

PRODUCT MONOGRAPH

Pr DOVONEX®

calcipotriol

**Cream and Ointment, 50 mcg/g
Scalp Solution, 50 mcg/mL**

**Topical Non-Steroidal
Antipsoriatic Agent**

**LEO Pharma Inc.
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L3T 7W8**

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	6
DRUG INTERACTIONS	7
DOSAGE AND ADMINISTRATION	7
OVERDOSAGE	9
ACTION AND CLINICAL PHARMACOLOGY	9
STORAGE AND STABILITY.....	11
DOSAGE FORMS, COMPOSITION AND PACKAGING	12
PART II: SCIENTIFIC INFORMATION	13
PHARMACEUTICAL INFORMATION.....	13
CLINICAL TRIALS.....	14
DETAILED PHARMACOLOGY	23
TOXICOLOGY	28
REFERENCES	28
PART III: CONSUMER INFORMATION.....	28

^{PR}DOVONEX®

calcipotriol

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
topical	Ointment and Cream, 50 mcg/g calcipotriol Scalp solution, 50 mcg/mL calcipotriol	none <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

DOVONEX (calcipotriol) cream and ointment is indicated for:

- the topical treatment of psoriasis
- combination use with a moderate to very potent topical corticosteroid, cyclosporin A or acitretin.

DOVONEX scalp solution is indicated for:

- the topical treatment of scalp psoriasis.

DOVONEX cream, ointment and scalp solution are not generally recommended for severe extensive psoriasis.

DOVONEX is not recommended for use on the face.

CONTRAINDICATIONS

- Patients who are hypersensitive to DOVONEX (calcipotriol) cream, ointment or scalp solution, to any ingredient in the formulations or components of the containers. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- NOT FOR OPHTHALMIC USE.
- When DOVONEX is used in combination with other antipsoriatic therapies, all available information on “CONTRAINDICATIONS” for the other antipsoriatic therapy/therapies apply and should be considered.

WARNINGS AND PRECAUTIONS

Carcinogenesis

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

General

When DOVONEX (calcipotriol) is used in combination with other antipsoriatic therapies, all available information on “WARNINGS AND PRECAUTIONS” for the other antipsoriatic therapy/therapies apply and should be considered.

DOVONEX cream, ointment and scalp solution are not generally recommended for severe extensive psoriasis. If calcipotriol is used for severe extensive psoriasis, it is important to monitor the serum calcium levels at regular intervals due to the risk of hypercalcemia secondary to excessive absorption of calcipotriol when there is extensive skin involvement. If the serum calcium level becomes elevated, calcipotriol therapy should be discontinued and the serum calcium level monitored in these patients until it returns to normal.

Skin

DOVONEX is not recommended for use 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 using calcipotriol to avoid inadvertent transfer to the face from other body parts. Should facial dermatitis develop in spite of these precautions, calcipotriol therapy should be discontinued.

DOVONEX should be used cautiously in skin folds, where the natural occlusion may give rise to an increase of the irritant effect of calcipotriol.

Special Populations

Pregnant Women: Safety for use during pregnancy has not yet been established, although studies in experimental animals have not shown teratogenic effects. Calcipotriol should be used in women during pregnancy only if the anticipated benefit clearly outweighs the potential risk.

Nursing Women: It is not known whether calcipotriol could be excreted in breast milk. Calcipotriol should be used in women during breast feeding only if the anticipated benefit clearly outweighs the potential risk.

Infants (< 2yrs of age): There is inadequate experience with the use of calcipotriol in infants under 2 years of age to recommend use in this age group. Use beneath diapers has not been investigated and should be avoided as diapers may be occlusive.

Pediatrics (2-14 years of age): Administration to children should be supervised by a responsible individual to ensure proper administration and dosage. There is no experience in children with the use of DOVONEX in combination with other antipsoriatic therapies.

Monitoring and Laboratory Tests

Treatment with DOVONEX in the recommended amounts (See DOSAGE AND ADMINISTRATION) does not generally result in changes in laboratory values. However, it is recommended that baseline serum calcium levels be obtained in all patients before starting treatment with calcipotriol, with subsequent monitoring of these serum calcium levels at suitable intervals. The monitoring of serum calcium levels is particularly important if the total dose of calcipotriol exceeds the recommended amount or if calcipotriol is used for severe psoriasis with extensive skin involvement. If serum calcium becomes elevated, calcipotriol treatment should be discontinued and the levels of serum calcium should be measured once weekly until the serum calcium levels return to normal values. Patients with marginally elevated serum calcium may be treated with calcipotriol, provided that serum calcium is monitored at suitable intervals.

ADVERSE REACTIONS

In clinical trials reported to-date, the most common adverse reactions have been related to lesional and perilesional irritation. Some patients develop face and scalp irritation which is likely related to the inadvertent transfer of DOVONEX (calcipotriol) cream or ointment from other body parts. Facial irritation may also occur with the use of DOVONEX scalp solution from inadvertent transfer of the scalp solution to the face. One unconfirmed case of Koebner phenomenon and three unconfirmed cases of hypersensitivity reaction to calcipotriol have been reported. Occasionally hypercalcemia has been reported usually related to excessive (greater than the recommended weekly amount - See DOSAGE AND ADMINISTRATION) use of topical calcipotriol or when excessive absorption of calcipotriol has occurred when used for severe psoriasis with extensive skin involvement (See WARNINGS AND PRECAUTIONS).

Clinical studies have shown that combination of DOVONEX once daily plus a **moderately potent to very potent** topical corticosteroid once daily reduces skin irritation due to calcipotriol. Combination of DOVONEX plus cyclosporin A (2 mg/kg/day) or DOVONEX plus acitretin (20-70 mg/day) did not affect the incidence of short term adverse effects compared to cyclosporin A

or acitretin plus placebo ointment. The combination of Dovonex plus PUVA or UVB phototherapy did not affect the incidence of short term adverse effects compared to PUVA or UVB plus placebo ointment/cream.

