change in PASI score after 1 week of treatment), change in plaque thickness of a target lesion, investigators' overall assessment of treatment response (clearance or marked improvement) at the end of treatment, patient assessment of overall treatment response, change in redness and scaliness of a target lesion, adverse events, and serum biochemistry. Phase 2: general evaluation of transfer to Dovonex® maintenance therapy.</p> <p><u>Results:</u> Dovobet combination treatment was effective and provided a more rapid onset of action than either of the individual components in their currently marketed formulations (Dovonex® and Diprosone*). At the end of 4 weeks treatment, PASI score was reduced by 74% with Dovobet, 55% with Dovonex®, and 61% with Diprosone* (p<0.001). After 1 week of treatment PASI score was reduced by 47% with Dovobet, 31% with Dovonex®, and 40% with Diprosone* (p<0.001). The greatest reduction in target lesion thickness was observed with Dovobet. Plaque thickness was reduced by 79% with Dovobet compared to 63% with Dovonex®, and 62% with Diprosone* (p<0.001). The greatest treatment response according to the investigators' overall assessment was also observed in the Dovobet group. With Dovobet combination treatment 68% of patients achieved clearance or marked improvement compared to 39% with Dovonex®, and 47% with Diprosone* (p<0.001). Adverse reactions associated with Dovobet were predictable based on the individual components with mild pruritus being the most common adverse reaction. Patients were safely transferred to maintenance therapy with Dovonex®.</p> |

SUMMARY OF CLINICAL TRIALS (*continued*)

| STUDY CODE | STUDY DESIGN | EVALUATION CRITERIA AND RESULTS |
|--------------|---|--|
| MCB 9905 INT | <p><u>Design:</u> Multi-centre, randomised, double-blind, vehicle-controlled, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Plaque psoriasis amenable to topical treatment.</p> <p><u>Treatment Period:</u> Active topical treatment once or twice daily for 4 weeks. To maintain blinding, the once daily group received vehicle in the morning and study medication in the evening.</p> <p><u>Treatment Groups:</u> (1) Dovobet combination ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate) once daily, (n=150); (2) Dovobet ointment twice daily, (n=234); (3) Dovonex ® ointment (50 mcg/g calcipotriol) twice daily, (n=227); (4) Ointment vehicle twice daily, (n=207).</p> | <p><u>Evaluation Criteria:</u> Change in PASI score after 4 weeks of treatment, speed of response (change in PASI score after 1 week of treatment), change in plaque thickness of a target lesion, investigators' overall assessment of treatment response (clearance or marked improvement) at the end of treatment, patient assessment of overall treatment response, patient assessment of treatment acceptability, change in redness and scaliness of target lesion, adverse events, and serum biochemistry.</p> <p><u>Results:</u> Once daily Dovobet combination treatment was as effective as twice daily Dovobet treatment but more effective than twice daily Dovonex® treatment. At the end of 4 weeks, PASI score was reduced by 69% with Dovobet once daily, 59% with Dovonex® twice daily, and 27% with vehicle twice daily (p<0.001). Reduction in PASI after 4 weeks of twice daily Dovobet treatment (74%) was similar to that after once daily Dovobet treatment (p=0.052). After 1 week of treatment PASI score was reduced by 46% with Dovobet once daily, 34% with Dovonex® twice daily, and 20% with vehicle twice daily (p<0.001). The speed of response to Dovobet twice daily treatment was similar to that after Dovobet once daily treatment, with the reduction in PASI after one week being 48%. The greatest reduction in target lesion thickness was observed with Dovobet, with similar reductions occurring after once daily (74%) and twice daily (78%) treatment. The greatest treatment response according to the investigators' overall assessment was also observed in the Dovobet groups, with twice daily treatment favoured over once daily. Adverse reactions associated with Dovobet were predictable based on the individual components with mild pruritus being the most common adverse reaction.</p> |

