CURATODERM 4 MICROGRAMS/G LOTION

PL 00327/0149

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The MHRA today granted Crookes Healthcare Limited Marketing Authorisation (licence) for the medicinal product Curatoderm 4 microgram/g Lotion (PL 00327/0149). This is a prescription only medicine (POM) used to treat a condition known as psoriasis vulgaris especially on the scalp.

Curatoderm Lotion contains tacalcitol which is a drug that belongs to a group of medicines called antipsoriatrics and is a vitamin D derivative.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Curatoderm 4 microgram /g Lotion outweigh the risks, hence Marketing Authorisation has been granted.
CURATODERM 4 MICROGRAMS/G LOTION

PL 00327/0149

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisation for the medicinal product Curatoderm 4µg/g lotion on 19th July 2007. The product is a prescription only medicine.

The proposed product is a line extension of an authorised medicinal product Curatoderm 4µg/g Ointment containing tacalcitol, PL 00327 / 0114, granted August 1998. This was a change in the ownership of the licence, which was previously held by Merck Limited as PL 11648/0019, granted January 1996.

Curatoderm Lotion is used to treat a condition known as psoriasis vulgaris especially on the scalp. Psoriasis is a skin disorder in which itchy, red, flaky patches appear on the skin or scalp. Within affected areas of skin, new cells are being produced faster than normal, but old dead cells are only being shed at the normal rate. As live skin cells accumulate, the skin becomes thickened and inflamed. Curatoderm Lotion works by slowing down cell production and bringing it back to normal and helps to reduce inflammation.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Tacalcitol is a vitamin D₃ derivative, which inhibits keratinocyte hyper-proliferation and induces differentiation of these cells.

An appropriate specification is provided for the active substance tacalcitol.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

A satisfactory letter of access is provided.

Active tacalcitol is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting a shelf life of 3 years when protected from light and stored below 8°C.

DRUG PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients, namely Paraffin light liquid, medium chain triglycerides, octyldodecanol, macrocol 21 stearyl ether, di-isopropyl adipate, dodecyl gallate, propylene glycol, phenoxyethanol, disodium phosphate dodecahydrate, xanthan gum, potassium dihydrogen phosphate, disodium edentate, and water purified.

All excipients comply with satisfactory European Pharmacopoeial monograph, with the exception of dodecyl gallate which complies with the British Pharmacopoeia monograph and MACROGOL 21 STEARYL ETHER and DI-ISOPROPYL ADIPATE an in-house specification. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

 Manufacture
A description and flow-chart of the manufacturing method have been provided and are satisfactory.

In-process controls are satisfactory based on process validation data and controls on the finished product. Satisfactory controls for temperature, appearance and pH of the manufacturing process and filling of the assembly process are described.
Finished product specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Specifications and certificates of analysis for all packaging materials have been provided. These are satisfactory.

The applicant has confirmed that all packaging that comes into direct contact with the drug product complies with European Directive 90/128/EEC with respect to their contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Batches of finished product manufactured at the proposed finished product manufacturer, using active substance from the proposed active substance manufacturer and in packaging proposed for marketing were placed on stability at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH.

Based on the results, a shelf-life of 2 years has been set, which is satisfactory. The precautions ‘Keep the bottle in the outer container’ and ‘Do not store above 30°C’ have been included.

In-use stability data are provided, this has supported the proposed shelf-life.

SPC, PIL, Labels
The SPC, PIL, and Labels are pharmaceutically acceptable.

Conclusion
It is recommended that Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

1. INTRODUCTION
This is a standard abridged application for a new pharmaceutical form (cutaneous emulsion) containing tacalcitol 4 µg/g. The product is indicated in psoriasis vulgaris, especially on the scalp. Tacalcitol is already authorised in Curatoderm ointment (PL 00327/0114), which is indicated in psoriasis vulgaris. The dosing recommendations state that the lotion should be applied once daily to affected areas, preferably at bedtime. A maximum dose of 10ml lotion/day should be used. When used with Curatoderm ointment, the total dose of tacalcitol should not exceed 280 µg/week (equivalent to 30ml lotion + 40g ointment).

2. PHARMACODYNAMICS
2.1. Pharmacodynamics for the Proposed Indications
Tacalcitol (1α,24(R)-dihydroxycholecalciferol) is a synthetic vitamin D₃ analogue. Tacalcitol binds to vitamin D₃ receptors on keratinocytes to the same extent as does natural vitamin D₃. It inhibits hyper-proliferation of keratinocytes and induces their differentiation, which is the basis for efficacy in psoriasis.

In the human keratinocyte cell line HaCaT (a rapidly multiplying, spontaneously immortalised, non-tumourigenic cell line), tacalcitol inhibited both DNA and protein synthesis, with an IC₅₀ of 7x10⁻⁷M. Calcitriol and calcipotriol were also examined in this test system, over the same concentration range (10⁻¹¹ to 10⁻⁶ M), but their IC₅₀’s for inhibition of either DNA or protein syntheses were not reached within this range.

Tacalcitol concentration-dependently induces the activity of transglutaminase in cultured mouse and human epidermal cells. Transglutaminase acts as a rate-limiting enzyme on the terminal differentiation of epidermal cells. It also induced the activity of type I transglutaminase, which plays a role in the formation of the cornified envelope. Both of these actions promote the differentiation of epidermal cells, which is important factor in anti-psoriatic activity.

Other published studies have suggested that tacalcitol may have an anti-inflammatory action by an effect on the production of anti-inflammatory interleukins.

2.2 Secondary Pharmacology
Doses of between 10 and 100 µg/kg appeared to have no effect on CNS, respiratory, cardiovascular, gastrointestinal or renal systems, nor on blood or other bodily functions.

3. PHARMACOKINETICS
3.1. Absorption
Less than 0.5% of tacalcitol is absorbed through psoriatic skin from the ointment. ³H-Tacalcitol is absorbed through healthy skin in rats and dogs when applied at 0.1 to 1.6 µg/200g rat or 4 µg/10 kg dog. Cᵥₐₓ increased with dose. Autoradiography revealed that in rats, absorption occurs through the hair routes as well as the stratum corneum and epidermis.
3.2. Distribution
Tacalcitol is completely bound to plasma proteins (Vitamin D$_3$ binding protein) in vitro.

