

PRODUCT MONOGRAPH

<sup>Pr</sup>**XAMIOL®**

calcipotriol and betamethasone dipropionate

Gel

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

Topical Antipsoriatic Agent  
Vitamin D Analogue / Corticosteroid

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**Pr**XAMIOL®  
**calcipotriol and betamethasone dipropionate**

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

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

**INDICATIONS AND CLINICAL USE**

XAMIOL (calcipotriol and betamethasone dipropionate) gel is indicated for the topical treatment of moderate to severe scalp psoriasis for up to 4 weeks.

**CONTRAINDICATIONS**

- Known hypersensitivity to XAMIOL (calcipotriol and betamethasone dipropionate), to any ingredient in the formulation or to components of the tube. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- OPTHALMIC USE
- patients with known disorders of calcium metabolism.
- viral (e.g. herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis or syphilis, perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers and wounds.
- guttate, erythrodermic, exfoliative and pustular psoriasis.
- patients with severe renal insufficiency or severe hepatic disorders.

## **WARNINGS AND PRECAUTIONS**

### **General**

Due to the content of calcipotriol, hypercalcaemia may occur if the maximum weekly dose (100 g) is exceeded. Serum calcium is quickly normalised when treatment is discontinued. The risk of hypercalcaemia is minimal when the recommendations relevant to calcipotriol are followed (see Monitoring and Laboratory Tests).

### **Carcinogenesis**

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

### **Endocrine and Metabolism**

XAMIOL (calcipotriol and betamethasone dipropionate) contains a potent group III steroid and concurrent treatment with other steroids on the scalp must be avoided.

Application on large areas of broken skin or under occlusive dressings should be avoided since it increases systemic absorption of corticosteroids and the risk of adverse effects such as adrenocortical suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, and affects on the metabolic control of diabetes mellitus (e.g. hyperglycaemia, glucosuria) can also be produced in some patients by systemic absorption of topical corticosteroids.

In a study in patients with both extensive scalp and extensive body psoriasis using a combination of high doses of XAMIOL gel (scalp application) and high doses of DOVOBET® ointment<sup>1</sup> (body application), 5 of 32 patients (15.6%) showed a borderline decrease in cortisol response to adrenocorticotrophic hormone (ACTH) challenge after 4 weeks of treatment (see ACTION AND CLINICAL PHARMACOLOGY).

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<sup>1</sup> Dovobet® ointment (50 mcg/g calcipotriol and 0.5 mg/g betamethasone, as dipropionate)

### **Skin**

Facial skin is very sensitive to corticosteroids and XAMIOL is not indicated for use in this area. The face should only be treated with weaker corticosteroids. Uncommon local adverse reactions (such as eye irritation or irritation of facial skin) were observed when the drug was accidentally administered in the area of the face, or accidentally to the eyes or conjunctiva (see ADVERSE REACTIONS and CLINICAL PHARMACOLOGY). The patient must be instructed in the correct use of XAMIOL (for e.g. washing their hands after each application) to avoid accidental transfer or application to the face, mouth and eyes. Should facial dermatitis develop in spite of these precautions, XAMIOL therapy should be discontinued.

When lesions become secondarily infected, they should be treated with antimicrobiological therapy. However, if the infection worsens, treatment with corticosteroids should be stopped.

When treating psoriasis with topical corticosteroids, it is recommended that treatment be interrupted periodically. There may be a risk of generalised pustular psoriasis or of rebound psoriasis when discontinuing corticosteroids after prolonged periods of use. Medical supervision should therefore continue in the post-treatment period.

There is a risk of local and systemic corticosteroid adverse effects with XAMIOL, including striae or atrophy of the skin and adrenal suppression. Treatment should be discontinued in the case of corticosteroid adverse effects related to the use of XAMIOL.

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

### **Special Populations**

**Pregnant Women:** The safety of calcipotriol and/or topical corticosteroids for use during pregnancy has not been established. The use of XAMIOL is not recommended in pregnant women.

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

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

### **Monitoring and Laboratory Tests**

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

## **ADVERSE REACTIONS**

### **Overview**

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

The following adverse reactions led to discontinuation of treatment with XAMIOL in 0.1-0.2% of patients: pruritus, skin pain or irritation, dermatitis, eye irritation, rash, burning sensation, face oedema, folliculitis and dry skin.

**Clinical Trials**

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

Two pivotal and 4 supporting controlled clinical studies were conducted in scalp psoriasis. Table 1 summarizes adverse drug reactions reported by at least 1% of patients in any treatment group in the pivotal scalp studies. Overall, the incidence of patients with at least one ADR was lowest in the XAMIOL gel group.

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**

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

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

**Other Adverse Drug Reactions**

Adverse reactions observed for the individual drug substances calcipotriol and betamethasone dipropionate are described below.

**Calcipotriol**

Adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, aggravated psoriasis, photosensitivity and hypersensitivity reactions. There have been infrequent reports of angioedema and facial

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oedema. Isolated cases of hypercalcaemia or hypercalciuria have been reported (see WARNINGS AND PRECAUTIONS).

Betamethasone dipropionate

Local reactions can occur after topical use especially during prolonged application including, skin atrophy, telangiectasia, striae, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation and colloid milia. When treating psoriasis, there may be a risk of generalised pustular psoriasis.