DRUG INTERACTIONS

With the exception of topical corticosteroids, (See DOSAGE AND ADMINISTRATION), there is no experience of concomitant therapy with other topical antipsoriatic drugs applied to the same skin area.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- DOVONEX (calcipotriol) is FOR TOPICAL USE ONLY and not for ophthalmic use.
- There is no clinical trial experience with use of DOVONEX scalp solution in children.
- There is no experience in children with the use of DOVONEX in combination with other antipsoriatic therapies.

Recommended Dose and Dosage Adjustment

The maximum recommended weekly dose of DOVONEX cream and/or ointment is:

<u>Age (years)</u>	<u>Dovonex Cream or Ointment, g/week</u>	<u>Total Calcipotriol mg/week</u>
2-5	25	1.25
6 – 10	50	2.5
11 – 14	75	3.75
Adults (over 14)	100	5

The maximum weekly dose of DOVONEX cream and/or ointment for children is based on the adult dose of 100 g/week adjusted for body surface area (maximum 50 g/week/m²). The dosage

regimen is based on the following expected body surface area: age 2-5 years, 0.5 m² (25% of adult); age 6-10 years, 1.0 m² (50% of adult); age 11-14 years, 1.5 m² (75% of adult).

The maximum recommended adult weekly dose of DOVONEX scalp solution is 60 mL (3 mg calcipotriol). There is no clinical trial experience with use of DOVONEX scalp solution in children.

When the cream, ointment, or scalp solution are used together, the total dose of calcipotriol should not exceed the recommended weekly amount for each age group (i.e. 2-5 years, 1.25 mg; 6-10 years, 2.5 mg; 11-14 years, 3.75 mg; Adults, 5 mg in any week).

Missed Dose

If an application of DOVONEX is missed, it should be used as soon as the patient remembers and further dosing resumed as usual.

Administration

DOVONEX 50 mcg/g ointment or cream is available for use on the body and; a 50 mcg/mL scalp solution is available for hairy areas.

DOVONEX Used as Monotherapy:

DOVONEX should be applied topically to the affected areas twice daily (i.e. in the morning and in the evening). Application can be reduced to once daily (i.e. in the morning or in the evening) for maintenance treatment when appropriate. After satisfactory improvement has occurred, the drug can be discontinued. If recurrence takes place after discontinuation, the treatment may be reinstated.

DOVNEX Used as Combination Therapy:

DOVNEX can be used in combination with a moderately potent to very potent topical corticosteroid (See ACTION AND CLINICAL PHARMACOLOGY). DOVNEX and the steroid should be applied once daily at alternate times (i.e. morning versus evening application).

DOVNEX can be used twice daily in combination with low dose cyclosporin A (i.e. 2 mg/kg/day) or in combination with acitretin (20-70 mg/day) (See ACTIONS AND CLINICAL PHARMACOLOGY).

The use of DOVNEX in combination with other treatments (i.e. topical steroids, cyclosporin A or acitretin) improves efficacy allowing for dosage reduction of the other treatments. There is no experience in children with the use of DOVNEX in combination with other antipsoriatic therapies.

OVERDOSAGE

Hypercalcemia does not occur at the usual dose of DOVNEX (calcipotriol) (See DOSAGE AND ADMINISTRATION). Excessive use (i.e. more than the recommended weekly amount) may cause elevated serum calcium, which rapidly subsides when treatment is discontinued. In such cases, the monitoring of serum calcium levels once weekly until the serum calcium returns to normal levels is recommended.

ACTION AND CLINICAL PHARMACOLOGY**Mechanism of Action**

Calcipotriol is a non-steroidal antipsoriatic agent, derived from 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 (without any evidence of a cytotoxic effect) of keratinocytes, thus reversing the abnormal

keratinocyte changes in psoriasis. The therapeutic goal envisaged with calcipotriol is thus a normalization of epidermal growth.

Clinical Pharmacology

Clinical trials have shown DOVONEX cream and ointment (calcipotriol 50 mcg/g) and DOVONEX scalp solution (calcipotriol 50 mcg/mL) to be efficacious and well-tolerated in the topical treatment of psoriasis vulgaris (plaque psoriasis). Clinical improvement usually occurred rapidly and was evident within 2 weeks of treatment. The symptoms of thickness, erythema and scaling, as well as extent of psoriasis, were all markedly improved. The efficacy and safety of DOVONEX ointment and cream are similar with best results obtained at the end of up to 6 to 8 weeks of treatment. Long-term control of psoriasis lasting up to 12 months has been demonstrated in clinical trials with DOVONEX ointment.

Clinical trials have demonstrated the efficacy and safety of once daily DOVONEX administration in combination with once daily administration of a moderately potent to very potent topical corticosteroid. Twice daily application of DOVONEX is safe and effective when combined with systemic drug therapy (cyclosporin A or acitretin). In clinical studies, DOVONEX ointment was combined with either cyclosporin A (2 mg/kg/day) for up to 6 weeks or with acitretin (20-70 mg/day) for up to 12 weeks. Improved efficacy achieved through combination therapy allowed once daily steroid administration or reductions in the required dose of cyclosporin A or acitretin, thereby reducing the potential for dose related adverse effects associated with these agents. Combination of DOVONEX plus a moderately potent to very potent corticosteroid was also shown to reduce skin irritation due to calcipotriol. Combination of DOVONEX with systemic drug therapy did not affect the incidence of short term adverse events compared to systemic drug therapy alone.

Three pivotal trials to evaluate the safety and efficacy of DOVONEX scalp solution were conducted in patients with scalp psoriasis. There was a statistically significant improvement in

the scalp psoriasis with a positive effect on total sign score, redness, thickness, scaliness and extent of scalp psoriasis.

