

# PRODUCT MONOGRAPH

Pr DOVOBET\*

Ointment

50 mcg/g Calcipotriol / 0.5 mg/g Betamethasone (as dipropionate)

Topical Antipsoriatic Agent

Vitamin D Analogue / Corticosteroid

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**Control #077213**

**Date of Preparation:**

June 26, 2001

**Date of Revision:**

July 29, 2002



**PRODUCT MONOGRAPH****PRODUCT NAME**

Pr DOVOBET\*

Ointment

(50 mcg/g Calcipotriol / 0.5 mg/g Betamethasone (as dipropionate))

**THERAPEUTIC CLASSIFICATION**

Topical Antipsoriatic Agent

Vitamin D Analogue/Corticosteroid

**ACTION AND CLINICAL PHARMACOLOGY**

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 A<sub>2</sub> inhibitor proteins, preventing arachidonic acid release and the biosynthesis of potent mediators of inflammation.

A large, multicentre, randomised, 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.

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.

### ***INDICATIONS AND CLINICAL USES***

Dovobet ointment is indicated for the topical treatment of psoriasis vulgaris.

### ***CONTRAINDICATIONS***

Known hypersensitivity to any of the ingredients of Dovobet ointment. **NOT FOR OPHTHALMIC USE.**

Due to the corticosteroid component, Dovobet is contraindicated for the 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***

If Dovobet 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.

Application on large areas of damaged skin, in skin folds or under occlusive dressings should be

avoided since it increases the systemic absorption of corticosteroids. 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.

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.

*Use During Pregnancy and Lactation:* The safety of calcipotriol and/or topical corticosteroids for use during pregnancy and lactation has not been established. Although studies in experimental animals have not shown teratogenic effects with calcipotriol, studies with corticosteroids have shown teratogenic effects. The relevance of this finding to humans 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. Dovobet should only be used during pregnancy or lactation if the anticipated benefit clearly outweighs the potential risk to the fetus or the nursing infant.

*Children:* 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.

### **PRECAUTIONS**

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.

If long-term therapy is anticipated, it is recommended that treatment be interrupted periodically or that one area of the body be treated at a time. Prolonged use of corticosteroid containing preparations may produce striae or atrophy of the skin or subcutaneous tissues. Topical corticosteroids should be used with caution on lesions of the face, groin and axillae as these areas are more prone to atropic changes than other areas of the body. If skin atrophy occurs, discontinue treatment.

Treatment with Dovobet in the recommended amounts (See DOSAGE AND ADMINISTRATION) does not generally result in changes in laboratory values. However, if the total dose exceeds the maximum recommended weekly amount of 100 g (ie., 5 mg calcipotriol) then 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.

*Drug Interactions:* There is no experience of concomitant therapy with other antipsoriatic drugs.

### **ADVERSE REACTIONS**

In clinical trials, the most common adverse reaction associated with Dovobet 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 (ie., 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.

#### ***SYMPTOMS AND TREATMENT OF OVERDOSAGE***

Due to the calcipotriol component of Dovobet, excessive administration (ie., 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.

#### ***DOSAGE AND ADMINISTRATION***

Dovobet should be applied topically to the affected areas once daily. After satisfactory improvement has occurred, the drug can be discontinued. If recurrence takes place after discontinuation, treatment may be reinstated.

The recommended treatment period is 4 weeks. In this period the majority of patients will benefit satisfactorily. However, some patients will require longer treatment than 4 weeks which should be based on physician assessment of the benefit/risks of continuing the treatment regimen.

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

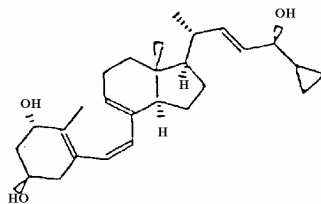
There is no clinical trial experience with the use of Dovobet in children.