Following percutaneous application of 100mg of ointment containing $^3$H-tacalcitol (4µg/g) to shaved skin of rats, concentrations of radioactivity were higher in liver and small intestine than in plasma after 24 hours, and radioactivity was detectable in adipose tissue 48 and 96 hours after administration.

Two hours after subcutaneous administration of 0.4 µg/kg $^3$H-tacalcitol to rats, highest levels of unchanged drug were found at the injection site, liver, kidney and intestine. Plasma:tissue concentration ratios at this time were 0.6 for liver and 0.5 for kidney. Elimination from adipose tissue was slow, and accumulation occurred following repeated dosing.

Administration of a single s.c. dose to pregnant rats on day 14 of gestation showed similar pharmacokinetics in maternal liver, uterus, placenta and amniotic fluid. When a similar study was performed on Day 19 of gestation, disappearance of radioactivity from the tissues was slightly delayed compared to that from plasma. Less than 1% of the dose was detected in fetal tissue up to 24 hours after dosing of the dams.

Enterohepatic circulation was found to occur in rats, with nearly 60% of an i.v. dose excreted in the bile.

3.3. Metabolism
The main metabolite of tacalcitol is $^{1}\alpha, 24, 25$(OH)$_3$ vitamin D$_3$, which is also the main metabolite of natural vitamin D$_3$. It is 5 to 10 times less active than the parent compound.

The water-soluble metabolite calcitroic acid was the main component in rat bile. No unchanged tacalcitol was found in urine.

3.4. Excretion
Elimination from the plasma is bi-phasic in rat and dog, and excretion occurs predominantly via the bile and faeces in these species. Following percutaneous administration, approximately 30% of the dose is recovered, compared to about 90% following s.c. or i.v. administration. Most of the dose is eliminated in 2 days, but radioactivity is still detectable in urine and faeces 10 days after a single dose.

Following a single sc dose of $^3$H-tacalcitol to nursing rats on day 14 of lactation, unchanged drug and the metabolite $^{1}\alpha, 24, 25$(OH)$_3$ D$_3$, were detected in the milk. The parent drug was present at 10% of the maternal plasma concentration. The metabolite was detected at 2 and 4 hours, but not by 8 hours post-dose.

4. TOXICOLOGY
4.1. Single Dose Toxicity Studies
Acute toxic effects are secondary to hypercalcaemia and LD$_{50}$’s vary depending upon the route and species as a result of the degree of hypercalcaemia induced. The lowest LD$_{50}$ was in dog using the s.c. route (10 µg/kg).

The main metabolite$^{1}\alpha, 24, 25$(OH)$_3$ D$_3$ was 7 to 8 times less acutely toxic than tacalcitol.
4.2. **Repeated Dose Toxicity Studies**

The toxic effects noted upon repeated administration were those associated with pharmacologically-induced disturbances of calcium homeostasis. Findings prior to death in rats included elongation of the incisors, corneal whitening, kyphosis and gait abnormalities. Gait abnormalities were also observed in dogs. Histopathological examination of those animals that died revealed widespread metastatic calcification of soft tissues including renal tubules, lungs, coronary vessels, aorta and cornea in rats but not in dogs. At non-lethal dosages, hypercalcaemic effects included elevated serum calcium and phosphate, urinary excretion of excess calcium and phosphate, metastatic calcification of renal tubules and bone hyperplasia. All except the urinary excretion of excess calcium and phosphate recovered after stopping treatment.

In 13-week and 12-month subcutaneous studies in the rat with s.c. administration, the NOEL was 4 ng/kg/day. Corresponding figures for s.c. studies in dogs were 2ng/kg/day and 1 ng/kg/day, respectively. The NOEL for a 13-week percutaneous study in the rat was 8 ng/kg/day.

5. **REPRODUCTION STUDIES**

Rat fertility was unaffected by tacalcitol. Embryotoxicity was observed in rats at maternally toxic doses (0.5µg/kg/day; NOEL = 0.1 µg/kg/day). There were no effects in a rabbit teratology study and pre- and post-natal development in the rat was unaffected by treatment.

For Curatoderm Lotion no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

'It is not known whether tacalcitol is excreted in human milk. Given the low systemic exposure in humans following topical treatment with tacalcitol, it is probably not necessary to stop breast-feeding during treatment, unless the breast area is affected. In that case, either the breast area should not be treated in lactating women who are breast-feeding, or breast-feeding should be stopped.'

6. **MUTAGENIC POTENTIAL**

Tacalcitol was negative in a battery of mutagenicity studies, including an Ames test, chromosome aberration tests in Chinese hamster lung cells and in vivo micronucleus tests in mice using the i.p. and s.c. routes.

7. **ONCOGENIC/CARCINOGENIC POTENTIAL**

Carcinogenicity studies have not been reported in the literature, but vitamin D3 derivatives have been used long-term for the treatment of, for example, osteoporosis. The effects of treatment, as observed in the repeated dose toxicity studies, are those resulting from hypercalcaemia and its sequelae. No pre-cancerous changes were noted in the 12-month s.c. studies in rat or dog. In addition, the low percutaneous absorption, known pharmacokinetics and negative genotoxicity assays suggest that treatment with tacalcitol is unlikely to carry a carcinogenic risk.
8. SPECIAL STUDIES
8.1. Local Tolerance (including Phototoxicity & Photosensitivity)
Local tolerance of the ointment was investigated in rabbit eye and skin, and phototoxicity, photosensitivity, contact sensitisation and antigenicity studies in the guinea pig. All were essentially negative. The local tolerance of the lotion formulation has been investigated in healthy volunteers. The lotion was applied under occlusion for 18 hours on day 1, then 6 hours/day for the three following days. The lotion and vehicle produced no clinically relevant irritant effect.

9. THE PHARMACO-TOXICOLOGICAL EXPERT REPORT
An expert report was provided, signed by Pharmacological and Toxicological Specialist. This expert report was submitted in support of a marketing authorisation application in Germany. In addition, an expert statement was provided, signed by Head of Medical Affairs for the applicant, which states that the expert report fully supports the proposed SPC for the UK marketing authorisation application for Curatoderm Lotion 4µg/g.