Pharmacokinetics

A pharmacokinetic study of DOVONEX ointment has demonstrated that the apparent systemic absorption of the applied dose of calcipotriol over 12 hours is approximately 5.5% of the dose in normal subjects and in psoriatic patients.

Special Populations and Conditions

Pediatric: The safety, efficacy and tolerability of DOVONEX ointment in children (ages 2 to 14 years) has been demonstrated by an 8 week open-label trial as well as an 8 week double-blind vehicle controlled trial. DOVONEX was significantly more effective than vehicle in reducing the symptoms of redness, thickness and scaliness, and in the overall assessment of efficacy. No significant effects on haematology, serum and urine biochemistry parameters (including calcium levels) and parameters of bone formation or resorption were observed after 8 weeks of treatment (maximum dose 50 g/week/m² body surface area).

FOR DETAILS OF EFFICACY AND SAFETY DATA OBTAINED FROM VARIOUS CLINICAL TRIALS, SEE PART II – CLINICAL TRIALS.

STORAGE AND STABILITY

Cream and Ointment: Store at room temperature (15-25°C).

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

Scalp Solution: Store below 25°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form:

DOVONEX (calcipotriol) is available as an ointment (faintly translucent white to yellowish ointment), cream (white, soft cream), and scalp solution (colourless, slightly viscous solution).

Composition:

<i>Ointment</i>	<i>Cream</i>	<i>Scalp Solution</i>
50 mcg calcipotriol per gram	50 mcg calcipotriol per gram	50 mcg calcipotriol per mL

Non-medicinal ingredients:

white soft paraffin	white soft paraffin	hydroxypropyl cellulose
propylene glycol	cetostearyl alcohol	isopropanol
liquid paraffin	liquid paraffin	levomenthol
polyoxyethylene-(2)-stearyl ether	glycerol 85%	sodium citrate
purified water	macrogol cetostearyl ether	propylene glycol
disodium phosphate dihydrate	disodium phosphate dihydrate	purified water
disodium edentate	disodium edetate	
DL- α -tocopherol	chloroallylhexaminium (dowicil 200) purified water	

Packaging:

Cream and ointment: 15g, 60g and 120g lacquered aluminium tubes and 240g laminate tubes (equipped with an aluminium membrane).

Scalp solution: 30 mL, 60 mL, and 120 mL polyethylene bottles.

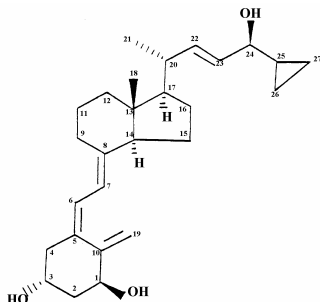
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

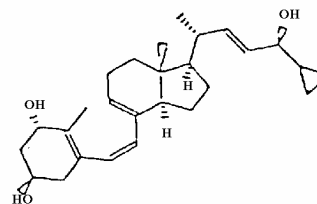
Drug Substance

Proper name (I.N.N.):	Calcipotriol
Chemical abstracts name:	9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol,24-cyclopropyl - , (1 α ,3 β ,5Z,7E,22E,24S)
Alternative chemical name:	20(R)-(3'(S)-Cyclopropyl-3'-hydroxyprop1'(E)enyl)-1(S),3(R)-dihydroxy-9,10-secopregna-5(Z),7(E),10(19)-triene
Laboratory code name:	MC 903 or MC 903-000
Molecular formula and mass:	C ₂₇ H ₄₀ O ₃ ; 412.6
Chirality:	The calcipotriol molecule is one single stereoisomer. The absolute configuration of the chiral centers at carbon atoms nos. 1, 3, 13, 14, 17, 20 and 24 is indicated in the structural formula below..

Structural formula:



Calcipotriol



"Pre-calcipotriol"

Physicochemical properties:

<i>Physical form:</i>	Calcipotriol is a white or almost white crystalline substance.
<i>Solubility at RT:</i>	Freely soluble in ethanol, soluble in chloroform and propylene glycol, practically insoluble in liquid paraffin. Solubility in water is 0.6 mcg/mL.
<i>Melting point:</i>	166-168°C
<i>Polymorphism:</i>	So far no signs have indicated the existence of polymorphic forms.
<i>Derivation:</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 above.

CLINICAL TRIALS

DOVONEX Used as Monotherapy

Twice daily DOVONEX (calcipotriol) administration has been shown to be effective for the treatment of psoriasis deemed amenable to topical treatment regardless of the baseline severity. Although once daily administration is clinically effective with respect to PASI reduction and attainment of marked clinical improvement or clearance of symptoms, it is less effective than twice daily administration. Therefore, once daily administration is only recommended for the maintenance phase of DOVONEX treatment. For further details, please see information on studies DE127-001, DE127-003, DE127-007, DE127-009, and MC 9302 INT in the Summary of Clinical Trials table below.

DOVONEX Used as Combination Therapy with Topical Steroids

Combination of DOVONEX once daily plus once daily administration of a potent or very potent topical corticosteroid has been shown to improve efficacy. Two weeks of combination treatment with DOVONEX ointment plus 0.05% halobetasol propionate ointment decreased overall severity by approximately 80% as compared to DOVONEX twice daily monotherapy (56%). Eight weeks of combination treatment with DOVONEX cream plus 0.1% betamethasone-17-valerate cream reduced the baseline PASI score by almost 60% as compared to DOVONEX twice daily monotherapy (48%). For further details, please see information on studies DE127-019 and MC 9302 INT in the Summary of Clinical Trials table below.

DOVONEX Used as Combination Therapy with Cyclosporin or Acitretin

In a clinical trial of 6 weeks duration, combination of DOVONEX twice daily plus low dose oral cyclosporin A (2 mg/kg/day) was significantly more effective than cyclosporin monotherapy. Combination treatment resulted in an approximate 80% reduction in PASI versus a 58% PASI reduction with cyclosporin monotherapy. For further details, including efficacy and safety information, please see study MC 9101 F in the Summary of Clinical Trials table below.

