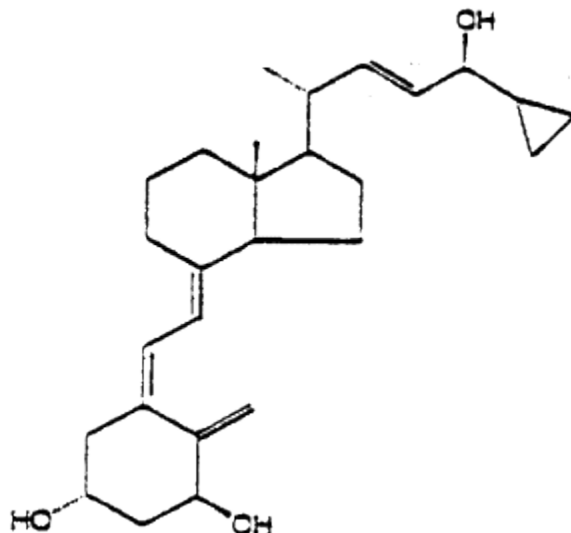


DATA SHEET

Daivonex[®] Ointment

Calcipotriol 50 microgram/g Ointment



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

Presentation

Calcipotriol is a white or almost white crystalline substance. It is freely soluble in ethanol, soluble in chloroform and propylene glycol, particularly insoluble in liquid paraffin. Solubility in water is 0.6 µg/mL and the melting point is 166 - 168°C. Calcipotriol 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.

DAIVONEX[®] Ointment contains the anhydrous form of calcipotriol. It also contains dl-α-tocopherol, disodium edetate, sodium phosphate - dibasic dihydrate, purified water, liquid paraffin, steareth-2, propylene glycol and soft white paraffin.

Uses

Actions

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 $1,25(\text{OH})_2\text{D}_3$ 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 - H_2O 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.

Clinical Trials

Clinical trials with DAIVONEX[®] Ointment undertaken in adults and children are summarised below.

Topical treatment of psoriasis in adults using twice daily calcipotriol 50 µg/g ointment regimen

Two double-blind, multicentre, randomised studies assessed the efficacy and safety of calcipotriol ointment 50 µg/g twice daily vs betamethasone 17-valerate ointment 0.1% twice daily in patients with psoriasis. The mean study duration was 6 weeks. The primary efficacy endpoint was the percentage reduction of the Psoriasis Area & Severity Index (PASI) score. The mean reduction in PASI score was statistically significant ($p < 0.001$) favouring calcipotriol in one study (MC 288); there was no significant difference between treatments in the second study (MC 188).

Table 1: Twice-daily administration of calcipotriol 50 µg/g ointment in adults

Study	MC 288	MC 188
Treatment administered:	Calcipotriol (n = 342) Betamethasone 17-valerate (n = 342)	Calcipotriol (n = 201) Betamethasone 17-valerate (n = 200)
Results: Percentage reduction in PASI (mean±sd or mean (95% CI))	Calcipotriol: 68.9±24 Betamethasone: 61.2±27.5 p<0.001	Calcipotriol: 57.7 (49.7, 59.3) Betamethasone: 51.7 (43.4, 54.2) p=n.s.

n.s. - not significant

Topical treatment of psoriasis in adults using once daily calcipotriol 50 µg/g regimen

Two double-blind, multicentre, randomised, vehicle-controlled studies of 8 weeks duration assessed the efficacy and safety of calcipotriol ointment 50 µg/g once daily. Efficacy was assessed using the Psoriasis Grading Scale to score erythema, scaling, plaque elevation and overall severity. The primary efficacy parameter was the plaque elevation subscore. There was a statistically significant difference (p<0.001) favouring calcipotriol.