**PHARMACEUTICAL INFORMATION****DRUG SUBSTANCE:**

<i>Common Name (I.N.N.):</i>	<u>Calcipotriol hydrate</u>	<u>Betamethasone dipropionate</u>
<i>Chemical Abstracts Name:</i>	9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-(1 $\alpha$ ,3 $\beta$ ,5Z,7E,22E,24S)	9-fluoro-11 $\beta$ ,17,21-trihydroxy-16 $\beta$ -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate
<i>Alternative Chemical Name:</i>	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 $\beta$ ,16 $\beta$ )
<i>Laboratory Code Name:</i>	MC 903 or MC 903-000	433 or 433/M

*Structural Formula:*Calcipotriol HydrateBetamethasone dipropionate

<i>Molecular Formula:</i>	C <sub>27</sub> H <sub>40</sub> O <sub>3</sub> , H <sub>2</sub> O	C <sub>28</sub> H <sub>37</sub> FO <sub>7</sub>
<i>Molecular Weight:</i>	430.6	504.59
<i>Chirality:</i>	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 above.	
<i>Physical Form:</i>	White or almost white crystalline substance.	White or almost white odourless powder.
<i>Solubility at Room Temperature:</i>	Freely soluble in ethanol, soluble in chloroform and propylene glycol, practically insoluble in liquid paraffin. Solubility in water is 0.6 mcg/ml.	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.
<i>Melting Point:</i>	166-168°C	176-180°C
<i>Polymorphism:</i>	So far no signs have indicated the existence of polymorphic forms.	
<i>Other Characteristics:</i>	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.	



## COMPOSITION:

*Non-Medicinal Ingredients:* white soft paraffin  
liquid paraffin  
polyoxypropylene-15-stearyl ether  
alpha-tocopherol

**STABILITY AND STORAGE RECOMMENDATIONS:**

Store at 5-25°C. Use within 6 months of first opening the tube.

For easy application: do not refrigerate (this is to prevent rubbing and pulling of delicate skin).

**AVAILABILITY OF DOSAGE FORMS**

*Dosage Form:* Ointment (faintly translucent white to yellowish ointment)

*Strength:* 50 mcg calcipotriol plus 0.5 mg betamethasone per gram

*Recommended Route of Administration:* For topical use only.

*Containers:* Available in 3 g, 30 g, 60 g, 100 g and 120 g lacquered aluminium tubes (equipped with an aluminium membrane).

***INFORMATION FOR THE CONSUMER*****PATIENT PACKAGE INSERT**

## DOVOBET Ointment

DOVOBET:

This leaflet is intended to give you some important information about using Dovobet for the treatment of your psoriasis. If you have any questions please talk to your doctor or pharmacist.

What is Dovobet?

Dovobet contains the vitamin D derivative calcipotriol (50 mcg/g) and the corticosteroid betamethasone (0.5 mg/g, as dipropionate). Calcipotriol is designed to control the excessive production of skin cells in areas affected by psoriasis and has proven benefits in the treatment of this condition. Topical steroids such as betamethasone dipropionate control inflammation. The combination of these two active ingredients in Dovobet ointment is more effective and provides a faster onset of action for the treatment of psoriasis than either individual ingredient used alone. Dovobet has been developed as a smooth preparation, making it easy to use.

BEFORE USING YOUR OINTMENTTell your doctor:

- If you are pregnant or breast feeding or if you become pregnant during your treatment.

USING YOUR OINTMENTHow should I use Dovobet?

- Remove the cap and check that the aluminium seal is intact before first use. To break the seal, reverse the cap and pierce.
- Dovobet should be applied once daily to the areas of your skin affected by psoriasis and gently rubbed in. Wash your hands after using Dovobet to avoid inadvertent transfer to your face from other body parts. Your usual clothes may then be worn as Dovobet need not be specially covered. Do not worry if you accidentally get some Dovobet on the surrounding

normal skin but wash it off if it spreads too far.