Systemic effects due to topical use of corticosteroids in adults occur infrequently but can be severe. Adrenocortical suppression, cataract, infections, impact on the metabolic control of diabetes mellitus and increase of intra-ocular pressure can occur, especially after long-term treatment. Application of XAMIOL under occlusion or for prolonged treatment periods may result in an increased risk of systemic adverse events, and is therefore not recommended (see WARNINGS AND PRECAUTIONS).

Table 1. Adverse Drug Reactions Occurring in  $\geq 1\%$  of Patients for the Pivotal Scalp Studies: safety analysis set

| Primary System Organ Class <sup>1</sup><br>Preferred Term <sup>1</sup> | Xamiol® gel<br>(n=1093) |     | Betamethasone gel<br>(n=1104) |     | Calcipotriol gel<br>(n=548) |     | Gel vehicle<br>(n=135) |     |
|--|-------------------------|-----|-------------------------------|-----|-----------------------------|-----|------------------------|-----|
|  | Number of<br>Patients   | %   | Number of<br>Patients         | %   | Number of<br>Patients       | %   | Number of<br>Patients  | %   |
| <b>Nervous system disorders</b>  |                         |     |                               |     |                             |     |                        |     |
| Headache   | 6                       | 0.5 | 11                            | 1.0 | 1                           | 0.2 | 1                      | 0.7 |
| Burning sensation  | 2                       | 0.2 | 6                             | 0.5 | 10                          | 1.8 | 0                      | 0.0 |
| <b>Skin and subcutaneous tissue disorders</b>                          |                         |     |                               |     |                             |     |                        |     |
| Pruritus   | 25                      | 2.3 | 18                            | 1.6 | 45                          | 8.2 | 7                      | 5.2 |
| Skin irritation  | 5                       | 0.5 | 5                             | 0.5 | 15                          | 2.7 | 3                      | 2.2 |
| Alopecia   | 4                       | 0.4 | 6                             | 0.5 | 3                           | 0.5 | 2                      | 1.5 |
| Erythema   | 4                       | 0.4 | 4                             | 0.4 | 16                          | 2.9 | 1                      | 0.7 |
| Dry skin   | 1                       | 0.1 | 3                             | 0.3 | 6                           | 1.1 | 0                      | 0.0 |
| <b>General disorders and administration site conditions</b>            |                         |     |                               |     |                             |     |                        |     |
| Pain   | 1                       | 0.1 | 0                             | 0.0 | 3                           | 0.5 | 3                      | 2.2 |

1) Coded according to MedDRA version 6.1.

## **DRUG INTERACTIONS**

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

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

- XAMIOL (calcipotriol and betamethasone dipropionate) is not recommended for use in children and adolescents below the age of 18 years.
- XAMIOL is FOR TOPICAL USE ONLY and not for ophthalmic use.

### **Recommended Dose and Dosage Adjustment**

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

The maximum daily dose including other calcipotriol-containing products on the body should not exceed 15 g and the maximum weekly dose should not exceed 100 g.

All affected scalp areas may be treated with XAMIOL gel. Up to 30% of the total surface area of the body may be treated with calcipotriol and betamethasone (XAMIOL gel on the scalp + DOVOBET® ointment on the body).

### **Missed Dose**

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

### **Administration**

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

Patients should shake the product prior to use.

**OVERDOSAGE**

Use of XAMIOL (calcipotriol and betamethasone dipropionate) above the recommended dose may cause elevated serum calcium which should rapidly subside when treatment is discontinued. In such cases, it is recommended to monitor serum calcium levels once weekly until they return to normal. Excessive prolonged use of topical corticosteroids may suppress the pituitary-adrenal functions, resulting in secondary adrenal insufficiency which is usually reversible. If this occurs, symptomatic treatment is indicated. In cases of chronic toxicity, treatment with XAMIOL must be discontinued gradually.

**ACTION AND CLINICAL PHARMACOLOGY****Mechanism of Action**

XAMIOL 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, vasoconstrictive and immunosuppressive properties. Through occlusion the effect can be enhanced due to increased penetration of the stratum corneum. As a result, the incidence of adverse events will increase. In general, the mechanism of the anti-inflammatory activity of topical steroids is unclear. Corticosteroids are thought to induce phospholipase  $\text{A}_2$  inhibitor proteins, preventing arachidonic acid release and the biosynthesis of potent mediators of inflammation.

### **Pharmacodynamics**

Adrenal response to ACTH was determined by measuring serum cortisol levels in patients with both extensive scalp and body psoriasis, using up to 106 g per week combined XAMIOL gel and DOVOBET® ointment. A borderline decrease in cortisol response at 30 minutes post ACTH challenge was seen in 5 of 32 patients (15.6%) after 4 weeks of treatment and in 2 of 11 patients (18.2%) who continued treatment until 8 weeks. In all cases, the serum cortisol levels were normal at 60 minutes post ACTH challenge. There was no evidence of change of calcium metabolism observed in these patients.

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

### **Pharmacokinetics**

**Absorption:** The systemic exposure to calcipotriol and betamethasone dipropionate from topically applied XAMIOL gel is comparable to DOVOBET® ointment in rats and minipigs. Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone dipropionate from the DOVOBET® ointment formulation is less than 1% of the dose (2.5 g) when applied to normal skin (625 cm<sup>2</sup>) for 12 hours. Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids.

