

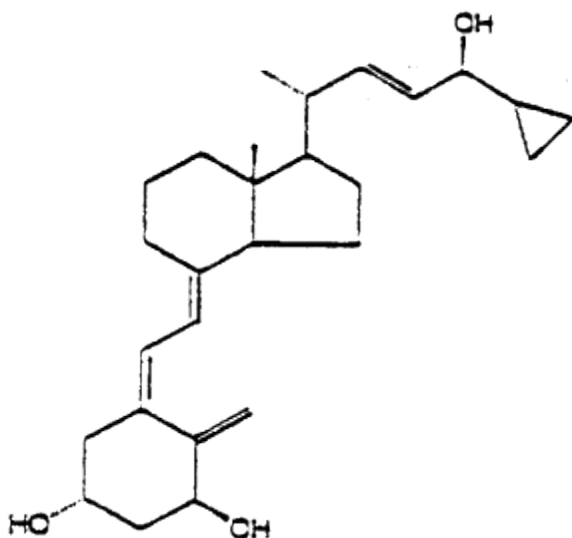
DATA SHEET

Daivonex[®] Cream

Calcipotriol 50 microgram/g Cream

Physical and Chemical Properties

Calcipotriol is a white or almost white crystalline substance. It is a vitamin D derivative and behaves in a similar manner to vitamin D, forming a reversible temperature-dependent equilibrium between calcipotriol and pre-calcipotriol.



Chemical structure of calcipotriol

Chemical name: (1S, 3R, 5Z, 7E, 22E, 24S) -24-Cyclopropyl-9, 10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol. CAS 112965-21-6

Daivonex[®] Cream contains the hydrated form of calcipotriol. It also contains macrogol cetostearyl ether, cetostearyl alcohol, quaternium-15, disodium edetate, sodium phosphate - dibasic dihydrate, glycerol, liquid paraffin, soft white paraffin and purified water.

Pharmacology

Calcipotriol is a non-steroidal antipsoriatic agent, derived from vitamin D. Calcipotriol exhibits a vitamin D-like effect by competing for the $1,25(\text{OH})_2\text{D}_3$ receptor. Calcipotriol is as potent as $1,25(\text{OH})_2\text{D}_3$, the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than $1,25(\text{OH})_2\text{D}_3$ in its effect on calcium metabolism. Calcipotriol induces differentiation and suppresses proliferation (without any evidence of a cytotoxic effect) of keratinocytes, thus reversing the abnormal keratinocyte changes in psoriasis. The

therapeutic goal envisaged with calcipotriol is thus a normalisation of epidermal growth.

Pharmacokinetics

Pharmacokinetic studies with ³H-calcipotriol have been performed in rats and minipigs. Oral absorption of calcipotriol was approximately 60% in rats and 40% in minipigs. The half-life of calcipotriol was 12 minutes in rats and 60 minutes in minipigs. The major metabolite of calcipotriol, MC1080, was present in the first plasma sample at 5 minutes; its half life was 54 minutes in rats and 1.8 hours in minipigs. Drug-related radioactivity was excreted in urine and faeces, and clearance was considered to be almost exclusively metabolic, as less than 5% of the administered radioactivity was excreted at the time of disappearance of all calcipotriol from plasma. Determination of the tissue distribution of calcipotriol was complicated by the appearance of ³H-H₂O from the metabolic degradation of ³H-calcipotriol. Autoradiography studies performed in rats, however, established that calcipotriol concentrations were highest in the liver, kidney and intestine. No drug-related radioactivity was present 24 hours after administration of ³H-calcipotriol.

Two main metabolites of calcipotriol, MC1046 and MC1080, were present in supernatants from minipigs, rabbit and human liver homogenates, and in plasma samples from rats and minipigs. Although the necessity of using very high dosages of calcipotriol precludes the study of calcipotriol metabolism in humans, the present evidence strongly suggests that calcipotriol metabolism is qualitatively similar in rats, minipigs, rabbits and humans.

Bioavailability studies of calcipotriol ointment in psoriatic and healthy patients demonstrated that approximately 2-10% of calcipotriol from the applied dose was systemically absorbed. Analogous data are not available for calcipotriol cream, but studies on cadaver skin appear to indicate that the cream is not as well absorbed as the ointment.