In a clinical trial of 12 weeks duration, the following treatments were compared: DOVONEX ointment twice daily plus oral acitretin (20-70 mg/day) versus placebo ointment twice daily plus oral acitretin (20-70 mg/day). At the end of treatment, combination with acitretin reduced baseline PASI by approximately 72% versus 48% in the acitretin group. Combination treatment provided marked improvement or clearance to a significantly greater number of patients while requiring significantly less acitretin as compared to acitretin monotherapy. For further details, including efficacy and safety information, please see study MC 9306 INT in the Summary of Clinical Trials table below.

DOVONEX Used as Combination Therapy with PUVA or UVB Phototherapy

DOVONEX in combination with PUVA or UVB phototherapy is not indicated for the topical treatment of psoriasis due to the observation in a hairless mice model of a reduced time to UVR-induced tumour formation. This preclinical finding suggests a possible enhancement effect for calcipotriol on the known carcinogenic effect of UVR. (see TOXICOLOGY, Photo(co)-carcinogenicity)

In a clinical trial of 12 weeks duration, the following treatments were compared: DOVONEX ointment twice daily for 2 weeks followed by twice daily DOVONEX in combination with PUVA (3 times weekly) for an additional 10 weeks versus placebo ointment twice daily for 2 weeks followed by twice daily placebo ointment in combination with PUVA (3 times weekly). At the end of treatment, combination of DOVONEX plus PUVA phototherapy resulted in a 91% PASI reduction with 91% of patients achieving marked improvement or clearance. Combination treatment was significantly more effective than PUVA alone and required significantly less UVA exposure (ie. 37% lower cumulative dose, 26% fewer irradiations and a 24% shorter duration of treatment). For further details, including efficacy and safety information, please see study MC 590 in the Summary of Clinical Trials table below.

In a clinical trial involving 12 weeks active treatment and 12 weeks follow-up, the following treatments were compared: DOVONEX cream twice daily plus UVB 2 times weekly versus

placebo cream plus UVB phototherapy 3 times weekly. DOVONEX plus UVB phototherapy twice weekly was equally effective as UVB three times weekly (ie. 77% PASI reduction versus 81%) but required a significantly lower cumulative dose of UVB and fewer treatments. For further details, including efficacy and safety information, please see study MCC 9504 CAN in the Summary of Clinical Trials table below. For additional studies, refer to study MC 9307 INT and MC 390 using DOVONEX ointment.

SUMMARY OF CLINICAL TRIALS

STUDY CODE	STUDY DESIGN	EVALUATION CRITERIA AND RESULTS
TOPICAL TREATMENT OF PSORIASIS		
DE127-001	<p><u>Design:</u> Multi-centre, randomised, double-blind, vehicle-controlled, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Stable plaque psoriasis involving 5-20% body surface.</p> <p><u>Treatment Period:</u> 2 week washout period and 8 weeks active treatment.</p> <p><u>Treatment Groups:</u> (1) Dovonex ointment (50 mcg/g calcipotriol), twice daily topical application; n=167 vs. (2) Placebo ointment, twice daily topical application; n=168</p>	<p><u>Evaluation Criteria:</u> Severity of erythema, scaling, plaque elevation, and overall disease severity, physician's global assessment, adverse events, serum biochemistry, haematology and urinalysis.</p> <p><u>Results:</u> Severity scores for all symptoms, overall severity score and physician's global assessment were significantly lower for Dovonex at weeks 1 through 8. At week 8, 70% of calcipotriol subjects were clear or markedly improved versus 22% with vehicle. No difference between groups in adverse reactions, frequency or time of onset of skin related adverse events. No effect on indices of haematology, or serum or urine biochemistry. Efficacy was similar between patients with “low” versus “high” baseline severity of psoriasis.</p>
DE127-003	<p><u>Design:</u> Multi-center, randomised, double-blind vehicle-controlled parallel group study.</p> <p><u>Inclusion Criteria:</u> Stable plaque psoriasis involving 5-20% body surface.</p> <p><u>Treatment Period:</u> 2 week washout period and 8 weeks active treatment.</p> <p><u>Treatment Groups:</u> (1) Dovonex ointment (50 mcg/g calcipotriol), twice daily topical application; n=139 vs. (2) Placebo ointment, twice daily topical application; n=138</p>	<p><u>Evaluation Criteria:</u> Severity of erythema, scaling, plaque elevation, and overall disease severity, physician's global assessment, adverse events, haematology, serum biochemistry and urinalysis.</p> <p><u>Results:</u> Severity scores for all symptoms, overall severity score and physician's global assessment were significantly lower for Dovonex at weeks 1 to 8. At week 8, 70% of calcipotriol subjects were clear or markedly improved versus 19% with vehicle. No difference between groups in adverse reactions, frequency, severity or time of onset of skin related adverse events. No effects on indices of haematology or serum or urine biochemistry. Efficacy was similar between patients with “low” versus “high” baseline severity of psoriasis.</p>

SUMMARY OF CLINICAL TRIALS (continued)