10. DISCUSSION
The expert has reviewed the relevant literature on the pharmacology, pharmacokinetics and toxicology of tacalcitol. The indications and recommended dosages are comparable for the authorised ointment. No new preclinical data have been provided, and none are necessary for this application. Preclinical local tolerance studies were conducted with the ointment formulation, but the proposed lotion formulation has been studied in healthy volunteers. The SPC sections 4.6 and 5 are identical to those for Curatoderm Ointment.

11. OVERALL CONCLUSIONS ON PRODUCT SAFETY
There are no major objections on preclinical grounds to the grant of a marketing authorisation for this product, and no points for clarification.
CLINICAL ASSESSMENT

1. INTRODUCTION
   This is a national abridged standard application for a marketing authorisation for Curatoderm Lotion, PL 00327/0149. The present application is a line extension of Curatoderm Ointment 4 micrograms/g, PL 00327/0114, being Crookes Healthcare Ltd the marketing authorisation holder. The application is made under article 4.8 of EC Directive 65/65, as amended.

2. BACKGROUND
   Tacalcitol is a vitamin-D3 analogue that inhibits proliferation and increases differentiation of epidermal keratinocytes, which is the basis of its use in psoriasis. Curatoderm ointment 4 micrograms/g is registered in several European countries including the UK. Curatoderm lotion 4 micrograms/g was developed for the topical treatment of psoriasis especially on the scalp.

3. INDICATIONS
   Psoriasis vulgaris, especially on the scalp.

4. DOSE & DOSE SCHEDULE
   Adults and the Elderly: Apply once daily to the affected areas, preferably at bedtime. The amount applied should not exceed 10 ml of lotion/day. When used together with Curatoderm Ointment, the total dose of tacalcitol should not exceed 280 micrograms/week (e.g. 30 ml of Curatoderm Lotion plus 40 g of Curatoderm Ointment). Normally duration of treatment depends on the severity of the lesions and should be decided by the physician. There is clinical trial experience with continuous and intermittent treatment with tacalcitol in adults up to twelve months.

   Curatoderm Lotion can be used on all areas of the body (including face, hairline, scalp, axilla and other flexures).

   Children: Not recommended. There is limited clinical experience with tacalcitol in children.

5. TOXICOLOGY
   See pre-clinical assessment report.

6. CLINICAL PHARMACOLOGY

   6.1 PHARMACOKINETICS
   Single or repeated application of tacalcitol ointment in humans results in less than 0.5% of the drug being systemically absorbed through psoriatic skin. Tacalcitol is completely bound to plasma proteins (vitamin D binding protein). The main metabolite is 1α, 24, 25 (OH)3 vitamin D3, a metabolite shared with the natural active vitamin, with 5-10 times less vitamin D activity. Tacalcitol and metabolites are excreted mainly in the faeces in rat and dog studies with excretion in urine in man. It cannot therefore be excluded that if there is
sufficient systemic absorption accumulation may occur in patients with renal failure.

One pharmacokinetic clinical phase II study has been conducted: CT09

Aim
To study the absorption and metabolism of Tacalcitol.

Design & Method
5 male patients with psoriasis vulgaris, aged 31-59 years, received Tacalcitol ointment 4 micrograms/g once daily without occlusion for 1 week, at a daily dose of approximately 1.5g to an affected area of 20 x 20 cm². On days 1 and 8 they received 3H-labelled ointment and on days 2-7 unlabelled ointment was used. Because the tacalcitol concentration in the ointment is relatively low it was necessary to use radiolabelled drug. For ethical reasons a higher dose of radioactivity was not possible. Sampling of blood, urine and faeces was taken before and after both applications with labelled drug. After 24 hours the application area was rinsed and residual radioactivity in bandage and cotton wools used for rinsing was determined.

Results
All subjects completed the study. No radioactivity was detected in any blood or faeces samples and therefore the metabolism studies had to be cancelled. Scintillation counting on bandages and cotton wools showed that 48-78% of the applied dose could be rinsed off the skin surface or adhered to the bandage 24 hours after application. Detectable radioactivity was found in urine samples until and including the 48-72 hour sample after the first and the last dose. On average 0.025%(range: undetectable- 0.08%) of the dose applied day 1 and 0.082%(range: undetectable- 0.27%) of the dose applied day 8 was excreted.

1.1 CONCLUSION
The absorption of tacalcitol through psoriatic skin is negligible.

Assessor comments
Less than 0.3% of the applied dose was absorbed through diseased skin upon repeated applications for 1 week. However, on day 8 only the radioactivity from the doses of days 1 and 8 are assessed and does not include the doses from days 2 to 7. As no more radioactivity in the 72-96 hour samples were detected after the first dose, the urine radioactivity after the dose on day 8 originated only from this last dose. 76% of the systemically absorbed dose was excreted during the first 24 hours on both occasions, indicating a systemic half-life less than the dose interval.
As the skin barrier is expected to improve along with the clinical improvement the figures above are expected to represent the clinical situation early during treatment.

6.2 PHARMACODYNAMICS
Tacalcitol is a vitamin D3 derivative, which inhibits keratinocyte hyperproliferation and induces differentiation of these cells. The normalisation of
these mechanisms is the basis for the efficacy in the treatment of psoriasis. In biopsies from patients treated with tacalcitol specific indicators for inflammation were improved. Tacalcitol binds to the keratinocyte vitamin D receptor to the same extent as natural active vitamin D3.

Three in vitro studies of human keratinocytes have been conducted using tacalcitol ointment (CT01, CT02, CT03). They confirmed that the effects of tacalcitol on the regulation of cell growth and differentiation in vitro are at least equal to those of calcitriol, which is the naturally active hormone.

Another in vitro study, CT04, indicated a possible anti-inflammatory activity of Tacalcitol ointment due to inhibition of IL-8 synthesis at 10-12 – 10-10 M concentrations.

