160 mm

IIE014-03 - 160 x 400 mm

## Calcipotriol Betamethasone

# Xamiol® Topical Gel 50 mcg/500 mcg per gram

ANTI-PSORIASIS

**Product Description**
Gel.
Almost clear, colourless to slightly off-white gel.

**Formulation**
Each g of gel contains:
Calcipotriol (as Monohydrate), Ph. Eur.....50mcg
Betamethasone (as Dipropionate), Ph. Eur.....500mcg

**Pharmacodynamic properties**
Calcipotriol is a vitamin D analogue. In vitro data suggest that calcipotriol induces differentiation and suppresses proliferation of keratinocytes. This is the proposed basis for its effect in psoriasis.
Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties, however, without curing the underlying condition. Through occlusion the effect can be enhanced due to increased
penetration of the stratum corneum. The incidence of adverse events will increase because of this. In general, the mechanism of the anti-inflammatory activity of the topical
steroids is unclear.

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 Daivobet® 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. With regard to HPA suppression, therefore, this study shows some evidence that very high doses of Xamiol® Gel and Daivobet Ointment may have a weak effect on the HPA axis.

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 2,900 patients with scalp psoriasis of at least mild severity according to the investigator more than 2,900 patients with scalp psoriasis of a 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® Gel was statistically significantly more effective than the comparators. Results for speed of onset based on similar data at week 2 also showed Xamiol® Gel to be statistically significantly more effective than the comparators.

| % of patients with absent or very mild disease | Xamiol® Gel (n=1,108) | Betame-thasone dipropionate (n=1,118) | Calcipotriol (n=558) | Gel vehicle (n=136) |
|---|---|---|---|---|
| week 2 | 53.2% | 42.8%[1] | 17.2%[1] | 11.8%[1] |
| week 8 | 69.8% | 62.5%[1] | 40.1%[1] | 22.8%[1] |

[1] Statistically significantly less effective than Xamiol® Gel (P<0.001)

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 Daivonex® 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® Gel was statistically significantly more effective than Daivonex® Scalp solution.

| % of patients with absent or very mild disease | Xamiol® Gel (n=207) | Daivonex® Scalp solution (n=105) |
|---|---|---|
| week 8 | 68.6% | 31.4%[1] |

[1] Statistically significantly less effective than Xamiol® Gel (P<0.001)

A randomised, double-blind long-term clinical study including 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. Adverse events possibly related to long-term use of corticosteroids on the scalp, were identified by an independent, blinded panel of dermatologists. There was no difference in the percentages of patients experiencing such adverse events between the treatment groups (2.6 % in the Xamiol® Gel group and 3.0 % in the calcipotriol group; P=0.73). No cases of skin atrophy were reported.

Paediatric population
Effects on calcium metabolism were investigated in two uncontrolled open 8-week studies including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Xamiol® Gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations, and reversible.

**Pharmacokinetic properties**
The systemic exposure to calcipotriol and betamethasone dipropionate from topically applied Xamiol® Gel is comparable to Daivobet® Ointment in rats and minipigs. Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Daivobet® Ointment formulation is less than 1% of the dose (2.5 g) when applied to normal skin (625 cm2) for 12 hours. Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids.
Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised. The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice). 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 both Xamiol® Gel and Daivobet® Ointment for extensive psoriasis involving the body and scalp. One metabolite of calcipotriol and one metabolite of betamethasone dipropionate were quantifiable in some of the patients.

**Indications**
Topical treatment of scalp psoriasis.

**Posology and method of administration**
Posology
Xamiol® Gel should be applied to affected areas of the scalp once daily. The recommended treatment period is 4 weeks. If it is necessary to continue or restart treatment after this period, treatment should be continued after medical review and under regular medical supervision.

When using calcipotriol containing products, the maximum daily dose should not exceed 15 g, and the maximum weekly dose should not exceed 100 g. The body surface area treated with calcipotriol containing medicinal products should not exceed 30%.

All the affected scalp areas may be treated with Xamiol® Gel. Usually an amount between 1 g and 4 g per day is sufficient for treatment of the scalp (4 g corresponds to one teaspoon).

Special populations
*Renal and hepatic impairment*
The safety and efficacy of Xamiol® Gel in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population
The safety and efficacy of Xamiol® Gel in children below 18 years have not been established. Currently available data in children aged 12 to 17 years are described in section Undesirable effects and Pharmacodynamic properties, but no recommendation on a posology can be made.

Method of administration
The bottle should be shaken before use and Xamiol® Gel applied to the affected area. Xamiol® Gel should not be applied directly to the face or eyes. The hands should be washed after use. In order to achieve optimal effect, it is not recommended to wash the hair immediately after application of Xamiol® Gel. Xamiol® Gel should remain on the scalp during the night or during the day.

