CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Calcipotriol Sandoz 0.05 mg/ml, cutaneous solution
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/1266/001/DC
Registration number in the Netherlands: RVG 101240

3 June 2010

Pharmacotherapeutic group:	other antipsoriatics for topical use
ATC code:	D05AX02
Route of administration:	cutaneous
Therapeutic indication:	mild to moderate scalp psoriasis
Prescription status:	prescription only
Date of authorisation in NL:	3 February 2009
Concerned Member States:	Decentralised procedure with DE, IE
Application type/legal basis:	Directive 2001/83/EC, 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 member states have granted a marketing authorisation for Calcipotriol Sandoz 0.05 mg/ml, cutaneous solution, from Sandoz B.V. The date of authorisation was on 3 February 2009 in the Netherlands. The product is indicated for the topical treatment of mild to moderate scalp psoriasis.

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. 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 hybrid application claiming essential similarity with the innovator product Daivonex cutaneous solution (NL RVG 21253) which has been registered in the Netherlands by Leo Pharma B.V. since 1997. 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.

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, as this is not required for a hybrid medicinal product.

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
The active substance is calcipotriol anhydrous, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Calcipotriol is a white to off-white crystalline powder, which is practically insoluble in water, and soluble in chloroform, dichloromethane, acetone, methyl formate, ethyl acetate, dimethyl sulfoxide, glycerol, and other organic solvents. Three isomers are mentioned: pre-calcipotriol, trans-calcipotriol, and 24-R-calcipotriol. They are also degradation products or related 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/EMEA 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
Calcipotriol is manufactured in 4 steps. The manufacturing process has been sufficiently described.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents. The loss on drying limit is tighter than the corresponding Ph.Eur. limit as are the limits for known related substances. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification has been provided for three full-scale batches.

Stability
Stability data on the active substance has been provided for 12 full-scale batches stored at -18 °C (48 months) and 2-8 °C (6 months). The batches were adequately stored. No specific up or downward trends were seen. The results under storage conditions of -18 °C ± 3 °C confirm the stability of the substance under the chosen storage conditions of -20 °C ± 5 °C. On the basis of the submitted results, the claimed re-test period could be granted: 12 months in well-closed containers, under inert gas protected from light.

** 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.*

Medicinal Product

Composition
Calcipotriol Sandoz 0.05 mg/ml is a clear, colourless solution with an odour of menthol.

The cutaneous solution is packed in polyethene bottles fitted with a polyethylene nozzle and closed with a polypropylene screw cap.

The excipients are: sodium citrate, hypromellose, propylene glycol, isopropyl alcohol, levomenthol, purified water.

Pharmaceutical development
The aim of development of Calcipotriol 0.005% scalp solution was to develop a product that would be essentially similar to the originator product manufactured by the innovator.The excipients are almost the same (qualitatively) as in the innovator product except for hypromellose. Hypromellose is widely used in oral and topical pharmaceutical formulations. Compared with other cellulose ethers it produces solutions of greater clarity with fewer undispersed fibers present.
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients used comply with their Ph.Eur. specifications. The aim of development of Calcipotriol 0.005% scalp solution was to develop a product that would be essentially similar to the innovator product. Pharmaceutical equivalence studies demonstrate that the quality of the product at issue is comparable to the innovator product. The impurity profile of both products comprises the same identified impurities.
Calcipotriol is sensitive to heat, light, acidic pH, oxidation and is incompatible with some solvents, especially those with acidic pH. Therefore, it was necessary to design an optimal manufacturing procedure where above mentioned risks are minimized. A 5 % overage of calcipotriol was incorporated in the formulation. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process of calcipotriol cutaneous solution is well known and standard. It was taken into consideration that calcipotriol is sensitive to light, oxidation and temperature. All the steps where calcipotriol was present, were performed protected from light. The manufacturing consists of dissolving, suspending and blending of solutions. The manufacturing process has been validated according to relevant European guidelines, except for stirring time and speed. Process validation data on the product has been presented for three full-scale batches.

Quality control of drug product
The product specification includes tests for appearance, pH, relative density, identity, assay, related substances/degradation products, microbiological quality and minimum fill. The release and shelf-life requirements/limits are not identical. Related substances/degradation products and assay are different. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site has been provided for three full-scale batches, demonstrating compliance with the release specification.