Two studies in patients with psoriasis vulgaris have demonstrated that cell proliferation rate is decreased in vivo. CT05 was an open, non-comparative study that assessed the biopsies from affected skin in 10 patients before and after twice daily treatment with Tacalcitol ointment 2 micrograms/g for 2 or 4 weeks. They found inhibition of DNA synthesis and nuclear division correlating with the degree of clinical improvement, being more pronounced after 4 weeks of treatment. This finding was confirmed in CT06, a double blind placebo-controlled study, which assessed the biopsies from 10 patients before and after treatment with Tacalcitol ointment 4 micrograms/g once daily for 8 weeks. This study demonstrated in vivo suppression of the clinically relevant pathogenic changes in psoriasis: increased cell turnover, immature cells and inflammation.

7. EFFICACY
The applicant has submitted 7 clinical studies.

7.1 CT 10: Concentration-efficacy relation (Ointment formulation)
This study was targeted to determine the optimal concentration for a once daily therapy with Tacalcitol ointment. 58 adult patients were randomised in a double-blind once daily treatment of eleven 2 cm² psoriasis affected areas for 23 consecutive days. The comparison was done between seven concentrations of Tacalcitol (0.25 – 16 micrograms/g), the Tacalcitol ointment vehicle and three positive controls: Calcipotriol 50 micrograms/g ointment, hydrocortisone butyrate 0.1% ointment and betamethasone dipropionate 0.05% ointment.

The conclusion was that Tacalcitol ointment 4 micrograms/g applied once daily is expected to be a safe and effective topical treatment for psoriasis vulgaris.

7.2 96606BS: Duhring Chamber Test with initially developed formulations
The aim of this randomised double-blind study was to evaluate dermal reactions for local tolerance. 23 healthy subjects were enrolled and all received the same treatments. Three initial Tacalcitol 4 micrograms/g lotions and the
corresponding vehicles were compared. They received occlusive application of 40 mg of each test preparation once daily for four days.

With the exception of eczematous reactions of unknown cause in one subject there were no adverse events related to the trial preparation. It is probable that the eczematous reaction was due to an allergy to one of the ingredients.

The conclusion was that if substances are well tolerated under exaggerated study conditions it can be assumed that the respective formulations will be very well tolerated and will not lead to irritant reactions when used as intended.

7.3 95923BS: Psoriasis Plaque Test with initial formulations
The aim was to determine the antipsoriatic efficacy of different tacalcitol preparations. The GCP-study was performed in 12 patients with stable plaque psoriasis.

The three test preparations containing Tacalcitol lotions (4 micrograms/g) and the two Tacalcitol-free vehicles were tested double-blind. An open-label positive control (0.1% betamethasone ointment) was included. The subjects received 200 mg of treatment over 14 days.

The primary objective was the quantification of the antipsoriatic efficacy using the USE-Index. This was additionally evaluated by a visual assessment score.

The three Tacalcitol lotions led to a reduction in the USE-index compared to baseline of 29.9%, 33.5% and 38.9% after 14 days treatment. The USE-index was reduced 2.7% using Tacalcitol-free vehicles and 91.8% with the 0.1% betamethasone ointment. The results of the visual assessment revealed a slight to moderate improvement under the treatment with Tacalcitol lotion preparations. No adverse reactions related to the test preparations were reported.

On the basis of this results the antipsoriatic efficacy of the Tacalcitol test preparations are classified as slight to moderate.

Due to methodological reasons a Psoriasis Plaque Test cannot be performed on the scalp and therefore a pilot, comparative parallel group design in patients with psoriasis on the scalp was chosen.

7.4 97301BS: Pilot study with one of the initial formulations
In this observer-blinded study the efficacy of one of the initial tacalcitol lotions was tested for treatment of scalp psoriasis compared to Calcipotriol solution, which is registered for treatment of scalp psoriasis. 1.5mg Tacalcitol 4 micrograms/g lotion applied once daily and 1.5 ml calcipotriol solution twice daily were the test and reference products respectively.

Twelve patients with psoriatic lesions on the scalp received the treatment over a period of 28 days. A reduction of at least 30% of the baseline values was considered to be clinically relevant effectiveness. The USE-index was the
primary efficacy variable for statistical evaluation. Clinical and overall assessment scores were secondary variables.

Both treatments led to a reduction in infiltrate of more than 35% compared to baseline. In general no significant differences were noted between the treatment groups. Both were well tolerated and no adverse effects were reported. Once daily treatment is more acceptable for the quality of life of the patient and therefore provides a product advantage.

7.5 97303BS: Psoriasis Plaque Test with the newly developed formulations

The aim of this study was to determine the antipsoriatic efficacy of four newly developed Tacalcitol lotion formulations in comparison to Calcipotriol solution and Curatoderm (Tacalcitol) ointment.

The Tacalcitol lotion formulations differed in their content of fatty compounds (15% or 30% fatty compounds) and additionally two formulations contained a penetration enhancer. In addition an oil formulation and the corresponding vehicle were tested to check whether the oil formulation shows a better efficacy than the lotion formulations. Calcipotriol solution and Tacalcitol ointment served as reference therapies.

19 patients with stable plaque psoriasis received the treatments. The primary objective was the quantification of the antipsoriatic efficacy of the test preparations using the USE-index. Additionally, there was an evaluation by visual assessment. With the exception of the alcoholic Calcipotriol solution and the label positive control (0.1% betamethasone ointment) all test formulations were tested randomly and double-blind. The assessment of treatment effects of the positive control and Calcipotriol solution was performed observer-blind.

A total of 10 test fields were examined per patient (Tacalcitol formulations, Tacalcitol ointment (Curatoderm), Calcipotriol solution and betamethasone ointment). This study was conducted in compliance with GCP standards.

The greatest improvement was noted in the fields treated with the positive control betamethasone. Tacalcitol ointment showed the best effect of all Tacalcitol preparations being closely followed by the Tacalcitol cream and the lotions with 30% fatty compounds. 30% fat tends to be better than 15% fat, but this difference was not significant. Tacalcitol scalp oil was significantly better than the vehicle alone. The results of the visual assessment were in agreement with the objective measurement with the exception, that 30% fat with penetration enhancer was better than 30% fat without penetration enhancer. Although the penetration enhancer seems to have a slight additional effect, the higher proportion of fat plays a more important role for the effectiveness of the lotion.