- Dovobet should not be used on the face as it contains the corticosteroid betamethasone. If it accidentally gets on your face, wash it off.
- Do not use more than the recommended weekly amount of 100 g of Dovobet. Dovobet is not recommended for use in children.
- Do not apply on large areas of damaged skin, in skin folds or under occlusive dressing. The most common adverse reaction to Dovobet is mild itching. Elevation in serum calcium levels may occur but this is usually related to excessive administration. In order to minimize the risk of adverse reactions, it is important not to exceed the maximum recommended dose of 100 g of Dovobet per week.
- If Dovobet ointment (50 mcg/g calcipotriol / 0.5 mg/g betamethasone (as dipropionate)) is used together with Dovonex Scalp Solution (50 mcg calcipotriol per ml), then the total dose of calcipotriol should not exceed the recommended amount of 5 mg per week. As an example, adults should not use more than 30 ml of Dovonex Scalp Solution plus one 60 g tube of Dovobet ointment.
- Dovobet should be applied once daily. Most patients will begin to see an improvement within the first week. Best results are seen within 4 weeks. When satisfactory improvement has been achieved, application can be discontinued. Follow your doctor's instructions carefully.

What should I do if I forget to use my ointment?

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

AFTER USING YOUR DOVOBET

- See your doctor if you develop any problems or if Dovobet upsets you in any other way.

#### STORING YOUR DOVOBET

- Keep Dovobet in a safe place where children cannot reach it.
- Keep Dovobet out of reach of pets. Ingestion of the active ingredient calcipotriol can be fatal to dogs. If your dog eats Dovobet contact a veterinarian immediately.
- Store at 5°C to 25°C. Use within 6 months of first opening the tube.
- Dovobet has an expiry date marked on the bottom of each tube. Please do not use the contents of the tube after this date.

## **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 D<sub>3</sub>, 1,25(OH)<sub>2</sub>D<sub>3</sub>. 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)<sub>2</sub>D<sub>3</sub>. 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)<sub>2</sub>D<sub>3</sub> receptor with the same affinity as 1,25(OH)<sub>2</sub>D<sub>3</sub> itself. *In-vivo* however, the effects of calcipotriol were significantly different from those of 1,25(OH)<sub>2</sub>D<sub>3</sub>. 1,25(OH)<sub>2</sub>D<sub>3</sub>, the active form of

vitamin D<sub>3</sub>, 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)<sub>2</sub>D<sub>3</sub>. 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 <sup>3</sup>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 <sup>3</sup>H-H<sub>2</sub>O from the metabolic degradation of <sup>3</sup>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 <sup>3</sup>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.

## IN VIVO PHARMACOKINETIC STUDIES WITH CALCIPOTRIOL IN THE RAT AND/OR RABBIT

TYPE OF STUDY	METHODS	MAJOR RESULTS AND INTERPRETATION
(1) Acute administration of <sup>3</sup> H-MC903 by i.v. and oral routes to rats.	_ rats dosed with <sup>3</sup> 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.	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 <sup>3</sup> H-H <sub>2</sub> O. 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]. <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, <sup>3</sup> H-H <sub>2</sub> O. <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%. <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.
(2) Acute topical administration of <sup>3</sup> H-MC903 to rats and rabbits.	6 rats, 2 rabbits, dosed once with topical <sup>3</sup> 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.	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 <sup>3</sup> H-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 <sup>3</sup> H-MC903 ranged from 0.4-1.1 ng-eqv/g.
(3) Acute oral and i.v. dosing of <sup>3</sup> 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.	<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. <i>Oral</i> : Similar to i.v. dosing, except more radioactivity in oral cavity, oesophagus and stomach. It 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.

### IN VIVO PHARMACOKINETIC STUDY WITH CALCIPOTRIOL IN THE MINIPIG

TYPE OF STUDY	METHODS	MAJOR RESULTS AND INTERPRETATION
(4) Acute oral and i.v. dosing of <sup>3</sup> H-MC903 to minipigs.	2 pigs/dose (1 <sub>-</sub> , 1 <sub>+</sub> ), 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 <sup>3</sup> H <sub>2</sub> 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 <sup>3</sup> H <sub>2</sub> O [Putative metabolic pathways discussed in study (5) below.]

