

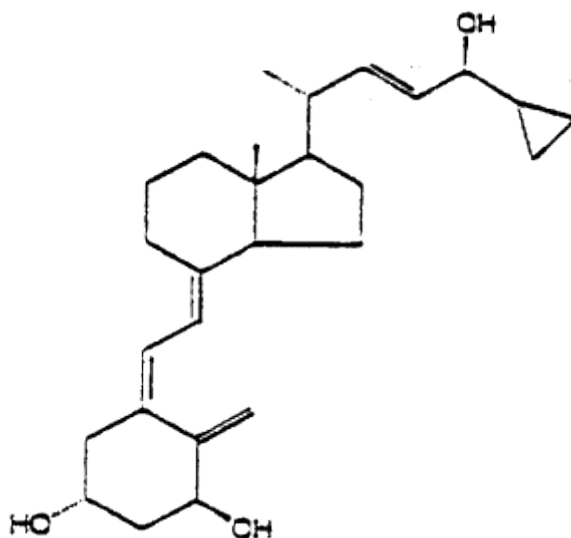
DATA SHEET

Daivonex[®] scalp solution

Calcipotriol 50 microgram/mL

Physical and Chemical Properties

Calcipotriol is a white or almost white crystalline substance. 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.



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[®] scalp solution contains the hydrated form of calcipotriol. It also contains menthol, hydroxypropylcellulose, sodium citrate, propylene glycol, isopropyl alcohol 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 minipig, 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 scalp solution in psoriatic and healthy volunteers demonstrated that 0.007 - 1.08% of calcipotriol from the applied dose was systemically absorbed. Approximately 30% of the dose was not recovered in these studies.

Clinical trials

Clinical trials using calcipotriol scalp solution assessed continuous use over a four to eight week period. Symptoms of psoriasis returned during the observation period and responded to retreatment. A summary of trials is presented in Table 1.

Table 1 - Summary of clinical trials using Calcipotriol Scalp Solution

STUDY		
	DE127-031	DE127-032
DESIGN	Multi-centre, randomised, double-blind, dose-ranging, vehicle-controlled, parallel group comparison	Multi-centre, randomised, double-blind, dose-ranging, vehicle-controlled, parallel group comparison
TREATMENT	<ol style="list-style-type: none"> 1. Calcipotriol Scalp Solution 50 microgram/mL - 79 patients 2. Placebo Scalp Solution - 75 	<ol style="list-style-type: none"> 1. Calcipotriol Scalp Solution 50 microgram/mL - 80 patients 2. Placebo Scalp Solution - 79

STUDY										
	DE127-031					DE127-032				
	patients					patients				
REGIMEN & DURATION	Applied twice daily for 8 weeks					Applied twice daily for 8 weeks				
MAIN RESPONSE CRITERION	Change in specified parameters rated in an ordinal scale from 0 to 8					Change in specified parameters rated in an ordinal scale from 0 to 8				
RESULTS			Day 1	End	Probability			Day 1	End	Probability
	Scaling	Calcipotriol: Placebo:	4.96 5.27	2.9 4 4.3 7	p = 0.0005	Scaling	Calcipotriol: Placebo:	4.71 4.94	2.5 9 3.0 9	NS
	Erythema	Calcipotriol: Placebo:	4.71 4.88	2.6 5 4.2 1	p = 0.0001	Erythema	Calcipotriol: Placebo:	4.44 4.53	2.4 1 3.3 0	p = 0.0003
	Plaque Elevation	Calcipotriol: Placebo:	4.17 4.31	2.2 2 3.6 5	p = 0.0001	Plaque Elevation	Calcipotriol: Placebo:	4.46 4.61	2.2 8 2.9 4	p = 0.0284
	Overall Severity	Calcipotriol: Placebo:	4.83 5.13	2.8 6 4.2 7	p = 0.0003	Overall Severity	Calcipotriol: Placebo:	4.73 4.94	2.4 4 3.2 6	p = 0.0052
	Pruritus	Calcipotriol: Placebo:	3.56 3.71	1.4 5 2.3 9	p = 0.0028	Pruritus	Calcipotriol: Placebo:	4.22 3.97	1.7 5 2.2 6	NS

Table 1 (Cont.) - Summary of clinical trials using Calcipotriol Scalp Solution

STUDY			
	MC1190	MC490	MC890
DESIGN	Multi-centre, randomised, double blind, parallel group, placebo-controlled trial	Multi-centre, randomised, double blind, parallel group, placebo-controlled trial	Open, single-centre, pilot study
TREATMENT	<ol style="list-style-type: none"> 1. Calcipotriol Scalp Solution 50 mcg/mL - 25 patients 2. Placebo Scalp Solution - 24 patients 	<ol style="list-style-type: none"> 1. Calcipotriol Scalp Solution 50 mcg/mL - 23 patients 2. Placebo Scalp Solution - 23 patients 	Calcipotriol Scalp Solution 50 mcg/mL - 11 patients