STUDY CODE	STUDY DESIGN	EVALUATION CRITERIA AND RESULTS
ONCE DAILY ADMINISTRATION		
DE127-007	<p><u>Design:</u> Multi-centre, randomised, double-blind, vehicle-controlled, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Plaque psoriasis.</p> <p><u>Treatment Period:</u> 8 weeks.</p> <p><u>Treatment Groups:</u> (1) Calcipotriol ointment (50 mcg/g) applied once daily; n=118 vs. (2) Placebo ointment applied once daily; n=117</p>	<p><u>Evaluation Criteria:</u> Severity of scaling, erythema and plaque elevation, assessment of overall disease severity, physician's global assessment of improvement/worsening of psoriasis and adverse events.</p> <p><u>Results:</u> Mean scores for erythema, scaling, plaque elevation and overall disease severity for calcipotriol ointment were significantly lower than vehicle from week 1 through the end of treatment (week 8). The physician's global assessment was significantly in favour of Dovonex from week 1 through to the end of treatment. No significant differences between treatment groups in the time to onset and frequency of skin-related adverse events.</p>
DE127-009	<p><u>Design:</u> Multi-centre, randomised, double-blind, vehicle-controlled, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Plaque psoriasis.</p> <p><u>Treatment Period:</u> 8 weeks.</p> <p><u>Treatment Groups:</u> (1) Calcipotriol ointment (50 mcg/g) applied once daily; n=99 vs. (2) Placebo ointment applied once daily; n=99</p>	<p><u>Evaluation Criteria:</u> Severity of scaling, erythema and plaque elevation, assessment of overall disease severity, physician's global assessment of improvement/worsening and adverse events.</p> <p><u>Results:</u> Mean scores for plaque elevation at week 1 and week 2 and scaling at week 2 were significantly lower for Dovonex compared to vehicle. Mean scores for all measures (erythema, scaling, plaque elevation, and overall disease severity) were significantly lower with Dovonex from week 4 through the end of treatment (week 8). The physician's global assessment was significantly in favour of Dovonex at week 1 through to the end of treatment. There were no statistically significant differences in the time to onset and frequency of skin-related adverse events between the treatment groups.</p>
MC 9302 INT	<p><u>Design:</u> Multi-centre, randomised, double-blind, comparative, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Psoriasis vulgaris. Lesions on the upper or lower extremities or trunk amenable to treatment with up to 120 g of cream per week.</p> <p><u>Treatment Period:</u> 2 week washout period and 8 weeks active treatment.</p> <p><u>Treatment Groups:</u> (1) Dovonex cream (50 mcg/g calcipotriol) once daily plus clobetasone 17-butyrate 0.05% cream once daily; n=175 vs. (2) Dovonex cream once daily plus betamethasone 17-valerate 0.1% cream once daily; n=176 vs. (3) Dovonex cream twice daily; n=174 vs. (4) Dovonex cream once daily plus placebo cream once daily; n=174</p>	<p><u>Evaluation Criteria:</u> Investigator assessment of PASI, investigator and patient assessment of overall response, adverse events, haematology and serum biochemistry.</p> <p><u>Results:</u> Although twice daily administration of Dovonex was more effective, once daily administration resulted in a 41% decrease in PASI and 28% of patients were judged to have marked improvement or clearance at the end of treatment. No difference between treatment groups in total adverse events.</p>

SUMMARY OF CLINICAL TRIALS (continued)

STUDY CODE	STUDY DESIGN	EVALUATION CRITERIA AND RESULTS
COMBINATION TREATMENT WITH MODERATE TO VERY POTENT TOPICAL CORTICOSTEROIDS		
<p>DE127-019</p>	<p><u>Design:</u> Multi-centre, randomised, double-blind, comparative, parallel group study.</p> <p><u>Inclusion Criteria:</u> Adults with stable plaque psoriasis having plaque elevation of at least moderate severity (grade 4 on a scale of 0-8) and 5% to 20% body coverage.</p> <p><u>Treatment Period:</u> 2 week washout period followed by 2 weeks active treatment.</p> <p><u>Treatment Groups:</u> (1) Dovonex ointment (50 mcg/g calcipotriol) twice daily; n=42 vs. (2) Halobetasol propionate 0.05% ointment twice daily; n=42 vs. (3) Dovonex ointment once daily plus halobetasol once daily; n=42</p>	<p><u>Evaluation Criteria:</u> Severity of erythema, scaling, and plaque elevation, assessment of overall disease severity, physician's global assessment and adverse events.</p> <p><u>Results:</u> Plaque elevation and overall severity were significantly lower in the combination group at day 14. The physician's global assessment was also lower at day 7 and 14. No difference between groups in adverse reactions.</p>
<p>MC 9302 INT</p>	<p><u>Design:</u> Multi-centre, randomised, double-blind, comparative, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Psoriasis vulgaris. Lesions on the upper or lower extremities or trunk amenable to treatment with up to 120 g of cream per week.</p> <p><u>Treatment Period:</u> 2 week washout period and 8 weeks active treatment.</p> <p><u>Treatment Groups:</u> (1) Dovonex cream (50 mcg/g calcipotriol) once daily plus clobetasone 17-butyrate 0.05% cream once daily; n=175 vs. (2) Dovonex cream once daily plus betamethasone 17-valerate 0.1% cream once daily; n=176 vs. (3) Dovonex cream twice daily; n=174 vs. (4) Dovonex cream once daily plus placebo cream once daily; n=174</p>	<p><u>Evaluation Criteria:</u> Investigator assessment of PASI, investigator and patient assessment of overall response, adverse events, haematology and serum biochemistry.</p> <p><u>Results:</u> At the end of treatment, a significantly greater decrease in PASI was observed for Dovonex plus betamethasone versus all other treatment groups. No difference between groups in total adverse events. Significantly less skin irritation with the two steroid combinations.</p>

SUMMARY OF CLINICAL TRIALS (continued)