Table 2: Once daily administration of calcipotriol 50 µg/g ointment in adults

(Intention to treat population)

Study		DE 127-007			DE 127-009		
Treatment administered:		Calcipotriol (n = 118) Vehicle (n = 116)			Calcipotriol (n = 99) Vehicle (n = 99)		
Results (mean±sd):		Baseline	End	p value	Baseline	End	p value
Plaque elevation subscore	Calcipotriol:	5.22±1.28	2.02±1.94	<0.001	5.05±1.12	2.00±1.41	<0.001
	Vehicle:	5.09±1.26	3.70±1.74		4.79±0.94	3.39±1.51	
Erythema subscore	Calcipotriol:	4.86±1.69	2.33±1.70	<0.001	4.75±1.37	2.51±1.25	<0.001
	Vehicle:	4.86±1.59	3.88±1.75		4.54±1.27	3.66±1.41	
Scaling subscore	Calcipotriol:	5.51±1.66	1.68±1.79	<0.001	4.96±1.47	1.68±1.14	<0.001
	Vehicle:	5.22±1.59	2.91±1.82		4.62±1.24	2.64±1.28	
Overall Severity subscore	Calcipotriol:	4.81±1.72	2.15±1.73	<0.001	4.60±1.43	2.12±1.36	<0.001
	Vehicle:	4.73±1.62	3.65±1.76		4.25±1.29	3.30±1.27	

Calcipotriol treatment of psoriasis with cyclosporin A in adults

One double-blind, randomised, multicentre, vehicle-controlled study assessed the efficacy and safety of calcipotriol ointment 50 µg/g twice daily with cyclosporin 2 mg/kg/day in patients with severe psoriasis for 6 weeks. Change in PASI score was the primary efficacy endpoint. There was a statistically significant difference ($p < 0.01$) favouring combination therapy.

Table 3.1: Administration of calcipotriol 50 µg/g ointment with cyclosporin A in adults

Treatment administered:	Calcipotriol + cyclosporin 2 mg/kg/day (n = 32)	Vehicle + cyclosporin 2 mg/kg/day (n = 34)
Results (mean±sd):		
Baseline PASI	25.25±5.90	25.40±4.16
End PASI	4.88±6.79	10.71±8.98
Change in PASI from baseline	20.37±8.55	14.64±8.58
	$p < 0.01$	

Calcipotriol treatment of psoriasis with acitretin in adults

One double-blind, multicentre, randomised, vehicle-controlled study assessed the efficacy and safety of calcipotriol ointment 50 µg/g twice daily with acitretin (20-70 mg/day) for 12 weeks in patients with severe/extensive psoriasis unresponsive to topical treatment alone. The percentage of patients achieving marked improvement or clearance at the end of treatment was the primary efficacy endpoint. There was a statistically significant difference ($p < 0.01$) favouring combination therapy.

Table 3.2: Administration of calcipotriol 50 µg/g ointment with acitretin in adults

(Intention to treat population)

Treatment administered:	Calcipotriol + acitretin 20-70 mg/day (n = 76)	Vehicle + acitretin 20-70 mg/day (n = 59)
Results:		
Patients with marked improvement or clearance	67.1%	40.7%
Baseline PASI (mean±sd)	17.8±8.9	17.4±8.6
End PASI (mean±sd)	4.6±5.4	8.6±8.4
	$p < 0.01$	

Topical treatment of psoriasis in children using twice daily calcipotriol 50 µg/g ointment

One double-blind, multicentre, randomised, vehicle-controlled study assessed the safety and efficacy of calcipotriol 50 µg/g ointment in children of 2 to 14 years with mild to moderate psoriasis not involving more than 30% of the body surface area. The study was of 8 weeks duration. The primary efficacy end point was the change in PASI score. Nine of the 77 children in the trial were under the age of 7 years; 22.2% of children below 7 years of age received calcipotriol. There was no statistically significant change observed over placebo.

Table 5: Administration of calcipotriol 50µg/g ointment in children

(Intention to treat population)

Treatment administered:	Calcipotriol (n = 43)	Vehicle (n = 34)
Results (mean±sd):		
Reduction in PASI from baseline to end		
<i>Baseline:</i>	6.70±5.80	6.33±3.51
<i>End:</i>	2.89±4.49	3.74±2.96
<i>Change:</i>	-3.47±5.82	-2.60±3.54
	p=n.s.	

Indications

DAIVONEX® ointment is indicated for the topical treatment of psoriasis vulgaris, including plaque psoriasis in adults and children (see Use in Children). In adult patients, DAIVONEX® ointment may also be used in combination with systemic acitretin or cyclosporin.

