CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Calcipotriol 0.05 mg/g, ointment Sandoz B.V., the Netherlands

calcipotriol

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0730/001/DC
Registration number in the Netherlands: RVG 33409

Date of first publication: 16 March 2009
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Pharmacotherapeutic group:	other antipsoriatics for topical use
ATC code:	D05AX02
Route of administration:	cutaneous
Therapeutic indication:	the topical treatment of mild to moderately severe psoriasis (*psoriasis vulgaris*).
Prescription status:	prescription only
Date of authorisation in NL:	1 May 2007
Concerned Member States:	decentralised procedure with DE, DK and IE
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Calcipotriol 0.05 mg/g, ointment from Sandoz B.V., the Netherlands. The date of authorisation was on 1 May 2007 in the Netherlands. The product is indicated the topical treatment of mild to moderately severe psoriasis (*psoriasis vulgaris*).

A comprehensive description of the indications and posology is given in the SPC.

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 mechanism. 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Daivonex 50 mg/g, ointment, which has been registered in Denmark by LEO Pharma, since 1990. In the RMS (NL), Daivonex ointment was authorised in 1992 (RVG 15334). In addition, reference is made to Daivonex authorisations in the individual member states (reference product).

The medicinal product is a locally applied and local acting drug for which bioequivalence cannot be demonstrated through bioavailability studies. As required by article 10(3) a comparative clinical trial has been performed to demonstrate therapeutic equivalence as showing bioequivalence by pharmacokinetics is not possible. The marketing authorisation is therefore granted based on article 10 (3) of Directive 2001/83/EC in DE, DK and IE.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. The current product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients
The active substance is calcipotriol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU. Calcipotriol is a white to off-white crystalline powder; the substance is soluble in chloroform, dichloromethane, acetone, methyl formate, ethyl acetate, dimethyl sulfoxide, glycerol, and other organic solvents. It is practically insoluble in water. Pre-calcipotriol as an isomer formed in the product by a reversible transition, by a slow process which starts when calcipotriol is dissolved and continues until equilibrium is reached, is mentioned. It is influenced by temperature. Therefore, pre-calcipotriol is not a true impurity, and the activity of calcipotriol is due to both substances.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
The synthetic process is described from simple compounds, ending in a final purification phase based on re-crystallisation. The molecular structure of the substance is adequately characterised. All reactions and purifications are under adequate control, assuring the exclusion of carried-over impurities to acceptable levels.

Specification
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional specifications for residual solvents and particle size. In solutions calcipotriol slowly and partially changes into pre-calcipotiol. The two isomers are in equilibrium. The activity is due to both isomers, so pre-calcipotriol is not an impurity. The assay is calculated as the sum of the assays of the isomers.
Batch analytical data demonstrating compliance with this specification have been provided for 3 full-scale batches.

Stability data on the active substance have been provided for 6 full-scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 30 months. Based on the data submitted, an adequate retest period could be granted of 30 months.

Medicinal Product

Composition
Calcipotriol 0.05 mg/g, ointment contains 0.05 mg (is equal to 50 micrograms) of calcipotriol per gram of ointment and is white to off-white.

The ointment is packed in a membrane closed aluminium tube with polyethylene neck and screw cap.

The excipients are: macrogol stearyl ether, disodium edetate, disodium phosphate dihydrate, α-Tocopheryl acetate, propylene glycol (E490), paraffin (light liquid), water (purified), and paraffin (white soft).

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

Pharmaceutical development
The composition of the test product is qualitatively similar to the composition of the reference product. The MAH uses a 5% stability overage; this is justified. The purity profile of the test ointment is comparable to the purity of the reference product of comparable age.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 commercial scale batches in accordance with the relevant European guidelines. The routine IPC's and release tests were performed. In addition, special attention was paid to the homogeneity of the bulk ointment mass before filling. Viscosity, water content, related substance levels and microbiological purity were also checked at a number of sampling times during the tube filling stage.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product includes tests for appearance, viscosity, water content, identification, assay, related substances, microbiological purity and minimum fill. Most test methods are directly from the Ph.Eur. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data of 3 commercial-scale batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Container Closure System
Membrane-closed, lacquered aluminium tubes with PE neck and screw cap, contents 30 and 120 g. This is a suitable packaging system for cutaneous ointments.