STUDY CODE	STUDY DESIGN	EVALUATION CRITERIA AND RESULTS
COMBINATION WITH SYSTEMIC DRUG TREATMENT (CYCLOSPORIN OR ACITRETIN)		
<p>MC 9101 F</p>	<p><u>Design:</u> Multi-centre, randomised, double-blind, comparative, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Adults with severe psoriatic lesions (PASI\geq20) without exceeding 50% body coverage and for whom cyclosporin A seemed appropriate.</p> <p><u>Treatment Period:</u> 2 week washout period followed by 6 weeks active treatment.</p> <p><u>Treatment Groups:</u> (1) Dovonex ointment (50 mcg/g calcipotriol) twice daily in combination with low dose oral cyclosporin A (2 mg/kg/day); n=35 vs. (2) Placebo ointment twice daily in combination with low dose oral cyclosporin A (2 mg/kg/day); n=34</p>	<p><u>Evaluation Criteria:</u> Investigator assessment of PASI, investigator and patient assessment of overall response, adverse events, haematology and serum biochemistry.</p> <p><u>Results:</u> Clearance or PASI reduction of \geq 90% was achieved by 50% of combination treated patients versus 12% with cyclosporin alone. At the end of treatment PASI was reduced by 80% with Dovonex combination versus 58% with cyclosporin. Investigator and patient overall assessment favoured Dovonex combination treatment. No difference between groups in number of adverse events. No effect on laboratory values including serum calcium in either group.</p>
<p>MC 9306 INT</p>	<p><u>Design:</u> Multi-centre, randomised, double-blind, comparative, parallel group study.</p> <p><u>Inclusion Criteria:</u> Patients with a clinical diagnosis of severe or extensive psoriasis vulgaris deemed not responsive to topical treatment alone.</p> <p><u>Treatment Period:</u> 2 week washout period and 12 weeks active treatment.</p> <p><u>Treatment Groups:</u> (1) Dovonex ointment (50 mcg/g calcipotriol) twice daily plus oral acitretin (20-70 mg/day); n=76 vs. (2) Placebo ointment twice daily plus oral acitretin (20-70 mg/day); n=59</p>	<p><u>Evaluation Criteria:</u> Investigator assessment of PASI, investigator and patient assessment of overall response, adverse events and serum biochemistry.</p> <p><u>Results:</u> At the end of treatment, PASI reduction and the investigators overall assessment was significantly in favour of Dovonex combination treatment. A significantly lower (20% lower) cumulative dose of acitretin was required to obtain clearance or marked improvement (67% of patients receiving combination treatment versus 41% treated with acitretin). No difference in adverse events. No effect on laboratory parameters including serum calcium in either group.</p>

SUMMARY OF CLINICAL TRIALS (continued)

STUDY CODE	STUDY DESIGN	EVALUATION CRITERIA AND RESULTS
COMBINATION WITH PHOTOTHERAPY (PUVA or UVB)		
<p>MC 590</p>	<p><u>Design:</u> Multi-centre, randomised, double-blind, comparative, parallel-group study.</p> <p><u>Inclusion Criteria:</u> Adults with extensive psoriasis covering $\geq 20\%$ and $\leq 50\%$ of the body surface and for whom PUVA therapy was indicated.</p> <p><u>Treatment Period:</u> 2 week washout period followed by 12 weeks active treatment.</p> <p><u>Treatment Groups:</u> (1) Dovonex ointment (50 mcg calcipotriol) twice daily for 2 weeks followed by twice daily Dovonex in combination with PUVA (3 times weekly) for 10 weeks; n=54 vs. (2) Placebo ointment twice daily for 2 weeks followed by twice daily placebo ointment in combination with PUVA (3 times weekly) for 10 weeks; n=53</p>	<p><u>Evaluation Criteria:</u> Investigator assessment of PASI, patient assessment of overall response, adverse events and serum biochemistry.</p> <p><u>Results:</u> At the end of treatment, a significantly greater % decrease in PASI was observed with Dovonex plus PUVA (91% versus 76%). Dovonex combination treatment required a significantly lower UVA dose (37%), fewer doses (26%) and shorter treatment period (24%). Patient assessment of overall response was significantly in favour of Dovonex combination. No difference between groups in number of adverse events. No effect on laboratory values including serum calcium. No phototoxicity or photosensitivity was reported.</p>
<p>MC 9307 INT</p>	<p><u>Design:</u> Multicenter, randomised, double-blind, right-left, comparative study.</p> <p><u>Inclusion Criteria:</u> Adults with a clinical diagnosis of psoriasis vulgaris. Symmetrical lesions on 1) the trunk and on the arms and legs, 2) the trunk alone, 3) arms and legs.</p> <p><u>Treatment Period:</u> 2 week washout period, 8 weeks active treatment and 8 weeks follow-up.</p> <p><u>Treatment Groups:</u> (1) Dovonex ointment (50 mcg/g calcipotriol) twice daily plus UVB three times weekly on one side of the body vs. (2) Placebo ointment twice daily plus UVB three times weekly on the other side of the body; n=77</p>	<p><u>Evaluation Criteria:</u> Investigator assessment of PASI, investigator and patient assessment of overall response, adverse events and serum biochemistry.</p> <p><u>Results:</u> After 2 weeks, the % PASI reduction and the overall assessment of response were significantly in favour of Dovonex plus UVB. At the end of treatment, all three assessments were similar between treatment groups. There was no effect on laboratory parameters including serum calcium.</p>