Dosage and Administration

DAIVONEX® ointment is indicated FOR TOPICAL USE ONLY and NOT FOR OPHTHALMIC USE.

Adults:

DAIVONEX® ointment therapy:

DAIVONEX® ointment should be applied topically to the affected area once or twice daily (i.e. in the morning and/or in the evening). Initially, twice daily application of the ointment is usually preferred. Application may then be reduced to once daily, provided individual clinical response is satisfactory. After satisfactory improvement

has occurred, treatment should be discontinued.

If recurrence develops after reduction in frequency of application or after discontinuation, the treatment may be reinstated at the initial dosage. Experience is lacking in the use of calcipotriol for periods longer than 1 year.

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

It should be noted that there are no long-term clinical studies assessing the safety of using DAIVONEX[®] ointment during exposure to 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.

Combination therapy:

Twice daily application of DAIVONEX[®] ointment in combination with systemic cyclosporin or acitretin has been shown to enhance the efficacy of cyclosporin or acitretin (see Clinical trials).

Children:

DAIVONEX[®] ointment therapy:

Children under 6 years:

There is limited experience of using DAIVONEX[®] ointment in this age group. A maximum safe dose has not been established.

Children aged 6 to 12 years:

DAIVONEX[®] ointment should be applied to the affected area twice daily. Maximum weekly dose should not exceed 50g.

Children over 12 years:

DAIVONEX[®] ointment should be applied to the affected area twice daily. Maximum weekly dose should not exceed 75g.

Combination therapy:

There is no experience of use of DAIVONEX[®] ointment in combination with other therapies for psoriasis in children.

DAIVONEX[®] ointment should not be used for more than 8 weeks in children.

Contraindications

- i. Allergic sensitisation to any constituent of DAIVONEX[®] ointment.
 - ii. Patients with known disorders of calcium metabolism.
 - iii. NOT FOR OPHTHALMIC USE.
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Warnings and Precautions

In view of the risk of hypercalcaemia secondary to excessive absorption of calcipotriol when there is extensive skin involvement, DAIVONEX[®] ointment should not be used for severe extensive psoriasis. In children under 6 years, the maximum safe dose has not been established; in children 6 to 12 years, the maximum weekly dose should not exceed 50g; and in children over 12 years, the maximum weekly dose should not exceed 75g. In adults, the maximum dosage of 100g ointment per week should not be exceeded. When using a combination of ointment and cream the total maximum dose should not exceed 100g per week.

DAIVONEX[®] ointment is not recommended for use in patients with generalised pustular psoriasis, guttate psoriasis and erythrodermic exfoliative psoriasis.

DAIVONEX[®] 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 DAIVONEX[®] ointment to avoid inadvertent transfer of ointment to the face from other body areas.** Should facial dermatitis develop in spite of these precautions, calcipotriol therapy should be discontinued.

DAIVONEX[®] ointment 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 DAIVONEX[®] ointment in adults in the recommended amounts up to 100g/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 DAIVONEX[®] 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, treatment with DAIVONEX[®] 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.

Treatment with DAIVONEX[®] ointment should be discontinued after satisfactory improvement has occurred and may be restarted if recurrence should develop after discontinuation.

The use of DAIVONEX[®] ointment for continuous treatment periods exceeding 1 year has not been studied.

The stability of calcipotriol in sunlight and UV light has not been demonstrated. No clinical trials have been conducted with calcipotriol in Australia, where there is a potential to be exposed to high levels of UV radiation. Therefore, 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.

The decision to administer DAIVONEX[®] ointment in combination with systemic or physical therapy requires careful consideration. Information on the dosages and risks associated with systemic or physical therapies can be found in the Product Information documents for the respective systemic therapies, or in standard texts, which should be consulted. Systemic or physical therapy poses serious risks of toxicity, and such therapy administered in combination with topical DAIVONEX[®] ointment should be reserved for those adults with refractory psoriasis who are considered suitable for systemic or physical therapy.

For combination therapy with either UVA or UVB there are no safety and efficacy data beyond 10 weeks.