Stability tests on the finished product
Stability data on the product have been provided for 6 full-scale batches (25ºC/60%RH and 40ºC/75%RH) in accordance with applicable European guidelines demonstrating the stability of the product over 24 months. On basis of the data submitted, a shelf life was granted of 2 years.

In-use stability
Stability data have been provided demonstrating that the product remains stable for 3 months following first opening. The labelled storage conditions are: *"Do not store above 25°C."*, *"Do not refrigerate or freeze."* and *"Store in the original package."*

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Daivonex, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of calcipotriol released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Clinical efficacy and safety
Calcipotriol is a well-known active substance with established efficacy and tolerability in psoriasis. Calcipotriol 0.05 mg/g ointment is a locally applied and local acting drug. As there is almost no systemic absorption, bioequivalence cannot be demonstrated through pharmacokinetic studies. Hence, the evidence of similarity to the innovator product has to come from comparative therapeutic equivalence studies (Directive 2001/83/EC, Article 10(3)).

Accordingly the MAH submitted one randomised, double-blind, vehicle-controlled clinical trial evaluating the efficacy and safety of Calcipotriol ointment and the innovator product i.e. Daivonex® ointment (Study 0903/2).

Design
Study 0903/2 concerned a randomized double-blind, three arms, placebo-ointment controlled, clinical trial in patients with mild to moderate psoriasis. The main objective was to show equivalent efficacy of the generic product (Calcipotriol 50 micrograms/g ointment) versus that of the innovator product (Daivonex, LEO Pharma B.V.).

Patients included received Calcipotriol 50 micrograms/g ointment or Daivonex (LEO Pharma B.V.) or placebo ointment (so-called vehicle) in a 4:4:1 ratio. The ointment was applied in a thin layer twice daily (morning and evening) to the affected areas. The maximal amount of ointment was 100 g/week. The study lasted 8 weeks.

The main assessment concerned the severity of psoriasis as measured by the Psoriasis Area and Severity Index (PASI), a global assessment of efficacy and safety. The PASI, as the name suggests, sums the severity of erythema, plaque elevation and desquamation taking into account the area involved. The PASI was modified excluding the head area as this area was not treated with study medication.

The primary efficacy endpoint was the percentage change in PASI from baseline to the end of treatment. For the primary comparison, Calcipotriol ointment versus Daivonex ointment, the equivalence was assessed by comparing the 95% confidence interval for the difference (see table below). If the confidence interval of the difference is within -10%, 10%, both products were considered therapeutic equivalent. The primary analysis set was the Per Protocol (PP) Population. Additional analyses based on the ITT population were used for confirmation. The PP population includes all patients randomised who completed the trial without any major protocol violations. For the analysis based on the ITT Population the method of last observation carried forward (LOCF) was applied. Results for both analyses should be confirmative. All secondary analyses were based on the ITT Population.

Safety evaluations were based on the Safety Population. All safety endpoints were summarized using descriptive statistics.

Baseline data
All the patients had a diagnosis of *psoriasis vulgaris*. The three treatment arms were well matched for demographic characteristics and disease duration. The mean (SD) duration of psoriasis was 20.3 (13.21) years. In table 1 the number of patients, some baseline features and main results are presented.

Ninety–six percent of the patients (96%) had previously used topical corticosteroids, 63% had previously used calcipotriol and 72% had used other treatments for psoriasis. Use of these different psoriasis treatments was generally comparable between the study groups. A higher proportion of patients in the

placebo group had previously used calcipotriol (78%) compared to patients in the Calcipotriol ointment group (63%) or the Daivonex group (59%).

The most common reasons for withdrawal were: withdrawal of consent, psoriasis type adverse events and poor patient compliance.
A small proportion of patients used concurrent medical conditions: nine patients (8%) in the Calcipotriol ointment (from Sandoz) group, ten patients (9%) in the Daivonex group and one patient (3%) in the placebo group.

Both active treatments separate from placebo. Hence a prerequisite for assessing the relative efficacy of the active compounds has been fulfilled.