Container closure system
Each bottle contains 30, 60 or 120 ml. The packaging materials comply with Directive 2002/72/EC and the applicable Ph.Eur. monographs. Since the packaging material is conform the Ph.Eur. and the drug product is for topical use, no extraction study is necessary according to the guideline on plastic immediate packaging materials.
The maximum product should be applied twice daily. The maximum weekly dose should not exceed 60 ml. This is to be considered possible with the packaging materials used.

Microbiological attributes
The concentration of alcohols, *i.e.* propylene glycol and isopropyl alcohol, as presented in the composition of the drug product assures that there is no risk of microbial contamination and consequentially the addition of preservative is not needed. Stability study results of microbiological quality performed at the

end of shelf-life period of 2 years as well as 3 months results 'after opening' comply with quality requirements of the specification.
The efficacy of antimicrobial preservation was challenged on a sample of the product. Testing was performed according to Ph.Eur., demonstrating compliance with the criteria for topical preparations.

Stability tests on the finished product
Stability data on the product has been provided for three full-scale batches packed in 30 and 120 ml HDPE bottles stored at 25°C/40% RH (24 months), 30°C/65% RH (6 months) and 40°C/25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Under all three conditions in all batches tested a decrease in assay and an increase in both individual and total related substances/degradation products can be seen. A shelf-life of 24 months when stored below 25°C could be granted. The product should not be refrigerated or frozen.

Photostability testing
A photostability test was carried out on 30 ml bottles, stored previously for 22 months at long term conditions. A slight increase of total related substances/degradation products was observed. Therefore, the product information includes the warning: '*Keep the bottle in the outer carton in order to protect from light*.'

In-use stability
In-use stability testing was performed on two samples, stored previously for 22 months at 25°C/40% RH. The bottles were opened and stored at 20-22°C/45-65% RH for 3 months. Based on the results, a shelf-life after opening of three months was granted.

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 active substance has been available on the European market for more than 10 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

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

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

Calcipotriol Sandoz 0.05 mg/ml, cutaneous solution is a locally applied and locally acting drug. Therefore, bioequivalence cannot be demonstrated through bioavailability studies. Essential similarity with the innovator product is discussed below.

Clinical efficacy
The question whether the differences observed between the current product and the innovator Daivonex - in excipient content and concentration - are clinically relevant, has been addressed in one clinical study.

Design
The study included 163 adult patients with the clinical diagnosis of mild to moderate scalp psoriasis, of two years duration as a minimum. Treatment with Calcipotriol Sandoz 0.05 mg/ml (n=83) was compared to treatment with the innovator Daivonex (n=80) in this multi-centre, double-blind, six week study. A placebo arm was lacking.

Before start of the study a (medication) washout period of 2 weeks was applied and during the study the patients were not allowed to use any medication for scalp psoriasis, only non-medicated, neutral hair shampoo was permitted. No systemic corticosteroids, immunotherapy, and other drugs which can have impact on the clinical signs/symptoms of psoriasis were allowed.

Efficacy was measured as the improvement in the severity of the psoriasis clinical signs (erythema, thickening, desquamation and itching as scored on a 4-point scale by an investigator and the patients self-assessed itching also on this 4-point scale (0=absent, 1=slight, 2=moderate, 3=severe).
The total sign score (TSS) was calculated for each assessment from the clinical signs data as the sum of the erythema, thickening, desquamation and itching grades (in total a score of 12 was the maximum).
Also mean size of all lesions on the scalp at baseline and at 6 weeks was assessed.
Time-points of assessment were at baseline and after 2, 4 and 6 weeks.

At the end of the therapy both the investigators and patients assessed overall treatment efficacy according to a 6-point scale as response from baseline:
4= excellent, all signs eliminated,
3= good, majority of signs/symptoms improved, skin alteration hardly visible,
2= satisfactory, visible improvement of signs/symptoms,
1= bad, improvement of signs/symptoms hardly visible,
0= no effect, no improvement of signs/symptoms,
-1= worsening of signs/symptoms).

Patient characteristics
The two groups were comparable in baseline characteristics. The mean age of the patients was 40 years, more men were included (98 vs. 65 females), the mean duration of psoriasis vulgaris was 15 years and most patients had moderate psoriasis. No patients with severe psoriasis vulgaris were included.

Results
For both treatment groups, the mean size of scalp lesions was significantly less than at baseline (see Table I).