SUMMARY OF CLINICAL TRIALS (continued)

| STUDY CODE | STUDY DESIGN | EVALUATION CRITERIA AND RESULTS |
|--------------|--|---|
| MCB 0003 INT | <p><u>Design:</u> Multi-centre, randomised, double-blind, vehicle-controlled, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Plaque psoriasis amenable to topical treatment.</p> <p><u>Treatment Period:</u> Active topical treatment once daily for 4 weeks.</p> <p><u>Treatment Groups:</u> (1) Dovobet combination ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate) once daily, (n=490); (2) Calcipotriol ointment (50 mcg/g calcipotriol) once daily, (n=480); (3) Betamethasone ointment (0.5 mg/g betamethasone dipropionate) once daily, (n=476); (4) Vehicle ointment once daily, (n=157).</p> | <p><u>Evaluation Criteria:</u> Change in PASI score after 4 weeks of treatment, controlled disease after 4 weeks of treatment, speed of response (change in PASI score after 1 week of treatment), treatment success, and adverse events.</p> <p><u>Results:</u> Once daily Dovobet combination treatment was more effective than once daily application of its individual components or vehicle. At the end of 4 weeks, PASI score was reduced by 71% with Dovobet, 46% with calcipotriol, 57% with betamethasone and 23% with vehicle (p<0.001). The percentage of patients with controlled disease at the end of treatment was 56% for Dovobet, 22% for calcipotriol, 37% for betamethasone and 10% for vehicle (p<0.001). After 1 week of treatment PASI score was reduced by 39% with Dovobet, 23% with calcipotriol, 33% with betamethasone and 18% with vehicle (p<0.001). The proportion of patients with treatment success was 65% with Dovobet, 29% with calcipotriol, 46% with betamethasone, and 10% with vehicle (p<0.001). Adverse reactions associated with Dovobet were predictable based on the individual components with mild pruritus being the most common adverse reaction.</p> |

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 overdose 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 $1,25(\text{OH})_2\text{D}_3$. 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 are summarized briefly here and in more detail by species in tabular form following this section. Pharmacokinetic studies with ^3H -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 ^3H - H_2O from the metabolic degradation of ^3H -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 ^3H -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.

IN VIVO PHARMACOKINETIC STUDIES WITH CALCIPOTRIOL

| TYPE OF STUDY | METHODS | MAJOR RESULTS AND INTERPRETATION |
|---|---|---|
| (1) Acute administration of ³ H-MC903 by i.v. and oral routes to rats. | Female rats dosed with ³ H-MC903, 0.10 mg/kg i.v. or 0.20 mg/kg p.o. In experiment 1, rats sacrificed at different time points for measurement of radioactivity in plasma and tissues. In experiment 2, same doses, radioactivity measured in urine and faeces during first few hours and for several days. Six rats per dose per route. | <p>Rapid <i>metabolism</i> of MC903, with a half-life of 12 min. after i.v. Main metabolite: MC1080 in first plasma sample after 5 min; half-life of MC1080 54 min. Much lower levels after oral dosing. After both routes slow decline in the late phase due to further metabolic degradation leading to formation of ³H-H₂O. MC903 also metabolized to MC1046 then to more polar compounds later [possible glucuronides and sulphates, as well as putative metabolism to calcitronic acid, discussed in Study (5) below].</p> <p><i>Renal excretion</i> 16% (p.o.) and 26% (i.v.) of administered dose, peaking on Day 1 at 6-24 h (both routes); declined slowly in accordance with large volatile component, ³H-H₂O.</p> <p><i>Faecal excretion</i> 43% (p.o.) and 40% (i.v.), also highest on the first day with both routes. Total excreted radioactivity 59% (p.o.) and 67% (i.v.); <100% presumably due to exhalation of volatile components. <i>Calculated absorption</i> of MC903; by ratio of urinary excretion after oral and i.v. dosing, approximately 60%.</p> <p><i>Tissue levels</i>: Highest amounts in liver, kidney and intestine; also in fat, muscle and spleen. Early measurements most accurate, ie. before formation of volatile radioactivity.</p> |
| (2) Acute topical administration of ³ H-MC903 to rats and rabbits. | 6 rats, 2 rabbits, dosed once with topical ³ H-MC903, 21-25 mcg/kg in rats, 9-10 mcg/kg in rabbits. Urine and faeces collected every 24 h for 144 h. Surplus ointment removed after 4 h to prevent licking. Samples taken of serum, liver, treated skin, urine, and faeces. | <p>Surplus ointment removed at 4 h had accounted for about 60% of radioactivity. At 4 and 144 h less than 2% (in total) recovered from cages. Small amount of radioactivity retained <i>in skin</i> at 144 h (0.5-3.1%); this is approximately 30 (rats) and 200 (rabbits) times higher than levels found after i.v. dosing. <i>Serum levels</i> of ³H-MC903 were 0.2-0.6 ng-eqv/mL. This compares to 17 ng-eqv/mL after i.v. dosing of 0.1 mg/kg (see above study in rats). <i>Percutaneous absorption</i> based on total recovery from urine and faeces was 17%, 27% and 10% for male rats, female rats and female rabbits, respectively. <i>Liver levels</i> of ³H-MC903 ranged from 0.4-1.1 ng-eqv/g.</p> |
| (3) Acute oral and i.v. dosing of ³ H-MC903 to rats, whole-body autoradiography. | 5 and 6 rats dosed orally and i.v., respectively, 2 controls, sacrificed at various times after dosing. Distribution of radioactively labelled, non-volatile material assessed by examination of x-ray films after ≈ 7 months exposure to tissue sections. | <p><i>I.V.</i>: Low radioactivity distributed uniformly to most tissues including brain. Higher levels in excreting organs, bile ducts, liver and to a minor extent, kidneys.</p> <p><i>Oral</i>: Similar to i.v. dosing, except more radioactivity in oral cavity, oesophagus and stomach. Is noted that MC903 passes the blood-brain barrier with p.o. or i.v. dosing, that biliary excretion was evident after 15 min. with both routes of administration and no secretion to the stomach via gastric mucosa was observed. 24 h after dosing levels of non-volatile MC903-like material were very low, with no evidence for accumulation.</p> |