STUDY												
	MC1190				MC490				MC890			
REGIMEN & DURATION	Applied twice daily for 4 weeks				Applied twice daily for 4 weeks				Applied twice daily for 6 weeks			
MAIN RESPONSE CRITERION	Change in total sign score, including redness, thickness and scaliness				Change in total sign score, including redness, thickness and scaliness				Change in total sign score, including redness, thickness and scaliness			
RESULTS		Baseline	End	Reduction		Baseline	End	Reduction		Baseline	End	Reduction
	Calcipotriol:	6.8 ± 1.2	3.6 ± 2.7	3.2 ± 2.4	Calcipotriol:	7.0 ± 1.9	4.0 ± 2.0	3.0 ± 2.6	Calcipotriol:	8.7 ± 1.2	4.8 ± 2.0	2.7 ± 2.1
	Placebo:	6.5 ± 1.4	5.3 ± 2.5	(p<0.001) 1.3 ± 2.3 (p=0.014)	Placebo:	7.5 ± 1.7	5.4 ± 2.4	(p<0.001) 2.1 ± 2.1 (p<0.001)				

Indications

Calcipotriol scalp solution is indicated for psoriasis of the scalp in adult patients.

Contraindications

- i. Allergic sensitisation to any constituent of calcipotriol scalp solution.
 - ii. Patients with hypercalcaemia or patients who are undergoing treatments which may increase serum calcium concentrations.
 - iii. NOT FOR OPHTHALMIC USE.
-

Precautions

The maximum dosage of 60 mL of scalp solution per week should not be exceeded. When using a combination of scalp solution, cream and ointment the total dose of calcipotriol should not exceed 5 mg in any week.

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

Calcipotriol scalp solution 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.

Treatment with topical calcipotriol in the recommended amounts up to 5 mg/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. **Because primary hyperparathyroidism and renal impairment are identified complicating factors associated with hypercalcaemia during treatment with calcipotriol, and as serum calcium and renal function monitoring are relevant tests for diagnosis, serum calcium and renal function should be monitored prior to commencing therapy and 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 clinical information about the possible effects of calcipotriol when used for long periods during exposure to sunlight and UVA/UVB light. 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.

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.

Use in Lactation

It is not known whether calcipotriol is excreted in breast milk.

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

Use in Children

Daivonex® scalp solution 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.

Carcinogenicity and mutagenicity

No genotoxic potential was demonstrated in a series of assays for gene mutations and chromosome damage.

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.

Adverse Reactions

The adverse events observed in clinical trials conducted for calcipotriol scalp solution are summarised in Table 2.

Table 2 - Adverse events of calcipotriol scalp solution

NUMBER OF PATIENTS	463
ADVERSE REACTIONS (%)	39

NUMBER OF PATIENTS	463
Lesional/Perilesional Irritation (%)	25
Face and/or Scalp Irritation (%)	13
WITHDRAWAL FROM THERAPY* (%)	5

* 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.

Occasionally, hypercalcaemia has been reported, usually related to excessive (greater than 5mg calcipotriol/week) use.

Dosage and Administration

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

Adults

Calcipotriol scalp solution 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 for periods longer than 1 year.

The maximum dosage of 60 mL of scalp solution per week should not be exceeded. When using a combination of scalp solution, cream and ointment, the total usage of calcipotriol should not exceed 5 mg in any week, for example:

- **60 mL of scalp solution plus one 30 g tube of cream or ointment**
- **30 mL of scalp solution plus two 30 g tubes of cream or ointment**

It should be noted that there are no long-term clinical studies assessing the safety of using Daivonex[®] scalp solution 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[®] scalp solution 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 5 mg calcipotriol/week) of calcipotriol ointment when used for the approved indication. Excessive use, i.e. more than 5 mg calcipotriol/week, 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.

Medicine Classification

Prescription Only Medicine

Presentation

DAIVONEX[®] scalp solution contains 50 micrograms of calcipotriol per mL in a colourless, slightly viscous, preservative free solution available in 30 and 60 mL bottles with a nozzle.

Storage

Store below 25°C.

Shelf life: Unopened container: 2 years

After first opening of container: 3 months

Do not use after the expiry date printed on the package. The alcohol base of DAIVONEX[®] scalp solution is flammable.

Name and Address

CSL (New Zealand) Limited
666 Great South Road
Central Park
Auckland
NEW ZEALAND

Ph: 09 579 8105

Produced by

LEO Pharma A/S
Registered proprietor of the trademark LEO[®], LION Device and DAIVONEX[®]

Date of Preparation

20 December 2011