**Contraindications**
Hypersensitivity to the active substances or to any of the excipients. Due to the content of calcipotriol, Xamiol® Gel is contraindicated in patients with known disorders of calcium metabolism. Due to the content of corticosteroid, Xamiol® Gel is contraindicated in the following conditions: Viral (e.g. herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis, perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers and wounds. Xamiol® Gel is contraindicated in, erythrodermic, exfoliative and pustular psoriasis.

**Special warning and precautions for use**
Effects on endocrine system
Adverse effects found in connection with systemic corticosteroid treatment, such as adrenocortical suppression or impact on the metabolic control of diabetes mellitus, may occur also during topical corticosteroid treatment due to systemic absorption.

Application under occlusive dressings should be avoided since it increases the systemic absorption of corticosteroids. Application on large areas of damaged skin or on mucous membranes or in skin folds should be avoided since it increases the systemic absorption of 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 Daivobet® Ointment (body application), 5 of 32 patients showed a borderline decrease in cortisol response to adrenocorticotropic hormone (ACTH) challenge after 4 weeks of treatment.

Effects on calcium metabolism
Due to the content of calcipotriol, hypercalcaemia may occur if the maximum weekly dose (100 g) is exceeded. Serum calcium is normalised when treatment is discontinued. The risk of hypercalcaemia is minimal when the recommendations relevant to calcipotriol are followed. Treatment of more than 30% of the body surface should be avoided.

Local adverse reactions:
Xamiol® Gel contains a potent group III steroid and concurrent treatment with other steroids on the scalp must be avoided. Skin of the face and genitals are very sensitive to corticosteroids. The medicinal product should not be used in these areas. The patient must be instructed in correct use of the product to avoid application and accidental transfer to the face, mouth and eyes. Hands must be washed after each application to avoid accidental transfer to these areas.

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

Discontinuation of treatment:
When treating psoriasis with topical corticosteroids, there may be a risk of generalised pustular psoriasis or of rebound effects when discontinuing treatment. Medical supervision should therefore continue in the post treatment period.

Long-term use:
With long-term use there is an increased risk of local and systemic corticosteroid undesirable effects. The treatment should be discontinued in case of undesirable effects related to long-term use of corticosteroid.

Unevaluated use:
There is no experience with the use of Xamiol® Gel in guttate psoriasis.

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**Mock-up Approval Stamp (MAS)**

1. PROOF FROM RBEDK
Date 24/11/2023

**New proof requested** ☐ Sign.: Date:

**Graphic Design** — According to: SOP_000647, SOP_000962, SOP_003993 and SOP_008676 ☐ 1st Sign.: Date: 2nd Sign.: Date:

**Editorial Proof** — According to: SOP_000647, SOP_000962 and SOP_008676 ☐ Sign.: Date:

**Second Approver**
- ☐ Product name
- ☐ Dosage form
- ☐ Strength/Stripes
- ☐ Pack size
- ☐ Prompts
- ☐ Material No./Reg. No.
- ☐ Barcode

Sign.: Date:

Concurrent treatment and UV exposure:
Daivobet® Ointment for body psoriasis lesions has been used in combination with Xamiol® Gel for scalp psoriasis lesions, but there is limited experience of combination of Xamiol® with other topical anti-psoriatic products at the same treatment area, other anti-psoriatic medicinal products administered systemically or with phototherapy.

During Xamiol® Gel treatment, physicians are recommended to advise patients to limit or avoid excessive exposure to either natural or artificial sunlight. Topical calcipotriol should be used with UVR only if the physician and patient consider that the potential benefits outweigh the potential risks.

Adverse reactions to excipients:
Xamiol® Gel contains butylated hydroxytoluene (E321) as an excipient, which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

**Interaction with other medicinal products and other forms of interaction**
No interaction studies have been performed.

**Fertility, Pregnancy and lactation**
Pregnancy:
There are no adequate data from the use of Xamiol® Gel in pregnant women. Studies in animals with glucocorticoids have shown reproductive toxicity, but a number of epidemiological studies (less than 300 pregnancy outcomes) have not revealed congenital anomalies among infants born to women treated with corticosteroids during pregnancy.
The potential risk for humans is uncertain. Therefore, during pregnancy, Xamiol® Gel should only be used when the potential benefit justifies the potential risk.

Lactation:
Betamethasone passes into breast milk, but risk of an adverse effect on the infant seems unlikely with therapeutic doses.
There are no data on the excretion of calcipotriol in breast milk.
Caution should be exercised when prescribing Xamiol® Gel to women who breast-feed.

Fertility:
Studies in rats with oral doses of calcipotriol or betamethasone dipropionate demonstrated no impairment of male and female fertility.

**Effects on the ability to drive and use machines**
Xamiol® Gel has no or negligible influence on the ability to drive and use machines.

