IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0711/093/001
Case No: 2042715

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/g Ointment

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 **21/08/2008** until **12/07/2012**.

Signed on behalf of the Irish Medicines Board this

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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/g Ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of ointment contains 0.05 mg (is equal to 50 micrograms) of calcipotriol.

Excipient: Propylene glycol 10 mg/g
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ointment
White to off-white ointment.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Calcil is indicated for the topical treatment of mild to moderately severe psoriasis (psoriasis vulgaris).

4.2 Posology and method of administration

Adults:
As monotherapy
Calcil should be applied to the affected skin once or twice daily. At the beginning of treatment, twice daily application is recommended. For maintenance therapy, the frequency of application may be decreased to once daily, depending on the response.
The maximum amount of ointment applied should not exceed 100 grams per week. If Calcil is used together with cream or solution containing calcipotriol, the total weekly dose of calcipotriol should not exceed 5 mg.

As combination therapy
Twice daily application of Calcil in combination with phototherapy, acitretin, ciclosporin and once daily application in combination with topical corticosteroids (e.g. administration of Calcil in the morning and steroid in the evening) is effective and well tolerated.
The duration of therapy depends on the clinical appearance. A pronounced therapeutic effect is generally seen after a maximum of 4-8 weeks. Therapy can be repeated.

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)
There is limited experience with the use of Calcil in children and adolescents under 18 years of age. The efficacy and long term safety of above mentioned dosage (under adults) has not been established in children and adolescents. Therefore its use in this population cannot be recommended.

4.3 Contraindications

- Hypersensitivity to the active substance calcipotriol or to any of the excipients
- Known disorders of calcium metabolism
- Hypercalcaemia

4.4 Special warnings and precautions for use

Calcil should not be used on the face.
Patients should be advised to wash their hands after applying the ointment in order to prevent the inadvertent transfer to other areas, especially the face.

The efficacy and long-term safety of this ointment in children has not been established**.**

Hypercalcaemia does not occur with the usual dosage (up to 100 g per week). Excessive use (50-100 g of ointment per day) may cause elevations in serum calcium levels which reverse rapidly on discontinuation of treatment. Studies on adults over a period of one year have not yielded any evidence of a risk of hypercalcaemia. However, the serum calcium level should be monitored on long-term use with application to extensive areas of skin.

In view of a possible effect on calcium metabolism, patients should be advised to use no more than the recommended dose (see section 4.2.) and the addition of penetration-promoting substances (such as salicylic acid) to the ointment is not permitted. Occlusion is undesirable for the same reason.

The clinical symptoms of hypercalcaemia may resemble those of cholecalciferol overdose, i.e. the hypercalcaemia syndrome or calcium intoxication (see section 4.9), depending on the intensity and duration of the hypercalcaemia. Persistent hypercalcaemia may result in ectopic deposits of calcium in the blood vessel walls, joint capsules, gastric mucosa, cornea and renal parenchyma.

There are data indicating that the combination of calcipotriol with UV-light may cause dark areas of hyperpigmentation; this is reversible. If calcipotriol is started during a course of UV-B therapy, photosensitive eczema may occur.

Patients with known severe renal or liver impairment should not be treated with Calcil due to limited experience.

Calcil contains propylene glycol. May cause skin irritations.

4.5 Interaction with other medicinal products and other forms of interaction

Although studies to-date have shown that the combination of Calcil with UV-A therapy, ciclosporin or acitretin is effective and well-tolerated, there is not enough data that the combination is more effective or that the dosage of the other medicinal products can be reduced.

Ointment will not increase the overall effectiveness of UV-B treatment. However, it has a light-saving effect when used in combination with UV-B in adults and response is achieved at a lower dose of UV-B. Calcil should be applied at least 2 hours before UV-B therapy. Combination of calcipotriol with UV-B light may cause dark areas of hyperpigmentation and photosensitive eczema (see section 4.4.). Ointment should not be initiated where patients may already be receiving an erythemogenic or sub-erythmogenic dose of UV-B.

Concomitant administration of calcipotriol and salicylic acid externals may cause an inactivation of calcipotriol. There is no experience of concomitant therapy with other antipsoriatic products applied to the same area of skin at the same time.

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 at 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 in pregnancy.

Lactation:
It 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 in lactation.

4.7 Effects on ability to drive and use machines

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 15% of the patients.

The most frequently reported undesirable effects are various transient skin reactions and in particular application site reactions, which seldom requires discontinuation of treatment.

The undesirable effects are listed by MedDra SOC and the individual undesirable effects are listed starting with the most frequently reported.

Skin and subcutaneous disorders
Common (>1/100 and <1/10)
Pruritus, skin burning sensation, skin stinging sensation, skin irritation, skin dry, erythema, rash*

Uncommon (>1/1,000 and <1/100)
Eczema, contact dermatitis, aggravated, psoriasis

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

Metabolism and nutrition disorders
Very rare (<1/10,000)
Hypercalcaemia, hypercalciuria

The following undesirable effects have been reported for calcipotriol cream, ointment and scalp solution during post-marketing experience: transient changes in skin pigmentation, transient photosensitivity reaction and hypersensitivity reaction including urticaria, angioedema, periorbital or facial oedema (very rarely). Perioral dermatitis may occur 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

Up to now, hypercalcaemia has not been reported in patients with psoriasis vulgaris at the usual dosage of up to 100 grams of ointment per week, although the possible occurrence of hypercalcaemia at this dosage cannot be completely excluded. Excessive use (50-100 grams per day) may result in an elevated serum calcium level, which disappears rapidly after cessation of treatment, and hypercalcaemia has been reported at lower doses in patients with generalised pustular or erythrodermic exfoliative psoriasis. The clinical signs of hypercalcaemia include anorexia, nausea, vomiting, constipation, hypotonia, depression, lethargy and coma.

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.

An effect, first of all on the desquamation, then on the infiltration and finally on the erythema, is seen after two to four weeks of treatment. The maximum effect is usually achieved after six weeks.

5.2 Pharmacokinetic properties

Data from a single study containing 5 evaluable patients with psoriasis treated with 0.3 – 1.7g 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 tissue distribution or excretion from the lungs.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol stearyl ether
Disodium edetate
Disodium phosphate dihydrate
α-Tocopheryl acetate
Propylene glycol (E490)
Paraffin, light liquid
Water, purified
Paraffin, white soft

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

After first opening: 3 months

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.
Store in the original package.

6.5 Nature and contents of container

Membrane closed aluminium tube with polypropylene screw cap.

Pack size: 30 gram.

Membrane closed almuninum tube with polyethylene neck and screw cap.

Pack sizes: 30 , 60, 90 and 120 gram

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

8 MARKETING AUTHORISATION NUMBER

PA 711/93/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th July 2007

10 DATE OF REVISION OF THE TEXT

January 2008