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

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of the parent compound.

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

Betamethasone dipropionate is metabolized to betamethasone 17-propionate and betamethasone, including the 6 $\beta$ -hydroxy derivatives of those compounds by hydrolysis. Betamethasone 17-propionate (B17P) is the primary metabolite.

## **STORAGE AND STABILITY**

Store at 15° C - 30° C. Do not refrigerate. Shake before use. Protect from light, keep the bottle in the outer carton. Use within 3 months of first opening the bottle.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Dosage Form**

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

### **Composition**

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

**Non-medicinal ingredients:** liquid paraffin, polyoxypropylene-15-stearyl ether, hydrogenated castor oil,  $\alpha$ -tocopherol and butylhydroxytoluene.

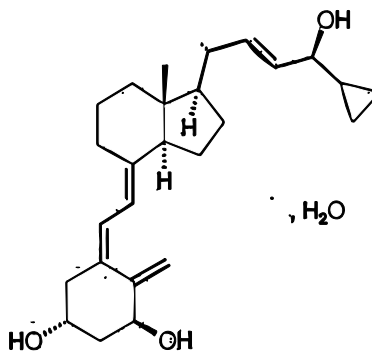
### **Packaging**

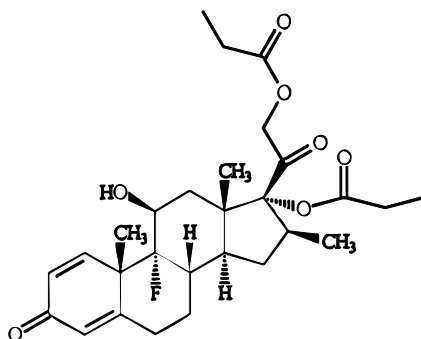
Available in 60 g polyethylene bottles.

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

|                            |   |   |
|----------------------------|---|---|
| Proper name (I.N.N.):      | <u>Calcipotriol monohydrate</u>   | <u>Betamethasone dipropionate</u>   |
| Chemical name:             | 9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-, monohydrate, (1 $\alpha$ ,3 $\beta$ ,5Z,7E,22E,24S)  | Pregna-1,4-diene-3,20-dione,9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-(11 $\beta$ ,16 $\beta$ ) |
| Alternative chemical name: | 20(R)-(3'(S)-Cyclopropyl-3'-hydroxyprop-1'(E)-enyl)-1(S),3(R)-dihydroxy-9-10-secopregna-5(Z),7(E),10(19)-triene, hydrate  | 9-fluoro-11 $\beta$ ,17,21-trihydroxy-16 $\beta$ -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate      |
| Laboratory code name:      | MC 903 monohydrate<br>MC 903, H <sub>2</sub> O  | 433 or 433/M  |
| Molecular formula:         | 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>   |
| Molecular mass:            | 430.6   | 504.6   |
| Chirality:                 | The calcipotriol molecule is one single stereoisomer. The absolute configuration of the chiral centres at carbon atoms nos. 1, 3, 13, 14, 17, 20 and 24 is indicated in the structural formula below. |   |

Structural formula:  
Calcipotriol monohydrate



Betamethasone dipropionate

## Physicochemical properties :

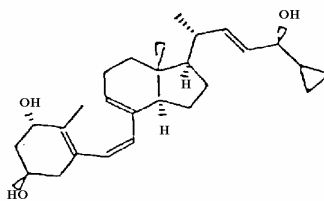
*Physical form:**Solubility at room temperature:**Melting point:**Polymorphism:**Other characteristics:*Calcipotriol monohydrate

White or almost white crystalline substance. Freely soluble in ethanol, soluble in chloroform and propylene glycol, practically insoluble in liquid paraffin. Solubility in water is 0.6 mcg/ml.

166-168°C

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

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

Betamethasone dipropionate

White or almost white crystalline powder. Freely soluble in acetone, in dioxane, in dichloromethane and in chloroform; soluble in methanol; sparingly soluble in alcohol; slightly soluble in ether; insoluble in water and in hexane.

176-180°C

## CLINICAL TRIALS

The efficacy of once daily use of XAMIOL gel was investigated in two randomised, double-blind 8-week clinical studies including a total of more than 1,000 XAMIOL treated patients with scalp psoriasis of at least moderate severity according to the Investigator's Global Assessment of disease severity (IGA). The number of patients with mild scalp psoriasis included in the studies was small making estimates of efficacy less reliable in this subgroup. Comparators were betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and (in one of the studies) the gel vehicle alone, all used once daily. Results for the primary response criterion (absent or very mild disease according to the IGA at week 8) showed that XAMIOL was statistically significantly more effective than the comparators (see table below). The majority of patients who responded achieved satisfactory improvement before 4 weeks of treatment. Further increases in efficacy beyond 4 weeks were minimal. Results for speed of onset based on data at week 2 also showed XAMIOL to be statistically significantly more effective than the comparators.