**Adverse Drug Reaction**
The estimation of the frequency of adverse reactions is based on a pooled analysis of data from clinical studies including post-authorisation safety studies and spontaneous reporting.

The most frequently reported adverse reaction during treatment is pruritus.

Adverse reactions are listed by MedDRA SOC and the individual adverse reactions are listed starting with the most frequently reported. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

| | |
|---|---|
| **Infections and infestations** | |
| Uncommon ≥1/1,000 to <1/100 | Skin infection*<br>Folliculitis |
| **Immune system disorders** | |
| Rare ≥1/10,000 to <1/1,000 | Hypersensitivity |
| **Eye disorders** | |
| Uncommon ≥1/1,000 to <1/100 | Eye irritation |
| **Skin and subcutaneous tissue disorders** | |
| Common ≥1/100 to < 1/10 | Pruritus |
| Uncommon ≥1/1,000 to <1/100 | Exacerbation of psoriasis<br>Dermatitis<br>Erythema<br>Rash**<br>Acne<br>Skin burning sensation<br>Skin irritation |
| | Dry skin |
| Rare ≥1/10,000 to <1/1,000 | Skin striae<br>Skin exfoliation |
| **General disorders and administration site conditions** | |
| Uncommon ≥1/1,000 to <1/100 | Application site pain*** |
| Rare ≥1/10,000 to <1/1,000 | Rebound effect |

* Skin infections including bacterial, fungal and viral skin infections have been reported.

** Various types of rash reactions such as rash erythematous and rash pustular have been reported.

*** Application site burning is included in application site pain.

The following adverse reactions are considered to be related to the pharmacological classes of calcipotriol and betamethasone, respectively:
Calcipotriol:
Adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, psoriasis aggravated, photo-sensitivity and hypersensitivity reactions including very rare cases of angioedema and facial oedema.

Systemic effects after topical use may appear very rarely causing hypercalcaemia or hypercalciuria.
Betamethasone (as 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 with topical corticosteroids, there may be a risk of generalised pustular psoriasis.

Systemic reactions due to topical use of corticosteroids are rare in adults, however, they can be severe. Adrenocortical suppression, cataract, infections and increase of intra-ocular pressure can occur, especially after long-term treatment. Systemic effects occur more frequently when applied under occlusion (plastic, skin folds), when applied on large areas and during long-term treatment.

Paediatric population
No new adverse events and no new adverse reactions were seen in 109 adolescents aged 12-17 years with scalp psoriasis treated with Xamiol® Gel for 8 weeks. However, due to the size of the studies, no firm conclusion can be drawn as to the safety profile of Xamiol® Gel in adolescents compared to that in adults.

**Overdose and Treatment**
Use above the recommended dose may cause elevated serum calcium which subsides when treatment is discontinued.
The symptoms of hypercalcemia include polyuria, constipation, muscle weakness, confusion and coma.

Excessive prolonged use of topical corticosteroids may suppress the pituitary-adrenal functions, resulting in secondary adrenal insufficiency which is usually reversible. In such cases, symptomatic treatment is indicated.

In case of chronic toxicity, the corticosteroid treatment must be discontinued gradually.

It has been reported that due to misuse one patient with extensive erythrodermic psoriasis treated with 240 g of Daivobet® Ointment weekly (corresponding to a daily dose of approximately 34 g) for 5 months (maximum recommended dose 15 g daily) developed Cushing's syndrome and then pustular psoriasis after abruptly stopping treatment.

**Preclinical safety data**
Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations).
In reproduction toxicity 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.
The relevance for humans is unknown.

A dermal carcinogenicity study with calcipotriol in mice and an oral carcinogenicity study in rats revealed no special risk to humans.

Photo(co)carcinogenicity studies in mice suggest that calcipotriol may enhance the effect of UVR to induce skin tumours.

A dermal carcinogenicity study in mice and an oral carcinogenicity study in rats revealed no special hazardrisk of betamethasone dipropionate to humans.
No photocarcinogenicity study has been performed with betamethasone dipropionate.

In local tolerability studies in rabbits, Xamiol® Gel caused mild to moderate skin irritation and a slight transient irritation of the eye.

**Incompatibilities**
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

**Special precautions for storage**
Do not refrigerate. Keep the bottle in the outer carton in order to protect from light.
Store at temperatures not exceeding 30°C.
Can be used for 3 months after opening.

Keep out of reach of children.

**Dosage Form and Packaging Available**
Topical Gel
15g, 30g and 60g

**Caution:**
Foods, Drugs, and Cosmetics Act prohibits dispensing without prescription.

**ADR Statement**
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph and to the DKSH Market Expansion Services Philippines, Inc. Pharmacovigilance at pharmacovigilance.ph@dksh.com or hotline +63998-965-4158. The patient should seek medical attention immediately at the first sign of any adverse drug reaction.

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**Renewal of the Authorization**
19 December 2019

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