IN VIVO PHARMACOKINETIC STUDIES WITH CALCIPOTRIOL (continued)

| TYPE OF STUDY | METHODS | MAJOR RESULTS AND INTERPRETATION |
|--|--|--|
| (4) Acute oral and i.v. dosing of ³ H-MC903 to minipigs. | 2 pigs/dose (1M,1F), doses 0.1 mg/kg i.v., 0.20 mg/kg oral, and placebo. Blood samples at specified times and collection of urine and faeces for 10 days. 6 weeks later females crossed over to alternate regimen, urine and faeces and certain tissues (no blood) examined for MC903. | <i>Absorption</i> with oral dosing rapid but incomplete (≈40%). No clear distribution phase following i.v. administration. Short <i>elimination half-life</i> of 1 h for parent. <i>Metabolite</i> MC1080 apparent after 5 min, with half-life of 1.8 h. No late elimination phase detected, indicating accumulation of MC903 with repeat dosing unlikely. Rebound levels observed in 1 pig at 4 hours, likely indicative of enterohepatic recirculation for parent and metabolite. Level of radioactivity after 12 h declined with half-life of ≈ 2.6 days, likely due to ³ H ₂ O. MC903 and metabolite MC1080 eliminated from plasma within 24 h; only 4% by renal, thus <i>elimination</i> mostly by metabolism. <i>Excretion</i> : Total cumulative recovery of 16% in urine and 44% in faeces. <i>Tissue</i> (mainly liver and kidney) radioactivity after 10 days mainly ³ H ₂ O [Putative metabolic pathways discussed in study (5) below.] |
| (5) Rats and Minipigs treated as described in 1 and 4 above. Metabolism further studied. | Synthetic samples of MC1080, MC1046, MC1024 and MC1235 obtained. Plasma samples from rat and minipig obtained after dosing described above in (1) and (4). Samples analyzed by HPLC. | MC903 disappeared rapidly from plasma in both species, with half-lives of ≈ 12 min (rat) and 60 min (pig). <i>Metabolites</i> of MC903, mainly MC1080, were observed in the first sample at 5 min after i.v. dosing. MC903, MC1080 and MC1046 account for most of the radioactivity in the samples during first hour after dosing both species. Distribution between parent and metabolites similar to <i>in vitro</i> studies; in rat MC1046 more prevalent after oral than i.v., possibly due to first pass. Minor metabolites more polar than MC1046 observed in both species. Content of radioactivity in eluate increases rapidly with time; 6 hours after dosing >80% radioactivity found in this fraction, both species, both routes; due mainly to radioactive water. Metabolism of MC903 to MC1080 and MC1046 involves oxidation at the 24-position, similar to oxidation of 1,25 dihydroxyvitamin D ₃ , active form of vitamin D ₃ . Likely that MC903 is metabolized to calcitronic acid, similar to 1,25 dihydroxyvitamin D ₃ . |