Results

Table I Results, n of patients, baseline features, main endpoint (PP population)

	Calcipotriol Sandoz ointment	**Daivonex ointment**	**Placebo**	**Comments**
n-randomised n-per protocol n of withdrawals	108 105 4 (3.7%)	108 103 7 (6.5%)	27 27 (7.4%)	
Age (ITT population)	50.1 (13.4)	49.0 (14.0)	50.7 (11.3)	Mean, SD
Compliance[A]	95%	95%	96%	
PASI Score				
Baseline	10.3 (3.80)	10.5 (3.77)	10.4 (4.02)	Mean, SD
Week 8	*3.4 (2.42)*	*3.4 (2.94)*	*5.4 (3.31)*	
Percentage change in PASI (PP population)	**-65.5% (24.06)**	**-68.9% (20.41)**	**-42.1% (41.02)**	**Primary endpoint: mean , SD**
Analysis				
vs. Placebo				
Difference	-23.4%	-26.8%		
$CI_{95\%}$	-34.4% ; -12.4%	-37.8% ; -15.8%		
Calcipotriol-Daivonex Difference	**3.4%**			**Main analysis**
$CI_{95\%}$	**-3.5%; 10.34%**			

[A]*Compliance: proportion of subjects with a good (missing applications less than 3 times) or very good compliance (applied the medication regularly and in accordance to the instructions) and not missing follow-up examinations.*

Treatment difference between Calcipotriol from Sandoz and Daivonex ointment was -3.396 ($CI_{95\%}$- -10.336; +3.544, 36) percentage points in the PP population. The upper bound of the 95% confidence interval was just outside the designated 10% limit for equivalence. The results for additional analysis in the ITT population were 1.852 (-5.529, 9.232).

Additional results from non-parametric analysis showed within the PP Population the difference in median percentage change in PASI from baseline to end of study after treatment with Calcipotriol and Daivonex

was 2.139 (-3.051, 7.516) percentage points. Comparing the 95% confidence interval with the equivalence interval of (-10, 10) equivalence between Calcipotriol and Daivonex was demonstrated. Within the ITT Population, using LOCF and without using LOCF, the median percentage change in PASI from baseline to end of study after treatment with Calcipotriol and Daivonex was 1.939 (-3.438, 7.486) percentage points and 1.826 (-3.403, 7.143) percentage points, respectively. Comparing the 95% confidence interval with the equivalence interval of (-10, 10) equivalence between Calcipotriol and Daivonex was again demonstrated in both analyses.

The percentage of patients achieving treatment success (marked improved, clear almost clear) as assessed by the investigator, were 61%, 65% and 22% for the Calcipotriol from Sandoz, Daivonex and placebo treatment groups, respectively.
The proportions of patients achieving a good response, as assessed by the patient, were 78%, 73% and 30% for the Calcipotriol from Sandoz, Daivonex and placebo treatment groups, respectively.

In conclusion: for a generic application the design of the submitted study was considered sufficient. However, during the procedure the clinical justification of the 10% equivalence margins and in fact equivalence margin have been discussed. The chosen equivalence value for the primary analysis was well justified with quoted references on the designs of studies with the comparator and other similar products. Most studies have used a difference of +10 percentage points between active treatments as being relevant. It is acknowledged that the 10% non-equivalence margin shown in the study has been just exceeded and thus formally equivalence has not been proven. However, this margin is just exceeded or just approached the 10% and equivalent efficacy has been demonstrated by the additional analyses. Therefore, it was concluded that therapeutic equivalence of Calcipotriol 0.05 mg/g ointment versus the innovator product is established and hence bridging to the Daivonex® dossier is justified.

The safety profiles of Calcipotriol from Sandoz and Daivonex are comparable. There were no unexpected adverse events in study 0903/2. Most of the adverse events were mild in severity.
Thirty-three patients (31%) experienced psoriasis type adverse events on Calcipotriol ointment from Sandoz, 37 patients (34%) on Daivonex and nine patients (33%) on placebo-ointment (table 2).Three patients in the active treatment groups had psoriasis type adverse events that lead to study withdrawal.

Table 2 Psoriasis type adverse events experienced by ≥ 10% of patients in any treatment group (Safety Population)

	Calcipotriol Sandoz Ointment (N= 108)	Daivonex Ointment (N=108)	Placebo Ointment (N=27)
Itching	20 (19%)	25 (23%)	8 (30%)
Burning sensation skin	16 (15%)	16 (15%)	3 (11%)
Erythema	13 (12%)	15 (14%)	2 (7%)
Dry skin	14 (13%)	10 (9%)	1 (4%)
Skin irritation	11 (10%)	7 (6%)	3 (11%)

Six patients (6%) on Calcipotriol ointment from Sandoz, seven patients (6%) on Daivonex and three patients (11%) on placebo experienced non-psoriasis type adverse events. The non-psoriasis type adverse events were mild in severity. None of these events were serious or lead to withdrawal.