### FURTHER IN VIVO STUDY WITH CALCIPOTRIOL IN RAT AND MINIPIG

(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 <sub>3</sub> , active form of vitamin D <sub>3</sub> . Likely that MC903 is metabolized to calcitronic acid, similar to 1,25 dihydroxyvitamin D <sub>3</sub> .
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**IN VITRO PHARMACOKINETIC STUDY WITH CALCIPOTRIOL IN THE RAT**

(6) Identification of metabolite of MC903 in rat liver homogenates.	Livers removed from 6-week old rats, homogenized, centrifuged and supernatants collected. Samples incubated at 37°C 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.
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**IN VITRO PHARMACOKINETIC STUDY WITH CALCIPOTRIOL IN RAT, MAN, RABBIT AND MINIPIG**

(7) 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 minipig, man and rabbit. Additional peak in man and rabbit due to metabolite MC1046; to a lesser extent in minipig and rat. MC1080 and MC1046, along with MC903 (parent) accounted for 71%-73% of radioactivity in rat, minipig 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.
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### CLINICAL PHARMACOLOGY

The atrophogenic potential and dermal tolerance of Dovobet 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 <sup>3</sup>H-calcipotriol and <sup>3</sup>H-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 (ie., 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.

## CLINICAL STUDIES

A large, multicentre, randomised, 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.

## 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. Dovobet ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate) versus betamethasone dipropionate ointment (0.5 mg/g). n=30. Phase II. Dovobet ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate) versus 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: Single 10 mcl application of Dovobet and betamethasone dipropionate ointment (Diprosone®) at a dose-duration corresponding to ED<sub>50</sub> (1h04min) on two sites each per forearm. Betamethasone was also applied on two sites per forearm at dose-durations corresponding to 0.5 times ED<sub>50</sub> (32 min.) and 2 times ED<sub>50</sub> (2h08min.)</p> <p><u>Treatment:</u> Pilot Phase: Diprosone® (0.5 mg/g betamethasone as dipropionate). (n=12) Pivotal Phase: Dovobet (50 mcg/g calcipotriol plus 0.5 mg/g betamethasone as dipropionate) ointment versus 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 ED<sub>50</sub> (half maximal response) of 1h04min., D<sub>1</sub> (0.5 times ED<sub>50</sub>) of 32 min and D<sub>2</sub> (2 times ED<sub>50</sub>) of 2h08 min. 67% of the included subjects were ‘detectors’ (AUC at D<sub>1</sub> was at least 1.25 time the AUC at D<sub>2</sub>).</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>
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 <sup>3</sup>H-labelled calcipotriol. (n=4)</p>	<p><u>Evaluation Criteria:</u> Pharmacokinetic parameters: Recovery of <sup>3</sup>H-radioactivity from gauzes, gloves, swabs and shorts; excretion of <sup>3</sup>H-radioactivity in urine and faeces; <sup>3</sup>H-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 <math>^3\text{H}</math> labelled ointment and single 12 hour application after 4 weeks of twice daily topical application of unlabelled ointment.</p> <p><u>Treatment Groups:</u></p> <p><b>Group I:</b> Single 12 hour application of 2.5 g Dovonex (50 mcg/g calcipotriol) ointment containing <math>^3\text{H}</math> labelled calcipotriol. Four weeks (28 days) of twice daily treatment with unlabelled Dovonex. On day 36, another single 12 hour application of Dovonex containing <math>^3\text{H}</math> labelled calcipotriol. (n=6)</p> <p><b>Group II:</b> Single 12 hour application of 2.5 g Dovobet (50 mcg/g calcipotriol plus 0.5 mg/g betamethasone dipropionate) ointment containing <math>^3\text{H}</math> labelled calcipotriol. Four weeks (28 days) of twice daily treatment with unlabelled Dovobet. On day 36, another single 12 hour application of Dovobet containing <math>^3\text{H}</math> labelled calcipotriol. (n=6)</p> <p><b>Group III:</b> Single 12 hour application of 2.5 g Dovobet ointment vehicle containing <math>^3\text{H}</math> labelled calcipotriol.</p> <p><b>Group IV:</b> Single 12 hour application of 2.5 g Dovobet ointment containing <math>^3\text{H}</math> labelled betamethasone.</p> <p><b>Group V:</b> Single 12 hour application of 2.5 g Dovobet ointment vehicle containing <math>^3\text{H}</math> labelled betamethasone.</p>	<p><u>Evaluation Criteria:</u></p> <p>Pharmacokinetic parameters: Recovery of <math>^3\text{H}</math> radioactivity from gauzes, gloves, swabs and shorts; excretion of <math>^3\text{H}</math> radioactivity in urine and faeces; <math>^3\text{H}</math> radioactivity levels in serum.</p> <p>Safety parameters: adverse events, local tolerability results, vital signs, ECG parameters and clinical laboratory parameters.</p> <p><u>Results:</u></p> <p>The absorption of calcipotriol after a single application of Dovobet is similar to absorption after application of the other marketed formulation of calcipotriol (ie., 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> Combination ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate; Dovobet). n=301; versus Calcipotriol ointment ( 50 mcg/g). n=308; versus Betamethasone dipropionate ointment (0.5 mg/g). n=313 versus 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&lt;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&lt;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&lt;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&lt;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, 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> <b>Phase 1:</b> Dovobet ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate, n=369) versus Dovonex® ointment ( 50 mcg/g calcipotriol, Leo Pharmaceutical Products, n=365) versus Diprosone® ointment (0.5 mg/g betamethasone dipropionate, Schering-Plough Ltd., n=363). <b>Phase 2:</b> 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&lt;0.001). After 1 week of treatment PASI score was reduced by 47% with Dovobet, 31% with Dovonex®, and 40% with Diprosone (p&lt;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&lt;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&lt;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> Dovobet combination ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate) once daily (n=150) versus Dovobet ointment twice daily (n=234) versus Dovonex® ointment (50 mcg/g calcipotriol) twice daily (n=227) versus 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 more effective than vehicle alone and Dovonex twice daily treatment. For some of the efficacy measures, once daily Dovobet was similar in efficacy to twice daily Dovobet. 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&lt;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&lt;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 (79%) treatment. The greatest treatment response according to the investigators' overall assessment was also observed in the Dovobet groups, <b>with twice daily treatment favoured over once daily.</b> 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)**