IN VITRO PHARMACOKINETIC STUDIES WITH CALCIPOTRIOL

| TYPE OF STUDY | METHODS | MAJOR RESULTS AND INTERPRETATION |
|--|--|---|
| (1) Identification of metabolite of MC903 in rat liver homogenates. | Livers removed from 6-week old rats, homogenized, centrifuged and super-natants collected. Samples incubated at 37° with MC903. Structure elucidation by proton NMR and mass spectrometry. | Structure elucidation by proton NMR and mass spectrometry revealed a <i>metabolite</i> that is identical to MC1080 detected in <i>in vivo</i> studies. |
| (2) Identification of metabolites in liver homogenates of rat, minipig, rabbit, and man. | Supernatants prepared from liver samples from rat, minipig, rabbit and man. Incubations with labelled or unlabelled MC903. | <i>Metabolite</i> identified from rat as MC1080. Also formed in substantial amounts with liver supernatants from pig, man and rabbit. Additional peak in man and rabbit due to metabolite MC1046; to a lessor extent in pig and rat. MC1080 and MC1046, along with MC903 (parent) accounted for 71%-73% of radioactivity in rat, pig and human; 7-15% due to more polar metabolites. Quantitative differences existed among the species, but the pattern of metabolism was similar for all species. |

Clinical Pharmacology

The atrophogenic potential and dermal tolerance of DOVOBET (calcipotriol and betamethasone dipropionate) ointment was compared with that of 0.5 mg/g betamethasone dipropionate ointment and placebo ointment in a randomized, double-blind, right/left comparison on the forearm of subjects (study MCB 9903 DE). Sonography demonstrated skin thinning with DOVOBET relative to placebo ointment when applied twice daily for 4 weeks. However, skin thinning with DOVOBET was similar to betamethasone (12.3% and 13.2% respectively). There were no clinical signs of atrophy, telangiectasia or irritation (erythema). There were no histological differences in epidermal or dermal thickness between DOVOBET and betamethasone.

The absorption and excretion balance of ³H-calcipotriol and ³H-betamethasone was evaluated after a single application of radiolabelled DOVOBET to healthy volunteers (study MCB 9901 NL). Subjects were also treated with DOVOBET for 4 weeks and then absorption and excretion was again evaluated after a single application of radiolabelled DOVOBET. The absorption of calcipotriol after a single application of DOVOBET is similar to absorption after application of the other marketed formulation of calcipotriol (i.e. DOVONEX, 50 mcg/g calcipotriol). Thus, the safety profile of DOVONEX is applicable to DOVOBET. Betamethasone dipropionate in DOVOBET does not influence the absorption rate of calcipotriol and vice versa calcipotriol does not affect the absorption of betamethasone. Absorption of calcipotriol is similar after 4 weeks of treatment with DOVOBET as it is after a single application.

A bioequivalence study of betamethasone dipropionate in DOVOBET ointment versus Diprosone® (Schering-Plough Ltd.) ointment, was conducted in healthy volunteers according to the FDA guideline for vasoconstrictor bioassay (study MCB 9902 FR). Betamethasone dipropionate is bioequivalent in the two preparations as the 90% confidence interval for the skin blanching response ratio (test to reference) is [0.81 ; 1.04] and within the interval of [0.80 ; 1.25] as defined by the FDA guideline.

TOXICOLOGY

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

Systemic Toxicity of 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 overdose. The kidney was the main target organ of toxicity and tubular lesions and calcifications were apparent after prolonged hypercalcemia in all species investigated. These types of changes, however, are not considered indicative of a human risk, since less than 1% of calcipotriol is absorbed through the skin in man and there is no evidence of calcitropic effects in man with the prescribed dose.

Dermal Toxicity of Calcipotriol

Dermal toxicity 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 steroids available for the treatment of psoriasis. Skin thinning, as seen with steroid application, was not observed with the calcipotriol ointment.

Dermal Tolerability of DOVOBET (50 mcg/g calcipotriol plus 0.5 mg/g betamethasone (as dipropionate)): Two dermal tolerability studies 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.