| <b>% of Patients with absent or very mild disease</b> | <b>XAMIOL gel (n=1,108)*</b> | <b>Betamethasone dipropionate (n=1,118)*</b> | <b>Calcipotriol (n=558)*</b> | <b>Gel vehicle (n=136)*</b> |
|---|------------------------------|--|------------------------------|-----------------------------|
| week 2  | 53.2%                        | 42.8% <sup>†</sup>                           | 17.2% <sup>†</sup>           | 11.8% <sup>†</sup>          |
| week 4  | 60.7%                        | 52.9% <sup>†</sup>                           | 24.7% <sup>†</sup>           | 14.7% <sup>†</sup>          |
| week 8  | 69.8%                        | 62.5% <sup>†</sup>                           | 40.1% <sup>†</sup>           | 22.8% <sup>†</sup>          |

<sup>†</sup> statistically significantly less effective than XAMIOL gel (p<0.001)

\* including patients graded as mild at baseline

Another randomised, investigator-blinded clinical study including 312 patients with scalp psoriasis of at least moderate severity according to the IGA, investigated use of XAMIOL gel once daily compared with DOVONEX® scalp solution twice daily for up to 8 weeks. Results for the primary response criterion (absent or very mild disease according to the IGA at week 8) showed that XAMIOL was statistically significantly more effective than DOVONEX® scalp

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solution (see table below).

| <b>% of Patients with absent or very mild disease</b> | <b>XAMIOL gel (n=207)</b> | <b>DOVONEX® scalp solution (n=105)</b> |
|---|---------------------------|--|
| week 4  | 55.1%                     | 18.1% <sup>†</sup>                     |
| week 8  | 68.6%                     | 31.4% <sup>†</sup>                     |

<sup>†</sup> statistically significantly less effective than XAMIOL gel (p<0.001)

### **Special Studies**

A randomised, double-blind, study of 873 patients with scalp psoriasis of at least moderate severity (according to the IGA), investigated the use of XAMIOL gel compared with calcipotriol in the gel vehicle. Both treatments were applied once daily, intermittently as required, for up to 52 weeks. The average amount of study drug used was 10.6 g/week. Adverse events possibly related to prolonged use of corticosteroids on the scalp, were identified by an independent, blinded panel of dermatologists. There was no difference between the treatment groups (2.6% in the XAMIOL group and 3.0% in the calcipotriol group; p<0.73) in the percentages of patients experiencing such adverse events. No cases of skin atrophy (based on a dermatologist's visual assessment) were reported.

Effects on adrenal function and calcium metabolism were investigated in an open-label study in 35 patients with extensive psoriasis on both scalp (at least 30% of scalp area) and body (15-30% of body surface area). Patients used an average of 23.7 g/week XAMIOL gel on the scalp and an average of 40.2 g/week DOVOBET ointment on the body. Adrenal response to ACTH was determined by measuring serum cortisol levels 30 and 60 minutes after ACTH challenge. A borderline decrease in cortisol response at 30 minutes post ACTH challenge was seen in 5 of the 32 evaluable patients (15.6%) after 4 weeks of treatment and in 2 of 11 patients (18.2%) who continued treatment until 8 weeks. In all cases, the serum cortisol levels were normal at 60 minutes post ACTH challenge. There was no evidence of a change in calcium metabolism observed in these patients.

## SUMMARY OF CLINICAL TRIALS

| STUDY CODE   | STUDY TYPE / DURATION  | STUDY DESIGN   | DOSAGE / ROUTE  | TREATMENT / PATIENT NO.   | RESULTS  |
|--------------|--|--|---|---|--|
| MBL 0405 INT | Efficacy, safety study in patients with scalp psoriasis<br><br>8 weeks | Multi-centre, randomised, double-blind, active- and vehicle-controlled, parallel group study<br><br><u>Primary endpoint:</u> % of patients with controlled disease at week 8 | 1. Xamiol® gel (50 mcg/g calcipotriol, as monohydrate + 0.5 mg/g betamethasone, as dipropionate)<br>2. Betamethasone in the gel vehicle (0.5 mg/g, as dipropionate)<br>3. Calcipotriol in the gel vehicle (50 mcg/g)<br>4. Gel vehicle<br><br>Once daily; topical | Xamiol®, n=541;<br>Betamethasone, n=556;<br>Calcipotriol, n=272;<br>Gel vehicle, n=136<br><br>Total 1505 randomized | Xamiol® gel (71.2%) was statistically significantly more effective than betamethasone in the gel vehicle (64.0%, p=0.011), calcipotriol in the gel vehicle (36.8%, p<0.001) and the gel vehicle (22.8%, p<0.001) at achieving controlled disease at wk 8.<br><br>AEs for Xamiol® gel and betamethasone in the gel vehicle were similar and favourable (34.5% vs. 34.9%, respectively) compared with calcipotriol in the gel vehicle (46.2%) and the gel vehicle (40%).<br><br>Lesional/perilesional AEs occurred in: 4.7% Xamiol® gel, 5.3% betamethasone in the gel vehicle versus 13.2% calcipotriol in the gel vehicle and 13.3% the gel vehicle.<br><br>Xamiol® gel was more effective in treating scalp psoriasis and the incidence of lesional/perilesional AEs was low. |
| MBL 0406 INT | Efficacy, safety study in patients with scalp psoriasis<br><br>8 weeks | Multi-centre, randomised, double-blind, active-controlled, parallel group study<br><br><u>Primary endpoint:</u> % of patients with controlled disease at week 8              | 1. Xamiol® gel<br>2. Betamethasone in the gel vehicle (0.5 mg/g, as dipropionate)<br>3. Calcipotriol in the gel vehicle (50 mcg/g)<br><br>Once daily; topical   | Xamiol®, n=568;<br>Betamethasone, n=563;<br>Calcipotriol, n=286<br><br>Total 1417 randomized                        | Xamiol® gel (68.4%) was statistically significantly more effective than betamethasone in the gel vehicle (61.0%, p=0.008) and calcipotriol in the gel vehicle (43.4%, p<0.001) at achieving controlled disease at wk 8.<br><br>AEs for Xamiol® gel and betamethasone in the gel vehicle were similar and favourable (38.7% vs. 41.0%, respectively) compared with calcipotriol in the gel vehicle (46.1%).<br><br>Lesional/perilesional AEs occurred in: 6.2% Xamiol® gel and 5.8% betamethasone in the gel vehicle versus 12.8% calcipotriol in the gel vehicle.<br><br>Xamiol® gel was more effective in treating scalp psoriasis and the incidence of lesional/perilesional AEs was low.  |