Therefore, the antipsoriatic efficacy of the tacalcitol test preparations can be classified as slight for the scalp oil or the 15% fat lotion and as moderate for calcipotriol solution, the 30% fat lotions, the cream and the ointment.
Based on the results of this study the Tacalcitol lotion formulation with 30% fatty compounds was chosen for the pivotal study. This formulation without penetration enhancer achieved a better result in the USE-index and it was decided not to use the penetration enhancer for the final lotion formulation.

7.6 Study H364 000 03/96: Efficacy and safety parallel group comparison with final formulation

Aim

To assess the efficacy and safety of a once daily topical application of 4 micrograms/g Tacalcitol lotion for the treatment of mild to moderate psoriasis vulgaris on the scalp.

Design & Method

European multi-centre, double-blind, randomised, placebo-controlled parallel group comparison. The study started with a 2 weeks washout period. After this eligible patients were randomised for an 8 week treatment. Primary outcome measure was the sumscore of the clinical signs erythema, infiltration and desquamation. Secondary outcomes included the individual scores (erythema, infiltration and desquamation), the extent of the scalp psoriasis, the patient’s assessment of flaking and itching of the scalp and the investigators as well as the patients’ assessment of the treatment response.

This study was conducted in compliance with GCP standards.

Laboratory tests were performed at screening and at the end of the treatment period. The following parameters relevant to the calcium metabolism were measured: serum calcium, phosphate, creatinine, PTH and calcitonine. In patients who agreed to collect 24-hour urine, calcium, phosphate and creatinine were analysed. Additionally Vitamin D3 metabolites were examined from serum of UK patients.

A total of 273 patients with plaque psoriasis of the scalp were randomised. 123 patients of the Tacalcitol group and 119 of the vehicle group completed the study. There were more withdrawals in the vehicle group than in the Tacalcitol group, mainly due to treatment failure. 47 major protocol violations occurred with similar distribution among the two treatment groups. The majority were due to violations of the visit schedule. In general, results did not differ greatly between the intent to treat and the valid case populations.

Results

For all the efficacy assessed aspects of psoriasis, the comparison of the two treatment groups resulted in statistically significant differences in favour of tacalcitol.
Conclusion
The condition of patients with mild to moderate psoriasis of the scalp improved with treatment with tacalcitol 4 micrograms/g lotion applied once daily for 8 weeks. The safety and tolerability profile for the tacalcitol lotion was good.

7.7 **98923BS: Duhring Chamber Test with final formulation**
This was a double-blind study comparing the final formulation containing Tacalcitol 4 micrograms/g and the corresponding vehicle in 20 healthy volunteers. The aim was to study the local tolerance for Tacalcitol lotion following repetitive occlusive application.

The test formulations were applied under occlusion for 18 hours on day 1 and 6 hours daily for 3 additional days. All subjects received the same treatments. There were no dropouts.

The results showed that both formulations alone did not lead to clinically relevant irritant reactions. There were no adverse events associated with the test products other than the dermal reactions recorded as primary objective.

If substances are locally well tolerated under exaggerated conditions of occlusion, it can be assumed that the respective formulations will be very well tolerated when used under open application.

**Efficacy summary**
Efficacy data are available from 4 controlled trials on a total of 307 adult patients with psoriasis vulgaris, treated once daily with the final Tacalcitol 4 micrograms/g lotion formulation. No experience is available in pregnant or nursing women or children.

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The clinical efficacy of Tacalcitol lotion 4 micrograms/g applied once daily was conclusive in all studies:

- The comparative pilot study demonstrated that Tacalcitol lotion formulation works on the scalp and that the results are practically comparable to the marketed Calcipotriol solution.
- Both PTTs showed that the Tacalcitol lotion formulations have an antipsoriatic effect.
- The pivotal multicentre study confirmed that the final Tacalcitol lotion formulation is efficacious and safe.

The time to onset of clinical improvement is relatively short with a larger amount of improvement at the beginning of the treatment. In none of the studies mean improvement reached a plateau towards the end of the treatment period. A longer treatment duration may be decided by the physician on an individual basis.

In addition, patient compliance is promoted by the once daily application of Tacalcitol lotion 4 micrograms/g, which can be performed in the evening.

8. SAFETY

8.1 Safety results of the studies

8.1.1 Duhring Chamber Test with initially developed formulations
With the exception of eczematous reactions in four treatment fields (two on Tacalcitol, two on vehicles) of unknown cause in one subject there were no adverse events (AEs) related to the trial preparation. It is probable that the eczematous reactions were due to an allergy to one of the ingredients.

8.1.2 PPT with the initial formulations
There were no AEs. As the total doses of active ingredients were low laboratory parameters were not controlled during the course of the study.

8.1.3 Pilot study with one of the initial formulations
No AEs were reported.

8.1.4 PPT with the final formulation
Active ingredients were low, laboratory parameters were not analysed during the course of the study.

8.1.5 European pivotal multicentre study
This was the major study for the assessment of the safety of the final Tacalcitol lotion formulation.

An overview of all AEs is given below:

<table>
<thead>
<tr>
<th></th>
<th>Tacalcitol</th>
<th>Vehicle</th>
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<tbody>
<tr>
<td></td>
<td>Total n = 135</td>
<td>Total n = 138</td>
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<tr>
<td></td>
<td>(100%)</td>
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<tr>
<td>n</td>
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<tr>
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<td>28.1</td>
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<tr>
<td>AEs not related</td>
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<tr>
<td>Related</td>
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<td>8.7</td>
</tr>
<tr>
<td>AE mild</td>
<td>19</td>
<td>14.1</td>
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</tbody>
</table>

18
The number of patients with adverse events (AEs) was very similar for both treatment groups with respect to causality and seriousness. There were more patients with mild but less patients with moderate AEs in the Tacalcitol treated group than in the vehicle group. In total 80 patients reported 83 AEs. No death occurred. Two serious AEs (SAEs) were recorded in the vehicle group and one in the tacalcitol treated group although none of these events were considered to be study-drug related.