Clinical Trials

The clinical trial using calcipotriol cream was of eight weeks duration. Data on local or systemic effects of the cream under conditions of high ultraviolet exposure such as those existing in Australia are not available. A summary of the trial is presented in Table 1.

Table 1 - Summary of clinical trial using Calcipotriol Cream

	STUDY MC190
DESIGN	Multi-centre, randomised, double blind, parallel group, placebo controlled trial
TREATMENT	Calcipotriol 50mcg/g cream - 161 patients
	Placebo cream - 87 patients
REGIMEN & DURATION	Applied twice daily for 8 weeks

STUDY MC190	
MAIN RESPONSE CRITERION	Change in Psoriasis Area Severity Index (PASI) from baseline to end of treatment
RESULTS	PASI Score
	Baseline End Reduction
	Calcipotriol 7.9±5.1 3.8±4.0 4.2±4.9
	Placebo 9.2±6.5 8.3±7.7 0.8±5.8
	(p = 0.29)

Indications

Calcipotriol cream is indicated for the topical treatment of psoriasis vulgaris, including plaque psoriasis in adult patients.

Contra-Indications

- i. Allergic sensitisation to any constituent of calcipotriol cream.
- ii. Patients with known disorders of calcium metabolism.
- iii. NOT FOR OPHTHALMIC USE.

Precautions

In view of the risk of hypercalcaemia secondary to excessive absorption of calcipotriol when there is extensive skin involvement, calcipotriol cream should not be used for severe extensive psoriasis. The maximum dosage of 100 g cream per week should not be exceeded. When using a combination of cream and ointment the total maximum dose should not exceed 100 g per week.

Calcipotriol cream is not recommended for use in patients with generalised pustular psoriasis, guttate psoriasis and erythrodermic exfoliate psoriasis.

Calcipotriol cream 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 calcipotriol to avoid inadvertent transfer to the face from other body areas.** Should facial dermatitis develop in spite of these precautions, calcipotriol therapy should be discontinued.

Calcipotriol cream should be used cautiously in skin folds, where the natural occlusion may give rise to an increase of any irritant effect of calcipotriol. Occlusive dressings should not be used as they may increase absorption of calcipotriol.

Treatment with calcipotriol ointment in the recommended amounts up to 100 g per week for 1 year does not generally result in changes in laboratory values. Hypercalcaemia has been reported rarely at the recommended dose (i.e. up to 100g/week) of calcipotriol ointment when used for the approved indication. **Serum calcium and renal function should be monitored at 3 monthly intervals during periods of usage of topical calcipotriol.** If the serum calcium level is observed to be elevated, calcipotriol treatment 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.

Treatment with topical calcipotriol should be discontinued after satisfactory improvement has occurred and may be restarted if recurrence does occur after discontinuation.

The use of calcipotriol ointment for continuous treatment periods exceeding 1 year has not been studied.

There is no information about the possible effects of calcipotriol when used for long periods during exposure to sunlight and UVA/UVB light in patients. The stability of calcipotriol in sunlight and UV light has not been demonstrated. Treated areas should be protected from sunlight and UV light, 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.

Carcinogenicity and mutagenicity:

A dermal carcinogenicity study with calcipotriol 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 µg/kg/day (corresponding to 9, 30 and 90 µg/m²/day). The high-dose was considered to be the Maximum Tolerated Dose for dermal treatment of mice with calcipotriol. Survival was decreased at 10 and 30 µg/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 expected effect of treatment with high doses of calcipotriol or other vitamin D analogues. There were no dermal effects and no dermal or systemic carcinogenicity.

In a study where albino hairless mice were repeatedly exposed to both ultraviolet (UV) radiation and topically applied calcipotriol for 40 weeks at the same dose levels as in the dermal carcinogenicity study, a reduction in the time required for UV radiation to induce the formation of skin tumours was observed (statistically significant in males only), suggesting that calcipotriol may enhance the effect of UV radiation to induce skin tumours. The clinical relevance of these findings is unknown.