SUMMARY OF CLINICAL TRIALS *(continued)*

STUDY CODE	STUDY DESIGN	EVALUATION CRITERIA AND RESULTS
COMBINATION WITH PHOTOTHERAPY <i>(continued)</i>		
MC 390	<p><u>Design:</u> Multi-centre, randomised, double-blind, right-left, comparative study.</p> <p><u>Inclusion Criteria:</u> Adults with a clinical diagnosis of moderate to severe plaque psoriasis vulgaris. Symmetrical lesions on 1) the trunk and on the arms and legs, 2) the trunk alone, 3) arms and legs.</p> <p><u>Treatment Period:</u> 2 week washout period, 8 weeks active treatment and 8 weeks follow-up.</p> <p><u>Treatment Groups:</u> (1) Dovonex ointment (50 mcg/g calcipotriol) twice daily plus UVB three times weekly on one side of the body vs. (2) Dovonex ointment twice daily on the other side of the body; n=101</p>	<p><u>Evaluation Criteria:</u> Investigator assessment of PASI, investigator and patient assessment of overall response, adverse events and serum biochemistry.</p> <p><u>Results:</u> PASI reduction and the investigators overall assessment was significantly in favour of Dovonex plus UVB at all time points. No difference in adverse events. No effect on laboratory values, including serum calcium.</p>
MCC 9504 CAN	<p><u>Design:</u> Multi-centre, randomised, single-blind (Investigator), parallel group, comparative study.</p> <p><u>Inclusion Criteria:</u> Adults with a clinical diagnosis of extensive plaque psoriasis vulgaris (20-40% body coverage) for which UVB phototherapy was indicated.</p> <p><u>Treatment Period:</u> 1 week washout period followed by 12 weeks active treatment and 12 weeks follow-up.</p> <p><u>Treatment Groups:</u> (1) Dovonex cream (50 mcg/g calcipotriol) twice daily plus UVB 2 times weekly; n=80 vs. (2) Placebo cream twice daily plus UVB phototherapy 3 times weekly; n=80</p>	<p><u>Evaluation Criteria:</u> Investigator assessment of PASI, investigator and patient assessment of overall response, adverse events and serum biochemistry. Secondary criteria included the number of UVB treatments required for clearance and the number of patients attaining an 80% decrease in PASI.</p> <p><u>Results:</u> Dovonex plus UVB twice weekly was equally effective as UVB three times weekly based on reduction of PASI and overall response assessed by investigators and patients. The Dovonex group attained an 80% reduction in PASI or clearance of psoriasis with significantly fewer UVB treatments and a lower cumulative dose of UVB. No clinically significant effects on laboratory values (including serum calcium) were observed in either group.</p>

DETAILED PHARMACOLOGY

Animal Pharmacodynamic Studies

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.

Current therapeutic agents exert their effects mainly by non-specific cytostatic/cytotoxic effects on the proliferating cells or by 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.

In addition, calcipotriol was 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. 1,25(OH)₂D₃, the active form of vitamin D₃, 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 $1,25(\text{OH})_2\text{D}_3$. 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

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 minipigs, 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 IN THE RAT AND/OR RABBIT

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 STUDY IN THE RAT AND/OR MINIPIG

TYPE OF STUDY	METHODS	MAJOR RESULTS AND INTERPRETATION
<p>(4) Acute oral and i.v. dosing of ³H-MC903 to minipigs.</p>	<p>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.</p>	<p><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 ³H₂O. 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 ³H₂O [Putative metabolic pathways discussed in study (5) below.]</p>
<p>(5) Rats and Minipigs treated as described in 1 and 4 above. Metabolism further studied.</p>	<p>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.</p>	<p>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 D₃, active form of vitamin D₃. Likely that MC903 is metabolized to calcitronic acid, similar to 1,25 dihydroxyvitamin D₃.</p>

IN VITRO PHARMACOKINETIC STUDY IN THE RAT AND/OR MINIPIG, RABBIT, MAN

TYPE OF STUDY	METHODS	MAJOR RESULTS AND INTERPRETATION
(6) 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°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.
(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 pig, man and rabbit. Additional peak in man and rabbit due to metabolite MC1046; to a lesser 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

There are no consistent and generally accepted definitions for “mild”, “moderate” or “severe” psoriasis. There is also considerable variability among physicians in the interpretation of the existing guidelines for assessing the extent of psoriasis. In clinical practice, patients are not evaluated or categorized as having mild, moderate or severe psoriasis but rather whether they are amenable to topical treatment or whether they require systemic treatment. DOVONEX (calcipotriol) is indicated for the topical treatment of psoriasis. The following section is intended to provide clarity and consistency regarding the therapeutic positioning of DOVONEX.

For many patients no single therapy provides adequate long-term control of psoriasis. Various combination treatment regimens have therefore been developed to improve treatment efficacy and/or to minimize the development of adverse effects. DOVONEX has been shown to be safe and effective when used in combination with a moderate to very potent topical corticosteroid. When the extent and/or severity of psoriasis is such that topical therapy alone is no longer adequate, then various systemic treatments are used. No single quantitative grading system is used clinically to determine at which level of extent/severity of psoriasis that systemic treatments are used. It is difficult to assign a specific severity score below which psoriasis cannot be considered “severe”. To a large extent, the decision to use systemic treatment is patient specific and dependent on the level of disability (physical, occupational or psychological) associated with psoriasis.

Systemic treatments are generally reserved for severe/extensive psoriasis when topical monotherapy is inappropriate. However, treatment of extensive and/or severe psoriasis is by no means restricted to systemic monotherapy. Combination treatments are widely accepted and are widely used as an alternative approach to minimize exposure to systemic agents which are usually more potent but are also potentially more harmful. DOVONEX has been shown to be safe and effective when used in combination with systemic drug therapy (cyclosporin A or acitretin) or with phototherapy (PUVA or UVB). The use of DOVONEX in combination with

other antipsoriatic therapies offers an additional means of treating psoriasis that is not amenable to topical treatment alone (See CLINICAL TRIALS).

TOXICOLOGY

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

Systemic Toxicity

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

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.

Reproduction and Mutagenicity

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

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 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.

ACUTE TOXICITY

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

TEST COMPOUND	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

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

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

STUDY	ANIMAL	MC903 DOSAGE	IMPORTANT FINDINGS
Fertility and general reproductive performance	Rat (20 M, 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.

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PART III: CONSUMER INFORMATION

^{PR}DOVONEX®
calcipotriol

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

ABOUT THIS MEDICATION

What the medication is used for:

- Dovonex® cream and ointment is used for the topical treatment of psoriasis on your body.
- Dovonex® scalp solution is used for the topical treatment of scalp psoriasis.
- Dovonex® may be used together with a moderate to very potent topical corticosteroid, cyclosporin A (oral) or acitretin (oral).
- Dovonex® is not for use on the face.

What it does:

Dovonex® contains the active ingredient calcipotriol, a vitamin D-like agent.

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.