<b>STUDY CODE</b>	<b>STUDY DESIGN</b>	<b>EVALUATION CRITERIA AND RESULTS</b>
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> Dovobet combination ointment (50 mcg/g calcipotriol plus 0.5 mg betamethasone dipropionate) once daily (n=490) versus calcipotriol ointment (50 mcg/g calcipotriol) once daily (n=480) versus betamethasone ointment (0.5 mg/g betamethasone dipropionate) once daily (n=476), versus 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&lt;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&lt;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&lt;0.001). The proportion of patients with treatment success was 65% with Dovobet, 29% with calcipotriol, 46% with betamethasone, and 10% with vehicle (p&lt;0.001). Adverse reactions associated with Dovobet were predictable based on the individual components with mild pruritus being the most common adverse reaction.</p>

## ***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 overdosage. 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 F<sub>1</sub> 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 F<sub>1</sub> or F<sub>2</sub> generation. There was also no evidence for a mutagenic or clastogenic potential with calcipotriol.

## 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 <sub>50</sub> in mouse and oral LD <sub>50</sub> in rat ≈ 20 mg/kg. i.p. LD <sub>50</sub> 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 <sub>50</sub> for MC1046 ≈ 45 mg/kg. Oral LD <sub>50</sub> 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).

## LONG-TERM TOXICITY OF CALCIPOTRIOL

Calcipotriol (MC903)	Rat (20 rats/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.

**LONG-TERM TOXICITY OF CALCIPOTRIOL (CONT.)**

<b>Test Compound</b>	<b>Animal</b>	<b>Route/Dosage</b>	<b>Important Findings</b>
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**

<b>Test System</b>	<b>Test</b>	<b>MC903 Dosage</b>	<b>Important Findings</b>
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**

<b>Study</b>	<b>Animal</b>	<b>MC903 Dosage</b>	<b>Important Findings</b>
Fertility and general reproductive performance	Rat (20 _, 40 _)	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 CALCIPOTRIOL

Study	Animal	Calcipotriol 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 with the placebo group. The magnitude of the reactions were similar in both groups.
Skin irritation test	Rabbit (n=6)	100 ml 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 for placebo, 20 for MC903)	0.5-5 mcg/ml	MC903 was classified as a mild potential allergen.

**LOCAL TOLERANCE OF DOVOBET (50 mcg/ml calcipotriol plus 0.5 mg/ml 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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