One third of all AEs were related to the skin and appendages probably due to a predisposition to skin problems in the study population. Otherwise, the pattern of AEs included those whose background incidence is also known to be frequent in the general population.

Vital signs, physical examinations and laboratory values revealed no major changes during the course of the study. Laboratory tests were performed at screening and at the end of the treatment period. The following parameters relevant to the calcium metabolism were measured: serum calcium, phosphate, creatinine, PTH and calcitonine. In patients who agreed to collect 24-hour urine, calcium, phosphate and creatinine were analysed. Additionally Vitamin D3 metabolites were examined from serum of UK patients.

8.1.6 Duhring Chamber Test with the final formulation
The results showed that both formulations alone did not lead to clinically relevant irritant reactions. There were no adverse events associated with the test products other than the dermal reactions recorded as primary objective.

8.2 Postmarketing experience
As Tacalcitol lotion is not yet registered in any country, postmarketing experience is not available. For the already registered Tacalcitol ointment formulation (Curatoderm®) high dose and long term data are available. The data can be regarded supportive for the safety of the Tacalcitol lotion formulation, which has the identical drug concentration and application frequency (4 micrograms/g, once daily).

8.2.1 High dose data is available from three clinical studies. **CT26** assessed the safety effects in patients with psoriasis vulgaris treated with higher doses of Tacalcitol ointment for 4 weeks. The conclusion was that there was no influence of treatment on calcium haemostasis. Two studies, **CT20** and **CT21**, were conducted to investigate the systemic safety of topically applied Tacalcitol ointment in humans. The conclusion was that there was no influence on calcium haemostasis after high daily doses of Tacalcitol ointment.
and that daily application to affected skin of up to 80 micrograms had no detectable systemic effects in patients with psoriasis vulgaris. However, patient number in all the studies was low.

8.2.2 Long term data is available from two long-term projects. **H 322000-12/91** studied 58 patients with plaque psoriasis treated with a maximum of 20-g ointment once daily for at least 12 weeks and up to 62 weeks. Systemic safety variables did not show any clinically relevant influence of Tacalcitol on calcium metabolism and it was considered a safe treatment. These results were supported by a large European multicentre study, **H 322020-7/95**, with 304 patients with plaque psoriasis receiving Tacalcitol ointment 4 micrograms/g applied once daily for 18 months. The conclusion was that there was no evidence of impaired systemic safety and key laboratory markers related to calcium haemostasis remained statistically unchanged.

8.2.3 Post Marketing surveillance of the use of Tacalcitol ointment in the treatment of psoriasis including the scalp, indicate that Tacalcitol ointment, even if not the ideal formulation for the hairy area is safe.

8.3 Conclusions on safety analysis
Tacalcitol lotion has shown good local tolerability. The systemic safety of Tacalcitol ointment in the treatment of psoriasis vulgaris has been proved both under high doses and also in the long term and postmarketing surveillance has not revealed any cause of concern regarding safety. Clinical studies involving the final lotion formulation conclude that the safety profile of Tacalcitol 4 micrograms/g lotion applied once daily on psoriasis affected skin is good.

9. EXPERT REPORT
A Clinical Expert Report written by Chairman of the Department of Dermatology, has been submitted. The conclusion of the report is that the applicant product is safe and efficacious.

10. SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

11. PATIENT INFORMATION LEAFLET
This is satisfactory.

12. LABELLING
This is satisfactory.

13. MARKETING AUTHORISATION FORM
This is satisfactory.

14. DISCUSSION
This is a national abridged standard application for a marketing authorisation for Curatoderm Lotion, PL 00327/0149. The present application is a line
extension of Curatoderm Ointment 4 micrograms/g, with both formulations having the same drug concentration and application frequency.

The applicant has submitted efficacy data from 4 controlled trials on a total of 307 adult patients with psoriasis vulgaris, treated once daily with the final Tacalcitol 4 micrograms/g lotion formulation. The clinical efficacy was conclusive in all studies.

Tacalcitol lotion has shown good local tolerability. The systemic safety of Tacalcitol ointment in the treatment of psoriasis vulgaris has been proved both under high doses and also in the long term and postmarketing surveillance has not revealed any cause of concern regarding safety. Clinical studies involving the final lotion formulation conclude that the safety profile of Tacalcitol 4 micrograms/g lotion applied once daily on psoriasis affected skin is good.

In addition, patient compliance is promoted by the once daily application of Curatoderm lotion, which can be performed in the evening.

It is reasonable to conclude that the applicant product will exhibit a good efficacy and safety profile.

14. **CONCLUSIONS**

The efficacy and safety of the product are satisfactory for the grant of product licence.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Curatoderm 4micrograms/g lotion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for application of this type.

EFFICACY
The efficacy of Curatoderm 4 micrograms / g Lotion has been well documented in the past. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for Curatoderm Ointment where necessary.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable. Extensive clinical experience with Curatoderm 4micrograms/g Lotion is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
CURATODERM 4 MICROGRAMS/G LOTION

PL 00327/0149

 STEPS TAKEN FOR ASSESSMENT

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<table>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 5\textsuperscript{th} July 2002</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 9\textsuperscript{th} September 2005</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested information relating to the quality dossiers on 4\textsuperscript{th} October 2006.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 21\textsuperscript{st} October 2006.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 19\textsuperscript{th} July 2007</td>
</tr>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Curatoderm 4 micrograms / g Lotion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Tacalcitol 4 micrograms/ g (as monohydrate)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Cutaneous emulsion
A white, thin emulsion

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Psoriasis vulgaris, especially on the scalp

4.2 Posology and method of administration
Adults and the Elderly: Apply once daily to the affected areas, preferably at bedtime. The amount applied should not exceed 10 ml of lotion/day. When used together with Curatoderm Ointment, the total dose of tacalcitol should not exceed 280 micrograms/week (e.g. 30 ml of Curatoderm Lotion plus 40 g of Curatoderm Ointment). Normally duration of treatment depends on the severity of the lesions and should be decided by the physician.

There is clinical trial experience with continuous and intermittent treatment in adults with tacalcitol ointment up to 18 months and with tacalcitol lotion for up to 8 weeks.