Reproduction and Mutagenicity with Calcipotriol

Reproduction studies have shown that calcipotriol has no effect on fertility in male and female rats nor on their F₁ generation progeny. Fetal toxicity and teratogenicity studies showed no evidence of embryotoxic or teratogenic effects in rats and rabbits. 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.

Carcinogenicity with 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.

Photo(co)carcinogenicity: 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. The clinical relevance of these findings is unknown.

No carcinogenicity or photocarcinogenicity studies have been performed with betamethasone dipropionate.

ACUTE TOXICITY OF CALCIPOTRIOL

| TEST COMPOUND | ANIMAL | ROUTE / DOSAGE | IMPORTANT FINDINGS |
|---|--------------|--|---|
| Calcipotriol (MC903) | Mouse Rat | Oral 0-20 mg/kg i.p. 0-20 mg/kg Oral 0-40 mg/kg i.p. 0-60 mg/kg | Oral and i.p. LD ₅₀ in mouse and oral LD ₅₀ in rat ≈ 20 mg/kg. i.p. LD ₅₀ in rat ≈ 40 mg/kg. Clinical symptoms due to hypercalcemia; subsequent soft tissue calcification was main symptom. Cause of death: Renal failure. Organs affected: Kidney, heart, thymus and liver in rat (at ≥ 20 mg/kg) and kidney in mouse (at ≥ 5 mg/kg). |
| MC1046 & MC1080 (main metabolites of MC903) | Rat | Oral 0-80 mg/kg i.p. 0-80 mg/kg for both compounds | Oral and i.p. LD ₅₀ for MC1046 ≈ 45 mg/kg. Oral LD ₅₀ for MC1080 ≈ 35 mg/kg and ≈ 2X as much for i.p. Clinical symptoms due to hypercalcemia; subsequent soft tissue calcification was main symptom. Cause of death: Renal failure. Organs affected: Kidney, heart, GI tract, lung and testes (at ≥ 20 mg/kg). |

LOCAL TOLERANCE OF CALCIPOTRIOL

| TEST SYSTEM | ANIMAL | MC903 DOSAGE | IMPORTANT FINDINGS |
|--|---|--|---|
| Skin irritation test | Rabbit (n=6) | 5 mcg/day for 3 weeks | Only minor skin reactions were seen. |
| Skin irritation test | Rabbit (n=6 / group) | 25 mcg/day ointment vs. placebo for 6 weeks | Treatment caused clinically well-defined to moderate skin reactions, as did placebo ointment. Reaction considered related to propylene glycol content in ointment base. No adverse histopathological changes were observed. |
| Skin irritation test | Rabbit (n=6) | 100 mg of 50 mcg/g cream vs placebo for 6 weeks | Only slight irritancy developed. The irritancy developed quicker with the calcipotriol group than the placebo. The magnitude of the reactions was similar in both groups. |
| Skin irritation test | Rabbit (n=6) | 100 mcl of 50 mcg/mL scalp solution vs placebo for 6 weeks | Only very slight irritancy was observed. Thickening of the epidermis was observed in areas treated with calcipotriol. |
| Acute eye irritation | Rabbit (n=3) | 5 mcg ointment single dose | Only transient, fully reversible swelling of the conjunctivae was observed. |
| Allergenic potential maximization test | Guinea pig (n=10, placebo; n=20, MC903) | 0.5-5 mcg/mL | MC903 was classified as a mild potential allergen. |