Calcipotriol was not genotoxic in assays for gene mutations (Ames test and mouse lymphoma TK locus assay) or chromosomal damage (human lymphocyte chromosomal aberration or mouse micronucleus test).

Use in Pregnancy (Category B1)

Safety for use in pregnancy has not been established. Studies 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 18 mg/kg/day and in rabbits (reduced skeletal ossification) at oral doses of 36 mg/kg/day. The significance of these findings for humans is not known. Therefore calcipotriol should not be used during pregnancy unless benefits clearly outweigh the risks.

Use in Lactation

It is not known whether calcipotriol is excreted in breast milk, therefore, the drug should be used during lactation only if the benefits clearly outweigh the risks.

Calcipotriol should not be applied to the chest area during breast feeding to avoid possible ingestion by infants.

Use in Children

Daivonex[®] cream should not be used in children.

Renal Impairment

Safety has not been established in patients with renal impairment.

Hepatic Impairment

Safety has not been established in patients with hepatic impairment.

Interactions with other drugs

There is no experience of concomitant therapy with other topical antipsoriatic drugs applied to the same skin area or with oral antipsoriatic drugs.

Calcipotriol should not be used concurrently with calcium or vitamin D supplements, or with drugs which enhance the systemic availability of calcium.

Adverse Reactions

The adverse events observed in clinical trials conducted for calcipotriol cream are summarized in Table 2.

TABLE 2 - Adverse events of Calcipotriol Cream.

NUMBER OF PATIENTS	368
ADVERSE REACTIONS (%)	31.8
Lesional/Perilesional Irritation (%)	13.9
Face and/or Scalp Irritation (%)	10.6

NUMBER OF PATIENTS	368
Other Skin Reactions (%)	4.9
Exacerbation of Psoriasis (%)	2.4
WITHDRAWAL FROM THERAPY*(%)	2.4

* calcipotriol therapy was stopped as a result of skin irritation

Photosensitivity reactions, skin discolouration, bullous eruption, skin exfoliation, contact dermatitis and allergic reactions have been reported with topical calcipotriol therapy.

Occasional hypercalcaemia has been reported, usually related to excessive (greater than 100 g/week) use.

Dosage and Administration

Calcipotriol is indicated FOR TOPICAL USE ONLY and NOT FOR OPHTHALMIC USE.

Adults

Calcipotriol cream should be applied topically to the affected area twice daily (i.e. in the morning and in the evening). Less frequent application may be indicated after the initial period of treatment. After satisfactory improvement has occurred, treatment should be discontinued. If recurrence takes place after discontinuation, the treatment may be reinstated. Experience is lacking in the use of calcipotriol ointment for periods longer than 1 year.

The maximum recommended weekly dose of calcipotriol cream is 100g/week. When using a combination of cream and ointment the total maximum dose should not exceed 100 g per week.

It should be noted that there are no long-term clinical studies assessing the safety of using calcipotriol during exposure to UV and/or sunlight. Therefore, all psoriasis-affected areas treated with calcipotriol should be, where possible, protected from direct sunlight and UV-light with items of clothing. Furthermore, topical calcipotriol should only be used with UV radiation if the physician and patient consider that the potential benefits outweigh the potential risks.

Children

Daivonex[®] cream should not be used in children, as there is inadequate experience with its use.

Symptoms and Treatment of Overdose

Hypercalcaemia has been reported rarely at the recommended dose (i.e. up to 100 g/week) of calcipotriol ointment when used for the approved indication. Excessive use, i.e. more than 100g/week, may cause elevated serum calcium, which rapidly subsides when treatment is discontinued; in such cases, the monitoring of serum calcium levels once weekly or more frequently as required by clinical circumstances until the serum calcium returns to normal levels is recommended.

Contact the Poisons Information Center on 0800 764 766 for further advice on overdose management.

Medicine Classification

Prescription Only Medicine

Presentation

Daivonex[®] cream contains 50 microgram calcipotriol per g in a smooth, white cream base. It is available in tubes of 15, 30 or 100 g.

STORAGE Store below 25°C.

Shelf life: Unopened container: 2 years

After first opening of container: 6 months

For ease of application, do not refrigerate.

PRODUCED BY

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DATE OF PREPARATION

20 December 2011

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