

# DUPISOR

Gel

## Composition

50 microgram/g Calcipotriol and 500 microgram/g betamethasone (as dipropionate).

## Action

Calcipotriol is a non-steroidal antipsoriatic agent, derived from vitamin D. Calcipotriol exhibits a vitamin D-like effect by competing for the 1,25(OH)<sub>2</sub>D<sub>3</sub> receptor. Calcipotriol is as potent as 1,25(OH)<sub>2</sub>D<sub>3</sub>, the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than 1,25(OH)<sub>2</sub>D<sub>3</sub> 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.

Betamethasone dipropionate is a potent topically-active corticosteroid producing prompt, marked and prolonged anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties, without curing the underlying condition. These effects can be enhanced under occlusive conditions due to increased penetration of stratum corneum (by approximately a factor of 10). The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.

## Pharmacokinetics

Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from 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.

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised. The main route of excretion of calcipotriol and betamethasone dipropionate is via faeces (rats, mice and minipigs).

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 gel and 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

- Dupisor gel is indicated for the topical treatment of scalp psoriasis.
- Dupisor gel is indicated for the topical treatment of mild to moderate “non scalp” plaque psoriasis vulgaris.

## Contraindications

- Hypersensitivity to the active substances or to any of the excipients.
- Patients with known disorders of calcium metabolism.
- Due to the corticosteroid content: viral lesions of the skin (eg herpes or varicella), fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis or syphilis, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, rosacea, ulceration and wounds, and perianal and genital pruritis.
- Guttate, erythrodermic, exfoliative and pustular psoriasis.
- Patients with severe renal insufficiency or severe hepatic disorders.
- NOT FOR OPHTHALMIC USE.

## Adverse Reactions

data from clinical trials show that the only common adverse drug reaction is pruritus. The uncommon adverse events are burning sensation of the skin, skin pain or irritation, folliculitis, dermatitis, erythema, acne, dry skin, exacerbation of psoriasis, rash, pustular rash and eye irritation. These adverse events were all non-serious local reactions.

Adverse events observed for Calcipotriol and betamethasone are provided below.

#### *Calcipotriol*

Potential adverse events include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, aggravation of psoriasis, photosensitivity, transient changes in skin pigmentation and allergic and hypersensitivity reactions including very rare cases of angioedema and facial oedema. After topical use, systemic effects, causing hypercalcaemia or hypercalciuria may appear very rarely.

#### *Betamethasone*

This product contains a potent corticosteroid.

Local reactions can occur after topical corticosteroid use, especially during prolonged application, including skin atrophy, telangiectasia, striae, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation and colloid milia. When used for the treatment of psoriasis, there may be the risk of generalized pustular psoriasis. There may be a risk of rebound when discontinuing long term treatment with corticosteroids.

Systemic effects due to topical corticosteroids are rare in adults, however, they can be severe. HPA suppression, hypercalcemia, cataract, infections, impact on the metabolic control of diabetes mellitus and increase in intra-ocular pressure can occur, especially after long term treatment. Systemic effects occur more frequently when applied under occlusion, when applied on large areas or during long treatment.

## **Warnings and Precautions**

FOR EXTERNAL USE ONLY

Treatment of more than 30% of the body surface should be avoided.

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 face, or accidentally to the eyes or conjunctives. 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.

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

The gel contains a potent WHO group III steroid and concurrent treatment with other steroids must be avoided. Adverse effects found in connection with systemic corticosteroid treatment, such as adrenocortical suppression or impact on the metabolic control of diabetes mellitus, may also occur 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. Skin of the face and genitals are very sensitive to corticosteroids. These areas should only be treated with weaker corticosteroids.

The gel should be applied to the affected areas of the scalp once daily for up to 4 weeks, and to other affected areas of the body for up to 8 weeks. After this period the gel may be used according to need under medical supervision. With long-term use there is an increased risk of local and systemic corticosteroid undesirable effects, including hypothalamic pituitary adrenal (HPA) axis suppression.

The treatment should be discontinued in case of undesirable effects related to long-term use of corticosteroid. There may be a risk of rebound when discontinuing long-term treatment with corticosteroids. Medical supervision should therefore continue in the post-treatment period.

There is no experience with concurrent use of other anti-psoriatic products administered systemically or with phototherapy.

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

Due to the content of calcipotriol, hypercalcemia may occur if the maximum weekly dose (100 g) is exceeded. Serum calcium is, however, quickly normalized when treatment is discontinued. The risk of hypercalcemia is minimal when the recommendations relevant to calcipotriol are followed.