No patients had albumin corrected serum calcium changes deemed clinically significant.

It was concluded that safety profiles of both active products appear to be similar. The study duration of 8 weeks is sufficient for this generic application. For long-term exposure the safety profile is already known for the innovator product. Both products have qualitatively similar formulations. The present exposure data are therefore sufficient and hence bridging to the Daivonex® dossier is justified.

Risk Management Plan

Calcipotriol was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of calcipotriol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Daivonex marketed by LEO Pharmaceuticals.

Readability test

The package leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The questionnaire contains 16 questions on the content of the PIL and three questions to obtain feedback on the general layout and appearance of the PIL. The test consisted of two rounds with 10 participants in the first round and 20 participants in the second round. Adults of either sex were recruited. The demographics, e.g. sex, age, occupation and highest educational achievement, of the test population were provided. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The first round showed that participants experienced some difficulty with two specific questions. In both cases, a recommended change to the questionnaire was adopted. In the second round, 96% of the participants were able to locate the requested information. In conclusion, the readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Calcipotriol is a well-known active substance with an established efficacy and tolerability in psoriasis.

Calcipotriol ointment 0.05 mg/g, ointment has a proven chemical-pharmaceutical quality and is essentially similar to Daivonex 50 mg/g, ointment. Daivonex is a well-known medicinal product with an established favourable efficacy and safety profile in psoriasis. .

Calcipotriol 0.05 mg/g ointment is a locally applied and local acting drug. As there is almost no systemic absorption, bioequivalence cannot be demonstrated through pharmacokinetic studies. Hence the evidence of similarity to the innovator product has to come from comparative therapeutic equivalence studies (Directive 2001/83/EC, Article 10(3)). Accordingly the applicant submitted one randomised, double-blind, vehicle-controlled clinical trial evaluating the efficacy and safety of Calcipotriol ointment and the innovator product i.e. Daivonex® ointment (Study 0903/2). It was concluded that therapeutic equivalence of Calcipotriol 0.05 mg/g ointment versus the innovator product is established and hence bridging to the Diavonex® dossier is justified.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other calcipotriol containing products.

The Board followed the advice of the assessors. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Calcipotriol 0.05 mg/g, ointment with the reference product, and have therefore granted a marketing authorisation.

The decentralised procedure was finished on 15 February 2007. Calcipotriol 0.05 mg/g, ointment was authorised in the Netherlands on 1 May 2007.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from February 2007 till February 2010.

The date for the first renewal will be: February 2012.

No post-approval commitments have been made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
LOCS	Last observation carried forward
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PASI	Psoriasis Area and Severity Index
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PP	Per protocol
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name and/or address of a manufacturer of the finished product.	NL/H/0730/ 001/IA/001	IA	28-11-2007	12-12-2007	Approval	N
Change in the qualitative and/or quantitative composition of the immediate packaging material. Semi-solid and liquid pharmaceutical forms	NL/H/0730/ 001/IB/002	IB	28-11-2007	28-12-2007	Approval	N
Change in the pack size of the finished product. Change in the fill-weight/fill volume of non-parenteral multi-dose products.	NL/H/0730/ 001/IB/003	IB	28-11-2007	28-12-2007	Approval	N
Addition of manufacturing site of the finished product (Salutas DE), with consequential changes: -Addition Salutas primary packaging -Scale up batch size -Alternative parameters for manufacturing process	NL/H/0730/ 001/II/004	II	10-12-2007	10-7-2008	Approval	N
Addition of API supplier	NL/H/0730/ 001/II/005	II	10-12-2007	10-7-2008	Approval	N
Change of the specs of the final product	NL/H/0730/ 001/II/006	II	10-4-2008	10-6-2008	Approval	N
Change in re-test period of the active substance.	NL/H/0730/ 001/IB/007	IB	19-2-2009	21-3-2009	Non approval	N
Update of DMF (applicant's part).	NL/H/0730/ 001/II/009	II	3-7-2009	11-1-2010	Approval	N