SUMMARY OF CLINICAL TRIALS (*continued*)

| STUDY CODE   | STUDY TYPE / DURATION  | STUDY DESIGN   | DOSAGE / ROUTE   | TREATMENT / PATIENT NO.   | RESULTS   |
|--------------|--|--|--|---|---|
| MBL 0503 INT | <p>Efficacy, safety, relapse and rebound study in patients with scalp psoriasis</p> <p>8 weeks treatment + 8 weeks observation period (treatment-free)</p> | <p>Multi-centre, randomised, investigator-blinded, active-controlled, parallel group study</p> <p><u>Primary endpoint:</u> % of patients with controlled disease at week 8</p> | <p>1. Xamiol® gel (50 mcg/g calcipotriol, as monohydrate + 0.5 mg/g betamethasone, as dipropionate)</p> <p>2. Dovonex® scalp solution (50 mcg/g calcipotriol)</p> <p>Once daily; topical</p> | <p>Xamiol®, n=207;<br/>Dovonex® scalp solution, n=105</p> <p>Total 312 randomized</p> | <p>Xamiol® gel (68.6%) was statistically significantly more effective than Dovonex® scalp solution (31.4%, <math>p&lt;0.001</math>) at achieving controlled disease at wk 8. QoL measures favoured Xamiol® gel.</p> <p>Frequency of AEs in the Xamiol® gel group (34.5%) were significantly lower (<math>p&lt;0.001</math>) than in the Dovonex® scalp solution group (56.7%).</p> <p>Lesional/perilesional AEs in the Xamiol® gel group (3.4%) were significantly lower (<math>p&lt;0.001</math>) than in the Dovonex® scalp solution group (19.2%).</p> <p>Xamiol® gel was more effective than Dovonex® scalp solution in treating scalp psoriasis.</p> |

## DETAILED PHARMACOLOGY

### Preclinical Pharmacology

**Animal Pharmacodynamic Studies with Calcipotriol:** The pharmacodynamic studies performed with calcipotriol have been aimed at establishing the activity of the compound as a regulator of cell differentiation and proliferation in cells possessing the receptor for the active form of vitamin 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>. The active form of vitamin D<sub>3</sub>, 1,25(OH)<sub>2</sub>D<sub>3</sub>, had potent effects on calcium metabolism and overdose resulted in hypercalcemia and hypercalciuria.

From studies performed in rats, it was shown that the effect of calcipotriol on calcium metabolism was at least 100 to 200 times lower than that of  $1,25(\text{OH})_2\text{D}_3$ . This low activity on calcium metabolism might be an intrinsic property of the calcipotriol molecule. However, the pharmacokinetic studies performed with calcipotriol suggested that the low activity on calcium metabolism was associated with a rapid metabolic degradation of the active compound.

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

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

*In vitro:* Two main metabolites of calcipotriol were observed in incubations of calcipotriol with rat liver homogenate supernatants. The two metabolites, MC1046 and MC1080, were isolated, identified and synthesized. Both metabolites were also present in supernatants from minipig, rabbit and human liver homogenates and in plasma samples from rats and minipigs. Although the necessity of using very high dosages of calcipotriol precludes the study of calcipotriol metabolism in humans, the present evidence strongly suggests that calcipotriol metabolism is qualitatively similar in rats, minipigs, rabbits and humans. In addition, both metabolites had lost most of the biological activity associated with calcipotriol thus constituting a deactivation pathway for the drug.

**Animal Pharmacokinetic Studies with Calcipotriol and Betamethasone:** Studies were conducted in rats and minipigs to determine the extent of absorption and excretion of [<sup>3</sup>H]-calcipotriol plus betamethasone and [<sup>3</sup>H]-betamethasone plus calcipotriol after single dermal administration of the drug combination in gel and ointment formulations. In minipigs, absorption of calcipotriol and betamethasone dipropionate from the gel and ointment formulations was similar. In the rat, calcipotriol from the gel was significantly less absorbed than calcipotriol from the ointment. The main route of excretion for the gel and ointment was via the faeces for both calcipotriol and betamethasone.