Curatoderm Lotion can be used on all areas of the body (including face, hairline, scalp, axilla and other flexures).  

Children: Not recommended. There is limited clinical experience with tacalcitol in children.

4.3 Contraindications
Hypersensitivity to any of the constituents. Hypercalcaemia. Other known disorders of calcium metabolism.

4.4 Special warnings and precautions for use
At the doctor’s discretion, in patients at risk of hypercalcaemia, or patients taking high Vitamin D preparations (in excess of 500 IU vitamin D) albumin corrected serum calcium levels should be closely monitored. Treatment should be stopped if hypercalcaemia occurs. Serum calcium levels should also be monitored in patients with renal impairment.

Care should be exercised in patients with generalised pustular or erythrodermic exfoliative psoriasis as the risk of hypercalcaemia may be enhanced.

When applying to the face avoid contact with the eyes. If Curatoderm Lotion accidentally comes into contact with the eyes, thorough rinsing with water is recommended. Patients should be advised to wash their hands after applying the lotion to avoid inadvertent transfer to other parts of the body.

4.5 Interaction with other medicinal products and other forms of interaction
No interactions are likely in patients using multivitamin preparations with up to 500 IU vitamin D.
UVB radiation can be combined with Curatoderm Lotion. This approach increases the efficacy of tacalcitol treatment and shortens the radiation period. UV radiation should be given in the morning and Curatoderm Lotion at bedtime. There has been limited experience of the concomitant use of tacalcitol with topical corticosteroids, urea, emollients, dithranol cream and PUVA.

4.6 Pregnancy and lactation

For Curatoderm Lotion no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal / foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

It is not known whether tacalcitol is excreted in human milk. Given the low systemic exposure in humans following topical treatment with tacalcitol, it is probably not necessary to stop breast-feeding during treatment, unless the breast is affected. In that case, either the breast area should not be treated in lactating women who are breast-feeding or breast-feeding should be stopped.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Skin and subcutaneous tissue disorders: Local skin reactions (itching, erythema, burning) are uncommon. In general, these local reactions are mild and transient.

4.9 Overdose

Overdosing by ingestion of a lotion is very unlikely. It cannot be excluded that topical application of excessive amounts may lead to hypercalcaemia. In this case Curatoderm treatment and other possible vitamin D or calcium supplement intakes must be stopped until serum calcium returns to normal.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antipsoriatics for topical use
ATC Code: D05A X04.

Tacalcitol is a vitamin D₃ derivative, which inhibits keratinocyte hyper-proliferation and induces differentiation of these cells. The normalisation of these mechanisms is the basis for the efficacy in the treatment of psoriasis. In biopsies from patients treated with tacalcitol specific indicators for inflammation were improved. Tacalcitol binds to the keratinocyte vitamin D receptor to the same extent as natural active vitamin D₃.

5.2 Pharmacokinetic properties

Single or repeated application of tacalcitol ointment in humans results in less than 0.5% of the drug being systemically absorbed through psoriatic skin. Tacalcitol is completely bound to plasma proteins (vitamin D binding protein) The main metabolite is 1α, 24, 25 (OH)₃ vitamin D₃, a metabolite shared with the natural active vitamin, with 5-10 times less vitamin D activity. Tacalcitol and metabolites are excreted mainly in the faeces in rat and dog studies with excretion in urine in man. It cannot therefore be excluded that if there is sufficient systemic absorption accumulation may occur in patients with renal failure.

5.3 Preclinical safety data

The toxic effects of tacalcitol are typical of those expected from excessive pharmacological activity of calciferols and resultant hypercalcaemia. The NOEL in rats treated subcutaneously for 12 months was 4ng/kg/day.

Reproductive toxicity studies in rats and rabbits revealed no teratogenic effects.
Tacalcitol was negative in a battery of *in vitro* and *in vivo* mutagenicity studies.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Purified water, light liquid paraffin, medium-chain triglycerides, propylene glycol, octyl dodecanol, macrogol (21) stearylether, diisopropyl adipate, phenoxyethanol, disodium phosphate dodecahydrate, xanthan gum, potassium dihydrogen phosphate, disodium edetate, dodecyl gallate

#### 6.2 Incompatibilities

Tacalcitol must not be mixed with salicylic acid

#### 6.3 Shelf life

2 years

6 months after first opening the container

#### 6.4 Special precautions for storage

Do not store above 25°C.

Keep bottle in the outer carton.

#### 6.5 Nature and contents of container

20 ml, 30 ml or 50 ml HDPE plastic bottle (with translucent sight stripes at one or both of the smaller sides) and with HDPE screw cap.

#### 6.6 Special precautions for disposal

External use only

### 7 MARKETING AUTHORISATION HOLDER

Crookes Healthcare Limited
1 Thane Road West
Nottingham
NG2 3AA
UK

### 8 MARKETING AUTHORISATION NUMBER(S)

PL 00327/0149

### 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/07/2007

### 10 DATE OF REVISION OF THE TEXT

19/07/2007
PACKAGE LEAFLET: INFORMATION FOR THE USER
Curatoderm 4 micrograms/g Lotion
Tálcitol

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet please tell your doctor or pharmacist.

In this leaflet:
1. What Curatoderm Lotion is and what it is used for
2. Before you use Curatoderm Lotion
3. How to use Curatoderm Lotion
4. Possible side effects
5. Storing your Curatoderm Lotion
6. Further information

1. WHAT CURATODERM LOTION IS AND WHAT IT IS USED FOR:

Curatoderm Lotion contains tálcitol which is a drug that belongs to a group of medicines called antipsoriatics and is a vitamin D derivative.

Curatoderm Lotion is used to treat a condition known as psoriasis vulgaris especially on the scalp. Psoriasis is a skin disorder in which itchy, red, flaky patches appear on the skin or scalp. Within affected areas of skin, new cells are being produced faster than normal, but old dead cells are only being shed at the normal rate. As live skin cells accumulate, the skin becomes thickened and inflamed. Curatoderm Lotion works by slowing down cell production and bringing it back to normal and helps to reduce inflammation.

