DUPISOR

Ointment

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)2D3 receptor. Calcipotriol is as potent as 1,25(OH)2D3, the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than 1,25(OH)2D3 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 demonstrated less than 1% (95% CI: 0.1% to 0.3%) of Calcipotriol and betamethasone from the applied dose (2.5 g) was systemically absorbed when applied to normal skin (625 cm2) for 12 hours. When the skin is damaged absorption was increased (~24% of applied dose). Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids. Approximately 64% of the absorbed dose is protein bound. Plasma elimination half-life after intravenous administration is 5 to 6 hours. Elimination after dermal application is in order of days due to the formation of a depot in the skin.

Indications

Dupisor ointment is indicated for the once daily topical treatment of plaque-type psoriasis vulgaris amenable to topical therapy in adult patients 18 years and older.

Contraindications

- Allergic sensitization to any constituent of Dupisor ointment.
- 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 syphillis, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, ulceration, wounds, perianal and genital pruritus.
- Erythrodermic, exfoliative and pustular psoriasis.
- Patients with severe renal insufficiency or severe hepatic disorders.
- NOT FOR OPHTHALMIC USE.

Adverse Reactions

Data from clinical trials and post market use show that the common adverse events, in the order of most frequently reported, are pruritus, rash and burning sensation of the skin. Additional uncommon adverse events, in the order of most frequently reported include skin pain or irritation, dermatitis, erythema, exacerbation of psoriasis, folliculitis and application site pigmentation changes. Pustular psoriasis is a rare adverse effect.

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, and aggravation of psoriasis. 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 use, especially during prolonged application, including skin atrophy, telangiectasia, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation and colloid milia. When treating psoriasis there may be the risk of generalized pustular psoriasis. Systemic effects due to corticosteroids are rare, in adults; however, they can be severe. Adrenocortical suppression, hypercalcaemia, cataract, infections 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

The patient must be instructed on correct use of the product to avoid application and/or accidental transfer to the scalp, face, mouth or eyes. Dupisor ointment is not recommended for use on the face since it may give rise to itching and erythema of the facial skin. **Patients should be instructed to wash their hands after using Dupisor ointment to avoid inadvertent transfer of ointment to the face from other body areas.**

In view of the risk of hypercalcemia secondary to excessive absorption of Calcipotriol when there is extensive skin involvement, Dupisor ointment should not be used on more than 30% of the body surface area.

The risk of hypercalcemia is minimal when the recommendations relevant to Calcipotriol are observed. In adults, the maximum dosage of 100g ointment per week should not be exceeded.

Treatment with Dupisor ointment in adults in the recommended amounts up to 100 g per week does not generally result in changes in laboratory values. **Serum calcium and renal function should be monitored at 3 monthly intervals during periods of usage of topical Calcipotriol, including that in Dupisor ointment.** If the serum calcium level is elevated, treatment with Dupisor ointment should be discontinued and the condition should be treated appropriately. The levels of serum calcium should be measured once weekly until the serum calcium levels return to normal values.

As Dupisor ointment contains potent corticosteroid (classified as WHO group III steroid), concurrent treatment with other steroids should 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 occur also during topical corticosteroid treatment due to its systemic absorption.

Application of Dupisor ointment to large areas of damaged skin, under occlusive dressings, to mucous membranes, or in skin folds should be avoided as these conditions increase the systemic absorption of both corticosteroids and Calcipotriol. Elevated systemic absorption of Calcipotriol could, as previously mentioned, result in hypercalcemia in some patients.

If lesions become secondarily infected, they should be treated with antimicrobial therapy. However, if infection worsens, treatment with topical corticosteroids should be withdrawn.

When treating psoriasis with topical corticosteroids there may be a risk of generalized pustular psoriasis.

There is no experience of the use of Dupisor ointment on the scalp.

The stability of Calcipotriol in sunlight and UV light has not been demonstrated. No clinical trials have been conducted with Calcipotriol containing products in Australia, where there is a particularly high potential to be exposed to high levels of UV radiation. In addition, the phototoxic effects of Dupisor ointment have not been extensively studied in the clinic. Therefore, treated skin areas should be protected from sunlight and UV light (using physical coverings and/or sunscreens), particularly where exposure may be considerable for reasons such as occupation. Furthermore, topical Calcipotriol should only be used with UV radiation if the physician and patient consider that the potential benefits outweigh the potential risks.

Dupisor ointment has no or negligible influence on the ability to drive and to use machines.
With long-term use there is an increased risk of local and systemic corticosteroid adverse effects. The treatment should be discontinued in case of adverse effects related to long-term use of corticosteroids.

There may be a risk of rebound when discontinuing a long-term treatment with corticosteroids.

Pregnancy
There are no adequate data from the use of Dupisor ointment in pregnant women. Dupisor ointment 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 Dupisor ointment 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 ointment to breast-feeding women.
Application of Dupisor ointment to the breast area should be avoided. Dupisor ointment 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 ointment should not be applied to the chest area of breast feeding women. After applying Dupisor ointment to her skin, mothers should wash their hands thoroughly prior to handling her infant child.

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

Renal Impairment
Safety has not been established in patients with renal impairment.

Hepatic Impairment
Safety has not been established in patients with hepatic impairment.

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

Dosage and Administration
Dupisor ointment 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 ointment should be applied topically to the affected area once daily. The maximum daily dose should not exceed 15 grams.

The maximum recommended weekly dose of Dupisor ointment is 100 g/week.
The treated area should not be more than 30% of the body surface.

The recommended treatment period of Dupisor ointment is 4 weeks. At the completion of the treatment period, repeated treatment with Dupisor ointment can be initiated under medical supervision. There is no clinical experience with Dupisor Ointment beyond 52 weeks.

Children:
Dupisor ointment 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 ointment 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 30°C. Medicines should be kept out of the reach of children.

Presentation
Tube of 30 grams