**IN VIVO PHARMACOKINETIC STUDIES WITH CALCIPOTRIOL AND BETAMETHASONE**

| TYPE OF STUDY                                    | STUDY DESIGN  | MAJOR RESULTS   |
|--|---|---|
| Absorption and Excretion study in albino SD rats | <p>Single dose of calcipotriol and betamethasone in a gel formulation compared an ointment formulation</p> <p>6M, 6F rats per dose group (fed)<br/>Dermal application to 10cm<sup>2</sup> patch on the back</p> <p>1) [<sup>3</sup>H]-calcipotriol (50 µg/g) + betamethasone (500 µg/g)<br/>2) Calcipotriol (50 µg/g) + [<sup>3</sup>H]-betamethasone (500 µg/g)<br/>Sampling at 0, 6, 24, 48, 72, 96, 120, 144, 168 h</p> <p>Cumulative excretion of total (% of dose applied) radioactivity in urine, faeces, liver, serum, whole blood, dosed skin, carcass, cage wash</p>         | <p>1) <i>Transdermal absorption of calcipotriol</i>: gel 10% (M9.0%, F11.6%), ointment 19% ( male 15.8%, female 21.3%)<br/>Highest level found in faeces (gel, ointment), dosed skin (gel, ointment), and carcass (gel, ointment)</p> <p>2) <i>Transdermal absorption of betamethasone</i>: gel 8% (M8.1%, F7.7%), ointment 9% (M9.3%, F8.9%)<br/>Highest level found in faeces (gel, ointment) and urine (gel, ointment)</p> <p>Absorption of betamethasone from the gel and ointment was similar. However, absorption of calcipotriol from the gel was significantly less than from the ointment. The main route of excretion was via the faeces for both calcipotriol and betamethasone.</p> |
| Absorption and Excretion study in minipigs       | <p>Single dose of calcipotriol and betamethasone in a gel formulation compared to an ointment formulation</p> <p>4F minipigs per dose group (fasted)<br/>Dermal application to 2x150cm<sup>2</sup> patch on the upper flanks</p> <p>1) [<sup>3</sup>H]-calcipotriol (50 µg/g) + betamethasone (500 µg/g)<br/>2) Calcipotriol (50 µg/g) + [<sup>3</sup>H]-betamethasone (500 µg/g)<br/>Sampling at 0, 6, 24, 48, 72, 96, 120, 144, 168 h</p> <p>Cumulative excretion of total (% of dose applied) radioactivity in urine, faeces, liver, serum, whole blood, dosed skin, cage wash</p> | <p>1) <i>Transdermal absorption of calcipotriol</i>: gel 2.4%, ointment 3.5%<br/>Highest level found in cage wash (gel) and faeces (ointment)</p> <p>2) <i>Transdermal absorption of betamethasone</i>: gel 2.6%, ointment 3.5%<br/>Highest level found in faeces (gel, ointment) and cage wash (ointment)</p> <p>Absorption of calcipotriol and betamethasone from Xamiol® gel and Dovobet® ointment was similar. The main route of excretion was via the faeces for both calcipotriol and betamethasone.</p>  |

### **Clinical Pharmacology**

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

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

## **TOXICOLOGY**

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

### **Acute and Long-term Toxicity**

*Calcipotriol:* Despite the intended topical use of calcipotriol in the treatment of psoriasis, most of the toxicological studies were performed using the oral route of administration. This was done to assure maximum exposure to the compound. From these studies it was evident that toxicity associated with the administration of pharmacologically excessive doses of calcipotriol was due to the calcitropic activity of the compound. The maximum doses were 54 mcg/kg/day in rats, 18 mcg/kg/day in minipigs and 3.6 mcg/kg/day in dogs. In the acute, subacute and

chronic toxicity studies the main signs of toxicity were loss of bodyweight, increases in plasma or serum calcium, creatinine and urea, renal toxicity and soft tissue calcifications. These changes resulted from the exaggerated absorption of calcium and phosphorous from the intestine and are characteristic of vitamin D overdose. The kidney was the main target organ of toxicity and tubular lesions and calcifications were apparent after prolonged hypercalcemia in all species investigated. These types of changes, however, are not considered indicative of a human risk, since less than 1% of calcipotriol is absorbed through the skin in man and there is no evidence of calcitropic effects in man with the prescribed dose.

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

### **Local Tolerance**

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

***Calcipotriol and Betamethasone Dipropionate:*** Two dermal tolerability studies with calcipotriol and betamethasone ointment were conducted in rabbits. In the first study, no skin irritation was observed and only slight irritation attributed primarily to calcipotriol was observed in the second study. A gradual reduction in skin thickness was observed over 6 weeks which was attributed to betamethasone. However, the stratum corneum of rabbit skin is much thinner than that of humans and rabbits are very sensitive to skin irritants. Similar results were obtained for two dermal tolerability studies in rabbits using a gel formulation of calcipotriol and

betamethasone. In addition, an eye irritation study was conducted in rabbits using a single ocular application (approx. 100 mg) of calcipotriol and betamethasone gel. There was a temporary pink discolouration of the orbital ring and ptosis observed which cleared within 6 hrs.

### **Reproduction and Mutagenicity**

**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.

**Betamethasone:** Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations). In reproduction studies with long-term oral administration of corticosteroids to rats, prolonged gestation and prolonged and difficult labour were detected. Moreover, reduction in offspring survival, body weight and body weight gain was observed. There was no impairment of fertility.