LONG-TERM TOXICITY OF CALCIPOTRIOL

| TEST COMPOUND | ANIMAL | ROUTE / DOSAGE | IMPORTANT FINDINGS |
|----------------------|------------------|---|--|
| Calcipotriol (MC903) | Rat (20/dose) | Oral 0 (control), 6, 18 and 54 mcg/kg/day for 4 weeks. | Apart from a higher incidence of focal calcification at the cortico-medullary junction of the kidneys in the high dose animals, no other adverse effects were seen. The focal calcification can be attributed to the pharmacological effect of MC903. No mortality was seen. |
| Calcipotriol (MC903) | Dog (4/dose) | Oral 0 (control), 0.1, 0.3 and 0.9 mcg/kg/day for the first 4 weeks, ≤1.8-3.6 mcg/kg/day for the last 2 weeks. Total 6 weeks. | No changes were seen at doses up to 0.9 mcg/kg/day for 4 weeks, whereas raising the dose to 1.8 mcg/kg/day at week 5 and further to 3.6 mcg/kg/day at week 6 caused morphological changes in the kidneys, increases of kidney functioning and plasma calcium, all of which are attributed to the pharmacological activity of MC903. No mortality was seen. |
| Calcipotriol (MC903) | Rat (20/dose) | Dermal 0 (control) 6, 18 and 54 mcg/kg/day for 13 weeks. | Topical treatment for 13 weeks gave rise to slight skin reactions and some minor changes in the clinical chemistry parameters. The minimal focal calcification seen in the kidneys of all treatment group animals was a minor change which may be attributed to the calcitropic effect of MC903. The same changes occur spontaneously in lab rats. The changes recorded in the low dose group were within the level of spontaneous incidence. |
| Calcipotriol (MC903) | Rat (40/dose) | Oral 0 (control), 4, 12 and 36 mcg/kg/day for 26 weeks. | The target organ was identified as the kidneys. The main clinical chemistry findings were the dose-related increases in serum calcium, indicating a calcitropic effect of MC903. This was further confirmed at autopsy by increased kidney weights, lighter coloured appearance of kidneys, increased bone mineralization and renal focal and soft tissue calcification. One low dose female died on day 77, not considered as treatment-related. |
| Calcipotriol (MC903) | Minipig (6/dose) | Oral 0 (control), 1, 3 and 6 mcg/kg/day for the first 20 weeks and then up to 9-18 mcg/kg/day for the last 6 weeks. Total 26 weeks. | No changes were seen in low- and mid-dose animals. Increase in high-dose rapidly affected the animals by inducing distress, lethargy and bodyweight loss. These changes were accompanied by a slight decrease, still within normal range, in Hb, erythrocyte and hematocrit. Serum calcium and urea were increased, serum inorganic phosphate was decreased. At autopsy high-dose animals showed enlarged kidneys with pronounced striation of the medulla on cut surfaces. Urinary calculi were observed in 1 animal. Histopathology showed tubular necrosis and calcifications in the kidneys and the parotid gland in high-dose animals. No mortality was observed. |

MUTAGENICITY OF CALCIPOTRIOL

| TEST SYSTEM | TEST | MC903 DOSAGE | IMPORTANT FINDINGS |
|-------------------------------|-------------------------------------|-----------------|---|
| Ames Test | Salmonella typhimurium | 0.01-1 mg/plate | MC903 was not found mutagenic in this <i>in vitro</i> bacterial test at the dose levels tested. |
| Mouse lymphoma TK locus assay | Mouse lymphoma L5178Y (TK+/-) cells | 1-40 mcg/mL | MC903 demonstrates no evidence of mutagenic potential in this <i>in vitro</i> test system. |
| Metaphase chromosome analysis | Human lymphocytes | 2-1000 mcg/mL | MC903 has shown no evidence of clastogenic activity in this <i>in vitro</i> cytogenetic test system. |
| Micronucleus test | Mouse bone marrow | 1 mg/kg p.o. | MC903 did not show a mutagenic potential under the conditions of this <i>in vivo</i> micronucleus test. |

REPRODUCTION AND TERATOLOGY OF CALCIPOTRIOL

| STUDY | ANIMAL | MC903 DOSAGE | IMPORTANT FINDINGS |
|--|------------------|----------------------|--|
| Fertility and general reproductive performance | Rat (20M, 40F) | 6-54 mcg/kg/day p.o. | Treatment with MC903 did not give rise to any major abnormalities in the offspring or affect the reproductive performance, morphological development or auditory, visual or behavioural systems. |
| Fetal development | Rat (32/dose) | 6-54 mcg/kg/day p.o. | A few minor deviations occurred in pregnant rats given p.o. MC903 during days 6-15 of gestation, attributable to the pharmacological effects of MC903 on calcium metabolism. No teratogenic effects were observed. |
| Teratology | Rabbit (18/dose) | 4-36 mcg/kg/day p.o. | At 36 mcg/kg/day of MC903 from day 6-18 of gestation, maternal toxicity was observed, characterized by deaths, bodyweight 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 (bodyweight loss, reduced food intake, maternal death or abortion in 2/18 animals) and reduced mean fetal weight were seen. At 4 mcg/kg/day, no adverse maternal or fetal effects were observed. |
| Peri- and post-natal | Rat (32/dose) | 6-54 mcg/kg/day p.o. | Administration of MC903 to pregnant rats from day 15 of gestation to day 20 post-partum did not cause significant adverse effects on late fetal development, labour and delivery, lactation, neonatal viability and growth of the young or give rise to any major abnormalities. |

