

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0711/149/001

Case No: 2066595

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, Co. Cork, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Calcil 50 micrograms/ml Cutaneous Solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **07/09/2009** until **07/04/2014**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calcil 50 micrograms/ml Cutaneous Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of calcipotriol cutaneous solution contains 50 micrograms calcipotriol.

Excipient: Propylene glycol 30 mg/ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cutaneous solution

Clear, colourless solution with an odour of menthol.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Calcil 50 micrograms/ml Cutaneous Solution is indicated for the topical treatment of mild to moderate scalp psoriasis.

4.2 Posology and method of administration

Adults

Calcil 50 micrograms/ml Cutaneous Solution should be applied to the affected areas twice daily (morning and evening).

The maximum weekly dose should not exceed 60 ml.

If this solution is used together with cream or ointment containing calcipotriol, the total weekly dose of calcipotriol should not exceed 5 mg (for example 60 ml of Calcil 50 micrograms/ml Cutaneous Solution plus 30 g of cream or ointment, or 30 ml of Calcil 50 micrograms/ml Cutaneous Solution plus 60 g of cream or ointment).

Duration of treatment should be decided by the physician, but should normally not be for longer than 22 weeks.

Renal/hepatic impairment

Patients with known severe renal or liver impairment should not be treated with calcipotriol.

Children and adolescents (under 18 years of age)

Calcil 50 micrograms/ml Cutaneous Solution is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to the active substance calcipotriol or to any of the excipients
- Patients with severe renal or liver impairment
- Known disorders of calcium metabolism or treatment with other medicinal products which increase serum calcium level
- Hypercalcaemia

4.4 Special warnings and precautions for use

Application of Calcil 50 micrograms/ml Cutaneous Solution to the face may cause local irritation. Calcil 50 micrograms/ml Cutaneous Solution should therefore not be applied directly to the face. Patients should be advised to wash their hands after applying the solution in order to prevent inadvertent transfer to the face.

The efficacy and long-term safety of this solution in children has not been established. Therefore its use in this population cannot be recommended.

Patients should be advised to use no more than the maximum weekly dose since hypercalcaemia, which rapidly reverses on cessation of treatment, may occur.

During calcipotriol treatment physicians are recommended to advise patients to limit or avoid excessive exposure to either natural or artificial sunlight. Topical calcipotriol should be used with UV radiation only if the physician and patient consider that the potential benefits outweigh the potential risks (see section 5.3).

Calcil 50 micrograms/ml Cutaneous Solution contains propylene glycol. It may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

4.6 Pregnancy and lactation

Pregnancy:

For calcipotriol no data on pregnant patients are available. A limited absorption is expected after local application of Calcil 50 micrograms/ml Cutaneous Solution on small areas. If used as indicated no disturbance of the calcium homeostasis is to be expected. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of calcipotriol during pregnancy.

Lactation:

It is unknown whether calcipotriol is excreted in breast milk. The excretion of calcipotriol in milk has not been studied in animals. As a precautionary measure, it is preferable to avoid the use of calcipotriol during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

In view of the nature of the product and the indications for its use, no effect on the ability to drive and use machines is to be expected.

4.8 Undesirable effects

Based on the clinical data undesirable effects occurred in approximately 25% of the patients.

The most frequently reported undesirable effects are various transient skin reactions and in particular application site reactions.

The undesirable effects are listed by MedDra SOC and the individual undesirable effects are listed starting with the most frequently reported. The following convention has been used for the classification of frequency of undesirable effects:

- Very common $\geq 1/10$
- Common $\geq 1/100$ and $< 1/10$
- Uncommon $\geq 1/1,000$ and $< 1/100$
- Rare $\geq 1/10,000$ and $< 1/1,000$
- Very rare $< 1/10,000$, not known (cannot be estimated from the available data)

Skin and subcutaneous disorders

Very common	Skin burning sensation and skin stinging sensation
Common	Pruritus, skin irritation, dry skin, erythema, rash*
Uncommon	Eczema, contact dermatitis, aggravation of psoriasis
Rare	Perioral dermatitis

*various types of rash reaction such as scaly, erythematous, maculo-papular and pustular have been reported.

Metabolism and nutrition disorders

Very rare	Hypercalcaemia, hypercalciuria
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The following undesirable effects have been reported on other products containing calcipotriol (cream, ointment, scalp solution) during post-marketing experience:

Transient changes in skin pigmentation, transient photosensitivity reactions and hypersensitivity reactions including urticaria, angioedema, periorbital or facial oedema (very rarely), perioral dermatitis (rarely).
Based on post-marketing data the total ‘reporting rate’ of undesirable effects is very rare being approximately 1:10,000 treatment courses.

4.9 Overdose

Use above the recommended dose (see section 4.2) may cause elevated serum calcium which disappears rapidly after cessation of treatment.

The clinical signs of hypercalcaemia include anorexia, nausea, vomiting, constipation, hypotonia, cognitive dysfunction, depression, lethargy, coma and renal dysfunction.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antipsoriatics for topical use, ATC code: D05AX02

Calcipotriol is a vitamin D derivative. *In vitro* data show that calcipotriol induces differentiation and suppresses proliferation of keratinocytes. The effect of calcipotriol in psoriasis is ascribed mainly to this.

5.2 Pharmacokinetic properties

No data are available on the absorption of calcipotriol following use of the scalp solution.

Data from a single study containing 5 evaluable patients with psoriasis treated with 0.3 – 1.7 g of a 50 micrograms/g tritium labelled calcipotriol ointment suggested that less than 1% of the dose was absorbed. However, total recovery of the tritium label over a 96 hour period ranged from 6.7 to 32.6%, figures maximised by uncorrected chemiluminescence. There were no data on ^3H tissue distribution or excretion from the lungs.

5.3 Preclinical safety data

The effect on calcium metabolism is approximately 100 times less than that of the hormonally active form of vitamin D3.

A dermal carcinogenicity study in mice revealed no special hazards for humans.

In another study where albino hairless mice were repeatedly exposed to both ultraviolet (UV) radiation and topically applied calcipotriol for 40 weeks at doses which correspond to 9, 30 and 90 $\mu\text{g}/\text{m}^2/\text{day}$ (equivalent to 0.25, 0.84 and 2.5 times the maximum recommended daily dose for a 60 kg adult, respectively), 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Hypromellose
Propylene glycol
Isopropyl alcohol
Levomenthol
Water, purified

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Before opening: 2 years
After first opening: 3 months

6.4 Special precautions for storage

Do not store above 25°C.
Keep the bottle in the outer carton in order to protect from light.
Do not refrigerate or freeze.

Keep the cutaneous solution away from fire or flames (the alcohol base is inflammable).

6.5 Nature and contents of container

Polyethene bottle fitted with polyethene nozzle and closed with polypropylene screw cap.
Packsizes: 30 and 60 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA711/149/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 April 2009

10 DATE OF REVISION OF THE TEXT