When it should not be used:

- Do not use this product if you are allergic to any of the ingredients in Dovonex® (calcipotriol) cream, ointment or scalp solution, or to components of the container.
- Dovonex® is not for use in your eyes.

What the medicinal ingredient is:

Calcipotriol

What the important nonmedicinal ingredients are:

Ointment: white soft paraffin, propylene glycol, liquid paraffin, polyoxyethylene-(2)-stearyl ether, purified water, disodium phosphate dehydrate, disodium edentate, DL- α -tocopherol.

Cream: white soft paraffin, cetostearyl alcohol, liquid paraffin, glycerol 85%, macrogol cetostearyl ether, disodium phosphate dehydrate, disodium edentate, chloroallylhexaminium (dowicil 200), purified water.

Scalp solution: hydroxypropyl cellulose, isopropanol, levomenthol, sodium citrate, propylene glycol, purified water.

What dosage forms it comes in:

Dovonex® is available in three topical formulations.

- Ointment, 50 mcg/g
- Cream, 50 mcg/g
- Scalp solution, 50 mcg/mL

WARNINGS AND PRECAUTIONS

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

If Dovonex® is used together with other psoriasis treatments, you should read the warning section of the consumer information for those treatments.

Dovonex® is not recommended for your face as it may cause skin irritation. Use the cream or ointment carefully on body areas with skin folds. If air can not reach the skin under the fold, this area may become irritated if treated with Dovonex®.

Children from 2 to 14 years of age should apply Dovonex® cream or ointment only when supervised by adults. The scalp solution is not recommended for use in children under 18 years old. Do not use Dovonex® in children under 2 years of age.

Dovonex® should only be used during pregnancy or while nursing if the benefit clearly outweighs the potential risk to your baby. Tell your doctor if you are pregnant, nursing, or become pregnant during your treatment.

If more than the maximum recommended weekly amount of Dovonex® is used (i.e., 100g), there is the risk of developing high blood calcium levels.

BEFORE you use Dovonex® talk to your doctor or pharmacist if:

- you have severe extensive psoriasis (the use of Dovonex® may not be recommended).
- you are using any other psoriasis treatments.
- 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 Dovonex® cream, ointment or scalp solution or to components of the container.

INTERACTIONS WITH THIS MEDICATION

Dovonex® has been used safely in combination with topical steroids. Except for steroids, there is no clinical trial experience on the interaction of Dovonex® with other topical drugs for psoriasis.

PROPER USE OF THIS MEDICATION

Usual dose:

At the start of your treatment Dovonex® should be rubbed onto affected skin areas twice a day (morning and evening). You should begin to see an improvement within 2 weeks. Best results are seen within 6-8 weeks.

Once your psoriasis improves your doctor may reduce the dose to once a day. Using Dovonex® once a day will help keep your psoriasis under control.

Your doctor may prescribe using Dovonex® together with a steroid. Use each medicine once a day and at different times of the day (i.e., one in the morning, the other in the evening).

Dovonex® may also be used twice daily in combination with cyclosporin A or acitretin. There are no clinical studies in children of combination therapy with Dovonex®.

How to use the cream or 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 Dovonex® on the areas of your skin affected by psoriasis. Wash your hands after using 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 Dovonex® onto the surrounding healthy skin, wash it off right away.
- Dovonex® may irritate your skin for a short while after you apply it, especially in skin folds. Try not to scratch the area.
- Dovonex® is not recommended for use on your face because it may irritate this more sensitive area of skin. If you accidentally get some on your face, wash it off right away.
- Do not use more than the maximum amount of Dovonex® in one week for your age group (see table below).

Age (years)	Total Dovonex per week cream (g), ointment (g)
2 – 5	25
6 – 10	50
11 – 14	75
Adults (over 14)	100

- If Dovonex® cream and ointment are used together then the total amount of Dovonex® should not be more than the maximum amount allowed for each age group in one week (see table above).

How to use the scalp solution:

The instructions below are for adults only, the scalp solution is not recommended for use in children under 18 years old.

- After washing your hair, dry it thoroughly before using Dovonex® scalp solution. Do not wash your hair immediately after using the scalp solution or you will wash out the medicine.
- Remove cap, place the nozzle through your hair next to the scalp. Squeeze the bottle gently and apply a few drops on to the affected area.
- Rub in gently with your fingertips. One or two drops should cover the area of a postage stamp.
- Wash your hands after using Dovonex® to avoid getting any on your face.
- Dovonex® may irritate your scalp for a short time after you apply it. Try not to scratch the area.
- Dovonex® scalp solution should not be used on your face because it could irritate your skin. If you accidentally get some on your face, wash it off right away. If you get the scalp solution in your eyes, flush your eyes with water.
- Do not use more than 60 mL of Dovonex® scalp solution in one week.
- If you use the scalp solution with Dovonex® cream or ointment then the total amount of Dovonex® should not be more than the maximum amount allowed; 100g or mL.

For example, if you use 60 g of cream or ointment, then you should not use more than 40 mL of scalp solution.

Overdose:

The calcipotriol in Dovonex® can lead to increased blood calcium levels if more than the maximum 100g weekly amount is used. This effect is reversible when treatment is stopped. If you have overdosed, contact your Doctor or go to the nearest Hospital Emergency.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effect is local irritation which is usually mild and temporary.

Face and scalp irritation is usually related to the accidental transfer of Dovonex® from other parts of your body. Rare cases of allergic reaction have been reported.

Use of calcipotriol can lead to high blood calcium levels but this is usually related to using more than the weekly maximum.

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	
Very rarely: hypercalcaemia (high blood calcium levels)	Fatigue, depression mental confusion, anorexia, nausea, vomiting, constipation, increased urination and in some patients, cardiac arrhythmias	✓		✓

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

HOW TO STORE IT

Cream and ointment: Store at room temperature (15-25°C).
Scalp Solution: Store below 25°C.

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

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada 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 Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrmpp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

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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