### **Carcinogenicity**

**Calcipotriol:** A dermal carcinogenicity study in mice showed no indications of increased carcinogenic risks. Calcipotriol solution was applied topically for up to 24 months at doses of 3, 10 and 30 mcg/kg/day (corresponding to 9, 30 and 90 mcg/m<sup>2</sup>/day). The high-dose was considered to be the Maximum Tolerated Dose for dermal treatment of mice with calcipotriol. Survival was decreased at 10 and 30 mcg/kg/day; particularly in the males. The reduced survival was associated with an increased incidence of obstructive uropathy, most probably caused by treatment-related changes in the urinary composition. This is an expectable effect of treatment with high doses of calcipotriol or other vitamin D analogues. There were no dermal effects and no dermal or systemic carcinogenicity.

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

**Photo(co)carcinogenicity**

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

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

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

## LONG-TERM TOXICITY OF CALCIPOTRIOL AND BETAMETHASONE DIPROPIONATE

| STUDY TYPE         | ANIMAL / STRAIN                         | DOSE / ROUTE / DURATION  | IMPORTANT FINDINGS   |
|--------------------|---|--|--|
| Repeat-dose        | Minipigs (Göttingen)<br>3M/3F per group | Calcipotriol/betamethasone ointment: 0, 2/20, 10/100, 50/500 mcg/g<br><br>Once daily topical application for 4 weeks   | Dose-dependent irritant effect on the skin at 50/500 mcg/g with no signs of systemic toxicity. NOAEL: 10/100 mcg/g calcipotriol/betamethasone<br>Very slight erythema in the 10/100 mcg/g group; slight to moderate erythema in the 50/500 mcg/g group.  |
| Repeat-dose        | Minipigs (Göttingen)<br>5M/5F per group | Calcipotriol/betamethasone ointment: 0, 2/20, 10/100, 50/500 mcg/g<br><br>Once daily topical application for 9 months  | Moderate to severe persistent erythema in the 10/100 and 50/500 mcg/g groups, respectively. Tendency towards treatment-related elevated urinary Ca and PO <sub>4</sub> (calcipotriol effect) and decreased adrenal organ weight and dermal atrophy (betamethasone effect). NOAEL: 2/20 mcg/g calcipotriol/betamethasone  |
| Dose-range finding | Mice (albino hairless)<br>10F per group | 1) Untreated<br>2) Calcipotriol solution: 0, 3, 10, 30 mcg/mL<br>3) Calcipotriol and betamethasone gel: 0/0, 3/30, 10/100 mcg/g<br><br>Once daily dermal application for 4 weeks | Skin reactions (30 mcg/mL and 30/300 mcg/g) including erythema, oedema, flaking, wrinkling and thickening and body weight losses (30/300 mcg/g) that resulted in termination of these groups after 6 d of administration.<br><br>Dose-dependent skin thinning and reduction in body weight in the calcipotriol and betamethasone gel formulation groups. Clinical findings (supported by histopathological evaluation) of dose-dependent skin inflammation for both formulations, including modification of the calcipotriol effects by the addition of betamethasone. |

## OTHER TOXICITY OF CALCIPOTRIOL AND BETAMETHASONE DIPROPIONATE

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

### LOCAL TOLERANCE OF CALCIPOTRIOL AND BETAMETHASONE DIPROPIONATE

| STUDY TYPE                          | ANIMAL                      | DOSE / ROUTE/ DURATION   | IMPORTANT FINDINGS  |
|-------------------------------------|-----------------------------|--|---|
| Dermal tolerability                 | Rabbit (n=6)                | Once daily application of 100 mg calcipotriol and betamethasone dipropionate ointment (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 calcipotriol and betamethasone dipropionate ointment (Dovobet®), calcipotriol (50 mcg/g), betamethasone (as dipropionate) (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.  |
| Dermal tolerability (non-occlusive) | Rabbit (NZW) (6M per group) | Once daily topical application of 100 mg of calcipotriol and betamethasone dipropionate gel (Xamiol®) and gel vehicle for 3 weeks  | Mild to moderate skin irritation. Mean score for erythema (max=4) on day 18 was gel vehicle 1.0 and Xamiol® gel 0.67. Irritation was ascribed to the vehicle. Xamiol® gel treated rabbits showed decreased weight gain and smaller adrenal glands.  |
| Dermal tolerability (non-occlusive) | Rabbit (NZW) (6M per group) | Once daily topical application of 100 mg of calcipotriol and betamethasone dipropionate gel (Xamiol®) and gel vehicle for 4 weeks  | Mild to moderate skin irritation. Mean score for erythema (max=4) on day 28 was gel vehicle 1.0 and Xamiol® gel 1.5. Irritation was ascribed to one or both active components and the vehicle. Treated and untreated areas showed a marked decrease in skin fold thickness (betamethasone effect). A temporary weight loss due to betamethasone was seen in the first 2 weeks of the study. |
| Eye irritation                      | Rabbit (NZW) (5M)           | Single ocular application of 2 drops (approx. 100 mg) of calcipotriol and betamethasone dipropionate gel (Xamiol®)   | The mean score of ocular lesions (max) based on 24, 48 and 72 hr assessments: cornea opacity 0 (4); iris lesion 0(2); conjunctiva erythema 0(3); conjunctivae chemosis 0(4). The only effects observed were ptosis and slight pink discoloration of the orbital ring at 1 hr after treatment but these effects disappeared within 6 hrs.  |

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LEO®

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

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

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

Xamiol® is used topically for up to 4 weeks to treat scalp psoriasis.