The stability of calcipotriol in sunlight and UV light has not been demonstrated. No clinical trials have been conducted with calcipotriol-containing products where there is a particularly high potential to be exposed to high levels of UV radiation. In addition, the phototoxic effects of the gel have not been studied in psoriasis patients. Therefore, treated skin areas should be protected from sunlight and UV light (using physical covering and/or sunscreens), particularly where exposure may be considerable for reasons such as occupation.

### **Pregnancy**

There are no adequate data from the use of the gel in pregnant women. The gel should only be used during pregnancy when the potential benefit clearly outweighs the potential risk.

Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations). Long-term oral administration of corticosteroids in rats has been shown to prolong gestation and make labour more difficult and prolonged. A reduction in postnatal survival and growth was observed in the offspring of these rats. Studies of Calcipotriol in animals have shown an increase in the incidence of skeletal variations in rats (wavy ribs, extra ribs, incomplete development of skull bones) at oral doses of 18mg/kg/day and in rabbits (reduced skeletal ossification) at oral doses of 36mg/kg/day. The relevance of these findings for humans is unknown.

### **Impairment of Fertility**

Possible effects of betamethasone in combination with Calcipotriol on fertility have not been investigated in animals. Studies of the oral administration of Calcipotriol in rats have shown no impairment of fertility.

### **Nursing Mothers**

Betamethasone is excreted into breast milk. It is unknown if topical application of the gel could result in sufficient systemic absorption to produce significant quantities of this corticosteroid in human breast milk. There are no data on the excretion of Calcipotriol in breast milk.

Caution should be exercised when prescribing Dupisor Gel to breast-feeding women. Application of Dupisor gel to the breast area should be avoided. Dupisor gel should only be used during lactation if the potential benefits clearly outweigh the potential risks.

NOTE: In order to avoid possible direct ingestion by infants, Dupisor gel should not be applied to the chest area of breast feeding women. After applying Dupisor gel to her skin, mothers should wash their hands thoroughly prior to handling her infant child.

### **Use in Children**

Dupisor gel is not recommended for use in children and adolescents below 18 years of age as the safety and effectiveness of Dupisor gel in this population has not been established.

### **Renal Impairment**

Safety has not been established in patients with renal impairment. Is contraindicated in patients with severe renal impairment.

### **Hepatic Impairment**

Safety has not been established in patients with hepatic impairment. Is contraindicated in patients with severe hepatic impairment

### **Effects on Laboratory Tests**

There are no data available on the effects of Dupisor on laboratory tests.

### **Dosage and Administration**

Dupisor Gel is indicated FOR TOPICAL USE ONLY and NOT FOR OPHTHALMIC USE.

All psoriasis-affected areas treated with Dupisor should be, where possible, protected from direct sunlight and UV-light with items of clothing. Topical Calcipotriol should only be used with UV radiation if the physician and patient consider that the potential benefits outweigh the potential risks. The potential phototoxic effects of Dupisor over long term exposure have not been fully investigated.

#### **Adults:**

Dupisor gel should be applied to affected areas once daily. The recommended treatment period is for 4 weeks for scalp areas and 8 weeks for non-scalp areas. After this period, Dupisor gel may be used according to need under medical supervision. There is experience with intermittent courses of Dupisor gel up to 52 weeks.

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

In order to achieve optimal effect, it is recommended that the hair and affected areas of the skin are not washed immediately after application of Dupisor gel. Dupisor gel should remain on the affected area during the night or during the day.

*If used on the scalp:* All the affected scalp areas may be treated with Dupisor 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).

#### **Children:**

Dupisor gel is not recommended for use in children and adolescents below the age of 18 years.

### **Overdosage**

Use at more than the recommended dose 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.

Excessive prolonged use of topical corticosteroids may suppress the hypothalamic pituitary adrenal axis (HPA), resulting in secondary adrenal insufficiency, which is usually reversible. In such cases symptomatic treatment is indicated.

In case of chronic toxicity the topical corticosteroid treatment must be withdrawn gradually. It has been reported that due to misuse one patient with extensive erythrodermic psoriasis treated with 240 g of Dupisor gel per week (maximum recommended dose is 100 g per week) for 5 months developed Cushing's syndrome and after abruptly stopping treatment, developed pustular psoriasis.

### **Storage**

Store below 25°C. Do not refrigerate. Medicines should be kept out of the reach of children.

**Presentation**

Tube of 30 grams