LOCAL TOLERANCE OF DOVOBET (50 mcg/g calcipotriol plus 0.5 mg/g betamethasone (as dipropionate))

| STUDY | ANIMAL | DOVOBET DOSAGE | IMPORTANT FINDINGS |
|---------------------|-----------------|--|--|
| Dermal tolerability | Rabbit (n=6) | Once daily application of 100 mg Dovobet and 100 mg vehicle ointment on separate skin areas for 6 weeks. | No skin irritation was observed. Histopathological changes consisting of squamous metaplasia of pilosebaceous tissue and comedogenic activity attributable to the ointment vehicle were observed. |
| Dermal tolerability | Rabbit (n=6) | Once daily application of 100 mg of Dovobet, calcipotriol (50 mcg/g), betamethasone (0.5 mg/g), and vehicle ointment on separate skin areas for 6 weeks. | 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. |

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PART III: CONSUMER INFORMATION**PR DOVOBET®
calcipotriol and betamethasone dipropionate**

This leaflet is part III of a three-part "Product Monograph" published when DOVOBET 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. Contact your doctor or pharmacist if you have any questions about this drug. This leaflet is also available on-line at www.dovobet.ca.

ABOUT THIS MEDICATION**What the medication is used for:**

DOVOBET should be used topically for up to 4 weeks to treat psoriasis plaques on your body.

DOVOBET should not be used on the face.

What it does:

DOVOBET contains two active ingredients; calcipotriol, a vitamin D-like agent and; betamethasone, a corticosteroid ("steroid").

Psoriasis results from skin cells growing and dividing too quickly, causing plaques (scaly, red patches) to form on the skin. Calcipotriol comes from naturally occurring vitamin D and acts to return the growth of skin cells to normal.

The topical steroid betamethasone acts to control the inflammation (redness, swelling) associated with psoriasis.

The combination of calcipotriol and betamethasone in DOVOBET ointment is more effective for the treatment of psoriasis and is faster acting than if these two ingredients were used alone.

When it should not be used:

- Do not use this product if you are allergic to any of the ingredients in DOVOBET ointment, or to components of the tube.
- DOVOBET is not for use in your eyes.
- Do not use to treat viral, fungal or bacterial skin infections, tuberculosis of the skin, syphilitic skin infections, chicken pox, eruptions following vaccinations, and in viral diseases such as herpes simplex, varicella and vaccinia because Dovobet contains a steroid.

What the medicinal ingredients are:

Calcipotriol (vitamin D analog) and betamethasone dipropionate (corticosteroid).

What the important nonmedicinal ingredients are:

White soft paraffin, liquid paraffin, polyoxypropylene-15-stearyl ether, alpha-tocopherol.

What dosage forms it comes in:

DOVOBET is available as a topical ointment containing 50 mcg/g

calcipotriol and 0.5 mg/g betamethasone (as dipropionate).

WARNINGS AND PRECAUTIONS

Calcipotriol, a medicinal ingredient of DOVOBET, when used with ultraviolet radiation (UVR) may increase the risk of developing skin cancer caused by UVR. Calcipotriol alone does not cause cancer.

DOVOBET is not recommended for use during pregnancy or while nursing. Tell your doctor if you are pregnant, nursing, or become pregnant during your treatment.

If you are at high risk of developing high blood calcium levels, you should be monitored with blood tests. If blood calcium levels increase, treatment with DOVOBET should be discontinued until calcium levels return to normal.

DOVOBET is not recommended for children under 18 years of age. Children may be more prone to side effects from the steroid in DOVOBET.

DOVOBET should not be applied to large areas of damaged skin, in skin folds or under air tight bandages/dressings.

It is best if your treatment is broken up occasionally and if one area of your body is treated at a time. The steroid contained in DOVOBET may cause stretch marks or shrinking of the skin or tissues under the skin. If this occurs, treatment should be stopped. There may a return of psoriasis if prolonged use of a steroid is stopped abruptly.