Use in Children

There are no long term efficacy and safety data in children. DAIVONEX[®] ointment should not be used for more than 8 weeks in children.

Experience of the use of DAIVONEX[®] ointment in children under 6 years of age is limited.

A maximum safe dose has not been established.

In children 6 to 12 years, the maximum weekly dose should not exceed 50g and in children over 12 years, the maximum weekly dose should not exceed 75g.

Renal Impairment

Safety has not been established in patients with renal impairment.

Hepatic Impairment

Safety has not been established in patients with hepatic impairment.

Pregnancy and Lactation (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 DAIVONEX[®] ointment should not be used during pregnancy unless benefits clearly outweigh the risks.

Studies in rats, at doses up to 54 µg/kg/day (318 µg/m²/day) of calcipotriol, demonstrated no impairment of fertility or general reproductive performance.

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

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

Other

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 did not elicit any genotoxic effects in *in vitro* assays for gene mutations (Ames mutagenicity assay and mouse lymphoma TK locus assay) or chromosomal damage (human lymphocyte chromosome aberration test or mouse micronucleus test).

Adverse Effects

Adults:

In the clinical trial program conducted for DAIVONEX® ointment, more than 1360 adult patients were evaluated for safety of calcipotriol. Adverse reactions following treatment with DAIVONEX® ointment were reported in 23% of patients and it was necessary to stop calcipotriol therapy in 2% of patients.

The majority of adverse events reported with DAIVONEX® ointment were localised to the skin at the site of application. Lesional/perilesional irritation was reported in 17% of patients, which included irritant contact dermatitis (on and around psoriatic lesions), flaking at the edge of lesions, increased sensitivity, tender psoriatic lesions and vesicles on psoriatic lesions. 2.5% of patients developed face and scalp irritation, including in studies which stipulated that calcipotriol should not be used on

the face and scalp, which is likely to be related to inadvertent transfer of the ointment from other body sites. There is also the potential for allergic and hypersensitivity reactions. Photosensitivity reaction and changes in pigmentation have also been reported during therapy with DAIVONEX[®] ointment.

For comparison, adverse events at the site of application were reported in 9.2% of patients receiving placebo therapy and in 10.8% of patients treated with betamethasone valerate (0.1%) ointment and in 39% of patients treated with dithranol (up to 2%).

One unconfirmed case of Koebner phenomenon has been reported and one unconfirmed case of allergic reaction to DAIVONEX[®] ointment. Occasionally, hypercalcaemia has been reported, usually related to excessive (greater than 100 g/week) use of the ointment.

Children:

The safety data for topical use of DAIVONEX[®] ointment in children are based on the study described under **Clinical Trials**. The most common adverse event was lesional and perilesional irritation, as was reported in adult patients. DAIVONEX[®] ointment treatment was discontinued in 2.3% of paediatric patients due to adverse events.

Adverse Events in the vehicle-controlled study

(Reported adverse events have been classified using standard WHO terms)

Adverse Event	% vehicle (n=34)	% DAIVONEX[®] ointment (n=43)
Skin and appendages disorders		
lesional/perilesional irritation	23.5	16.3
facial irritation	0	4.7
generalised skin inflammation	0	2.3
Gastro-intestinal system disorders		
gastroenteritis	0	2.3
Urinary system disorders		
crystals in urine	0	2.3

Interactions

Interactions with other drugs

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

DAIVONEX[®] ointment should not be used concurrently with calcium or vitamin D supplements, or with drugs which enhance the systemic availability of calcium.

Overdosage

Hypercalcaemia has been reported rarely at the recommended dose of DAIVONEX[®] ointment when used for the approved indication. Excessive use 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.

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

Pharmaceutical Precautions

Shelf Life and 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.

Medicine Classification

Prescription Only Medicine

Package Quantities

DAIVONEX[®] ointment contains 50 micrograms calcipotriol per g in a smooth, white preservative free ointment base. It is available in tubes of 15g, 30g or 100g.

Further Information

Nil

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Produced by

LEO Pharma A/S

Registered proprietor of the trademark LEO® LION Device and DAIVONEX®

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