**What it does:**

Xamiol® contains calcipotriol (a vitamin D-like substance) and betamethasone (a steroid).

Psoriasis lesions are areas of inflamed skin where skin cells are producing too quickly. This creates red, scaly, thick patches (plaques) of skin.

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

**When it should not be used:****Do not use Xamiol® if you:**

- are allergic to any of the ingredients or the container (polyethylene) of Xamiol®
- have problems with high calcium levels in your body
- have skin infections caused by viruses (e.g. cold sores, chicken pox), a fungus (e.g. athlete's foot, ringworm), bacteria, parasites (e.g. scabies)
- have tuberculosis or syphilis
- have perioral dermatitis (red mouth rash), ichthyosis (dry, scaly skin), acne (pimples), rosacea (flushed facial skin), ulcers or broken skin
- have thin skin, easily damaged veins, stretch marks
- have other types of psoriasis
- have severe liver disease
- have severe kidney disease

Xamiol is not for use in the eyes.

**What the medicinal ingredients are:**

Each gram of gel contains 50 mcg calcipotriol (as monohydrate) and 0.5 mg betamethasone (as dipropionate)

**What the important nonmedicinal ingredients are:**

Paraffin liquid, hydrogenated castor oil, polyoxypropylene-15-stearyl ether,  $\alpha$ -tocopherol and butylhydroxytoluene.

**What dosage forms it comes in:**

Xamiol® is an almost clear, colourless to slightly off-white gel. Available in 60 g bottles.

**WARNINGS AND PRECAUTIONS**

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

- have diabetes
- have skin infections
- use other medicines that contain steroids
- are pregnant or planning to get pregnant
- are breast feeding

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

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

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

Do not use Xamiol® on your face or on broken skin. Do not cover your scalp with a shower cap, bandages or dressings after applying Xamiol®.

Do not use more than 100 g per week in total of all products containing calcipotriol.

**INTERACTIONS WITH THIS MEDICATION**

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

**PROPER USE OF THIS MEDICATION**

Always use Xamiol® exactly as your doctor has told you.

**Usual dose:**

Apply once a day to the affected area of the scalp for up to 4 weeks. Do not use more than 15 g per day in total of all products containing calcipotriol or 100 g per week.

**Using the gel:**

For convenience apply Xamiol® before bed and wash out the next morning.

- Use only on areas of your scalp affected by psoriasis and not on skin that does not have psoriasis
- You don't need to wash your hair before applying Xamiol®
- Comb your hair first to remove any loose scales.
- SHAKE the bottle before use and remove the cap

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- Part your hair to see the lesions. Apply Xamiol® to the affected scalp area and rub in gently with your fingertips
- Tilt your head to make sure Xamiol® does not run onto your face or in your eyes.



- Wash your hands well after using Xamiol®
- If you accidentally get Xamiol® on your face wipe it off immediately
- Do not bandage, cover or wrap the treated scalp area.
- For best results, Xamiol® should remain on the scalp. Do not wash your hair immediately after applying Xamiol®.
- Xamiol® should not be applied in the 12 hrs before or after any chemical hair treatments (e.g. dyes, perms). Ask your doctor about using hair treatments with scalp psoriasis.
- After applying Xamiol®, keep your hair away from fabrics that are easily stained by grease.

**Overdose:**

If you have used more Xamiol® than you should, contact your doctor or poison control centre immediately.

**Missed Dose:**

If you forget to use Xamiol® use it as soon as you remember, then go on as before. Do not use more than once per day.

**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 |
|---|-------------------------------------|---|
| Uncommon: Worsening of psoriasis (red, scaly, thick patches of skin)  | ✓                                   |   |
| Rare: Pustular psoriasis (red area with yellowish pustules, headache, fever, chills, arthralgia, malaise, anorexia, nausea)                 |                                     | ✓   |
| Rare: Adrenal affects (weakness, increased urination/thirst, fatigue, weight loss), cataracts, infections                                   | ✓                                   |   |
| Very Rare: Allergic reaction (rash, itching, swelling, trouble breathing, dizziness)  |                                     | ✓   |
| Very Rare: High blood calcium (fatigue, depression, mental confusion, anorexia, nausea, vomiting, constipation, increased urination/thirst) |                                     | ✓   |

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

**HOW TO STORE IT**

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

- Keep Xamiol® out of the reach and sight of children
- Use the medicine within 3 months of first opening the bottle
- Do not use Xamiol® after the expiry date on the label (EXP)

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

The most common side effect with use of Xamiol® is itching.

Other uncommon effects reported for Xamiol® include: burning sensation of the skin, skin pain or irritation, inflammation of hair root, rash (with or without pustules), eye irritation, redness, acne, dry skin, facial swelling and outer ear infection.

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

**REPORTING SUSPECTED SIDE EFFECTS**

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

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

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

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

**MORE INFORMATION**

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

This leaflet is available on-line at [www.xamiol.ca](http://www.xamiol.ca).

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