2. BEFORE YOU USE CURATODERM LOTION

Do not use Curatoderm Lotion:
- if you are allergic (hypersensitive) to tálcitol or any of the other ingredients listed in section 6.
- if you have ever had problems with too much calcium in your blood (hypercalcæmia or other disorders of calcium metabolism).

If this applies to you, do not use this medicine and speak to your doctor.

Take special care with Curatoderm Lotion:
When applying Curatoderm Lotion to the face. Do not allow the lotion to come in contact with the eyes. If it does, rinse thoroughly with water.

Please tell your doctor if:
- you have or have had problems with your kidneys,
- you have a particular type of psoriasis called generalized pustular psoriasis or erythrodermic exfoliative psoriasis,
- you are taking high doses of vitamin D (more than 500IU).

Your doctor may want to check the level of calcium in your blood if you have any of these conditions.

**Using other medicines or therapies**
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Especially:
- Multivitamin products or vitamin D

If you are receiving ultraviolet (UV) therapy, this should be given in the morning and Curatoderm Lotion used at bedtime.

**Pregnancy and breast-feeding**
The potential risk to the baby if Curatoderm Lotion is used during pregnancy is unknown. Therefore if you are pregnant or likely to become pregnant whilst using Curatoderm Lotion, make sure your doctor knows.

It is not known if Curatoderm Lotion passes into breast milk. Only a small amount of tacalcitol is absorbed into the body after skin treatment. It is probably not necessary to stop breast-feeding during treatment. If the breast area is affected by psoriasis, it is recommended that the breast area is not treated with Curatoderm Lotion or breast-feeding should be stopped. Discuss this with your doctor.

**3. HOW TO TAKE CURATODERM LOTION:**

Children: Curatoderm Lotion is not recommended for use in children, as there is limited experience.

Curatoderm Lotion is for use by adults including the elderly.

Curatoderm Lotion can be used on all areas of the body including face, hairline, scalp, armpits, elbows and knees.

Follow your doctor’s instructions for use exactly. The following are general guidelines:
- Apply Curatoderm Lotion once a day, preferably at bedtime.
- Do not use more than 10ml of lotion (equivalent to 2 teaspoons) each day.
Curatoderm is also available as an ointment. If you are also using Curatoderm Ointment, take into account that the quantity of applied tacalcitol adds up. You should not use more than 280 micrograms of tacalcitol per week. That is for example equivalent to 30ml Curatoderm Lotion plus 40g Curatoderm Ointment per week.

- Spread the lotion over the areas of skin affected by psoriasis and then rub it in.
- To treat the scalp, part your hair and place the nozzle close to the affected area, apply a few drops, then rub the lotion in gently.
- Avoid transfer of the lotion to other areas of the body not affected by psoriasis.
- Wash your hands as soon as you have finished applying the lotion.
- Your doctor will tell you for how long you need to use the lotion.

**If you use more Curatoderm Lotion than you should**
If you have used too much Curatoderm Lotion, tell your doctor as it may be necessary to check the amount of calcium in your blood.

**If you forget to use Curatoderm Lotion**
If you forget to use Curatoderm Lotion at the usual time, use it as soon as you remember, then carry on as before.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Curatoderm Lotion can cause side effects, although not everybody gets them.

Local skin reactions such as itching, burning or redness may be experienced. These are usually mild effects and don’t last very long.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5. HOW TO STORE CURATODERM LOTION**

Keep out of the reach and sight of children.

Keep the bottle in the outer carton in order to protect it from light.
Do not store above 25°C.
Do not use Curatoderm Lotion after the expiry date that is stated on the label.
Do not use for longer than 6 months after first opening the container. Write the date of first opening the container bottle on the carton label.
Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Curatoderm Lotion contains
The active substance is tacalcitol

The other ingredients are: purified water, light liquid paraffin, medium-chain triglycerides, propylene glycol, octyldecanol, macrogol (21) steareylether, diisopropyl adipate, phenoxyethanol, disodium phosphate dodecahydrate, xanthan gum, potassium dihydrogen phosphate, disodium edetate, dodecyl gallate.

What Curatoderm Lotion looks like and contents of the pack
Curatoderm Lotion is a white, thin cutaneous emulsion.

Your medicinal product comes in either 20 ml, 30 ml or 50 ml HDPE plastic bottle (with translucent sight stripes at one or both of the smaller sides) and with HDPE screw cap. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Crookes Healthcare Limited, 1 Thane Road West, Nottingham NG2 3AA, United Kingdom

Manufacturer
Hermal, D-21465 Reinbek, Germany

This leaflet was last approved in
PMS 293 Vollton + gr.
PMS 2995
Use as directed by the doctor.

- Read the package leaflet before use.
- For external use only.
- KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
- Use within six months of first opening.
- Do not store above 25°C.
- Keep bottle in the outer carton.

**Version control**

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Bitte beachten: Farbdruck ist nicht farbverbindlich!
Attention: Please notice that the colour print is not obligatory!

Version: 2 / 19.02.2007
Programm: FreeHand 9.0
Schriften: Open Sans MM PL Leetos

PD5-Vorhaben XXX

Techn. Ausführung ok!

 Datum Unterschrift

Datum Unterschrift

Datum Unterschrift
UKPAR Curatoderm 4 Micrograms/g Lotion

1 g Lotion contains: Active ingredients: Tretinoin 4 micrograms/g. Other ingredients: Purified water, light liquid paraffin, macrogol 400, PEG 1500, macrogol 200, magnesium, disodium ethylenediaminetetraacetic acid, hydroxyisobutylcellulose, sodium hydroxide, citric acid, sodium hydroxide, citric acid, sodium hydroxide.

Store in a cool place within six months of opening.

Do not use above 25°C.

Keep bottle in the outer carton.

Croda Healthcare Ltd.,
Nottingham, NG2 3A, UK

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Version control

Preparat: Curatoderm Lotion
Pakungsgröße: 50 ml
Größe: 68
Größe: 38 x 55 mm

PHS-Code: XXX

Datum: 3/15.02.2007
Techn. Ausführung ok!

Datum: Unterschrift

Freigabe zum Druck
Datum: Unterschrift

Bitte beachten: Farbendruck ist nicht farbverbindlich!
Achtung: Please notice that the colour print is not obligatory!