BEFORE you use DOVOBET talk to your doctor or pharmacist if:

- you have viral, fungal or bacterial skin infections, tuberculosis of the skin, syphilitic skin infections, chicken pox, eruptions following vaccinations, viral diseases such as herpes simplex, varicella and vaccinia.
- you are currently using other topical corticosteroids.
- you are using sun tanning beds or sun lamps.
- you are currently using phototherapy for your psoriasis.
- you have allergies to any of the ingredients in DOVOBET ointment or to components of the tube.

INTERACTIONS WITH THIS MEDICATION

There is no clinical trial experience on the interaction of DOVOBET with other drugs for psoriasis.

PROPER USE OF THIS MEDICATION**Usual dose:**

DOVOBET should be gently rubbed onto affected skin areas once a day for up to 4 weeks. You should begin to see an improvement within the first week. The maximum amount of DOVOBET ointment you should use in one week is 100g.

adrenal glands may stop working properly.

Using the ointment:

- Remove the cap. Check that the aluminium seal has not been broken before you use it for the first time. To break the seal, use the other end of the cap to pierce the seal.
- Gently rub the ointment on the areas of your skin affected by psoriasis. Wash your hands after using DOVOBET to prevent getting any on your face. You can wear your usual clothes and no special dressing or cover is needed.
- If you accidentally spread DOVOBET onto surrounding healthy skin, wash it off right away.
- DOVOBET is not recommended for use on your face. If you accidentally get some on your face, wash it off right away.
- Do not apply DOVOBET on large areas of damaged skin, in skin folds or under an air tight bandage/dressing. This could increase your risk of side effects.
- If DOVOBET ointment is used together with DOVONEX® cream, ointment or scalp solution, then the combined total for all products together should not be greater than 100 g per week.

For example, if you use 60 g of DOVOBET ointment, you should not use more than 40 mL of DOVONEX scalp solution.

Overdose:

From calcipotriol:

The calcipotriol in DOVOBET can lead to increased blood calcium levels if more than the maximum 100g weekly amount of DOVOBET is used. This effect is reversible when treatment is stopped.

From betamethasone:

Long term use of topical steroids can lead to symptoms of hypercorticism, including Cushing's disease. Recovery is fast and complete once the steroid is stopped.

Missed Dose:

If you forget to use DOVOBET at the right time, use it as soon as you remember. Then go on as before.

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

| Symptom / effect | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|--|-------------------------------------|--------------|---|
| | Only if severe | In all cases | |
| Rare: pustular psoriasis (headache, fever, chills, arthralgia, malaise, anorexia, nausea) | | | T |
| Rare: adrenal effects (weakness, increased urination/thirst, fatigue, weight loss) | | T | |
| Rare: skin thinning (visible veins, stretch marks) | T | | |
| Very rare: allergic reaction (rash, itching, swelling, trouble breathing, dizziness) | | | T |
| Very rare: high blood calcium levels (fatigue, depression mental confusion, anorexia, nausea, vomiting, constipation, increased urination and in some patients, cardiac arrhythmias) | | | T |

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

HOW TO STORE IT

Store at 5 to 25°C. Use within 12 months of first opening the tube.

- For easy spreading and to prevent pulling of delicate skin do not refrigerate the ointment.
- Keep DOVOBET in a safe place where children cannot reach it.
- Keep DOVOBET away from your pets. The medicine (calcipotriol) can be fatal to dogs if eaten. If your dog eats DOVOBET contact a veterinarian immediately.
- Do not use DOVOBET past the expiry date marked on the bottom of the tube.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effect from the use of DOVOBET is itching which is usually mild.

The calcipotriol in DOVOBET may cause local irritation which is usually mild and temporary. Rare cases of allergic reaction to calcipotriol have been reported. Calcipotriol can lead to high blood calcium levels but this is usually related to using more than 100g of DOVOBET per week. Worsening of your psoriasis can occur.

Side effects from the steroid in DOVOBET are generally local and include dryness, itching, burning, local irritation, thinning of the skin, the appearance of surface veins, stretch marks, various types of skin rashes and red, swollen hair follicles. If applied to the face, an acne-like rash and swelling can occur. In rare cases, your

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 1-866-234-2345
By toll-free fax: 1-866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness
Information Bureau Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: If you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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

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