Table 1. Mean size of all psoriatic lesions on the scalp

Therapy	Check-up	N	Mean	Std. Deviation	Std. Error Mean
Daivonex	Baseline	80	142.5781	138.9904	15.5396
	Week 6	69	59.4964	101.4482	12.2129
Calcipotriol scalp solution	Baseline	83	124.9819	132.2414	14.5154
	Week 6	76	54.5461	94.9035	10.8862

Also, the MAH concludes that both groups showed marked and similar improvement in the severity of the clinical signs of scalp psoriasis (erythema, thickening, desquamation and itching), as presented in Table 2.

Table 2. Clinical efficacy study (number of patients in %)

		Baseline		Week 6	
		daivonex	Calcipotriol	daivonex	calcipotriol
Erythema	none	0%	0%	42%	34%
	mild	11%	8%	36%	54%
	moderate	53%	61%	17%	8%
	severe	35%	30%	4%	4%
Thickening	none	0%	0%	70%	66%
	mild	6%	7%	26%	29%
	moderate	70%	80%	4%	4%
	severe	24%	13%	0%	1%
Desquamation	none	0%	0%	55%	57%
	mild	10%	11%	32%	30%

	moderate	55%	59%	10%	9%
	severe	35%	30%	3%	4%
Itching	none	23%	22%	88%	83%
	mild	46%	33%	10%	14%
	moderate	28%	42%	1%	3%
	severe	4%	4%	0%	0%

At baseline the mean total signs score (TSS) was 7.8 in the daivonex group and 7.75 in the calcipotriol group (Table 3). This decreased gradually at subsequent visits, such that by the end of treatment the mean TSS values were 1.93 and 2.03 respectively (no significant difference between groups). The global assessment of efficacy of treatment following completion of treatment was scored on a 6 point scale
According to the physician assessment, the majority of patients exhibited an improvement to grade 3 or 4 by week 6 (in daivonex 38% grade 3 and 41% grade 4, in the calcipotriol group 46% grade 3 and 38% grade 4.). The patient's global efficacy assessment was similar to those scored by the physician.

Table 3. Average Total Sign Score (TSS)

	Therapy	N	Mean	Std. Deviation	Std. Error Mean
Week 0	Daivonex	80	7.7875	1.72615	0.19299
	Calcipotriol scalp solution	83	7.747	1.59911	0.17553
Week 2	Daivonex	80	5.25	1.92584	0.21532
	Calcipotriol scalp solution	80	5.3375	2.03727	0.22777
Week 4	Daivonex	75	3.2133	1.99522	0.23039
	Calcipotriol scalp solution	78	3.4487	2.16013	0.24459
Week 6	Daivonex	69	1.9275	2.03873	0.24543
	Calcipotriol scalp solution	76	2.0263	2.26847	0.26021

Evaluation of results
The MAH did not define *a priori* what the aim of the study was: to demonstrate non-inferiority or superiority. The non-inferiority margins were not defined either. In addition, a placebo-arm is lacking in this study. The fact that the clinical efficacy had to be assessed on the basis of one study without a placebo arm and with a *post hoc* definition of non-inferiority margins, made the evaluation problematic.

Two member states raised a major objection about the lack of a placebo-controlled study. It was agreed that such a study would have ensured assay sensitivity.
In the first round it was concluded that the equivalence in efficacy between Calcipotriol Sandoz 0.05 mg/ml cutaneous solution and Daivonex solution was not convincingly demonstrated. Therefore the MAH provided data for additional assessment. A responder (or treatment success) was either complete clearance of the lesions (grade 4) or a marked improvement in most of the clinical signs (grade 3). Based on the responders' rates and small corresponding intervals, i.e. 78.5% responders in the Daivonex group and 83.8% in the Calcipotriol Sandoz group (difference -5.26% , CI 95% -17.412% ; 6.874%), with a numerical favour for the Calcipotriol Sandoz arm, non-inferiority to the innovator product has been sufficiently demonstrated. From the literature is is known that the responders rate in a placebo group is 17% to 23% versus round 60% in the Daivonex® arm. Despite not having included a placebo arm in the study the MAH has been able to provide sufficient argumentation demonstrating the clinical efficacy of Calcipotriol 0.005% scalp solution which is comparable to the efficacy of the originator and separates from placebo.

Clinical safety

No new safety issues emerged in the clinical study submitted by the MAH. Hypercalcaemia and hypercalciuria were not mentioned in the submitted dossier. Serum calcium has not been measured, because in two originator's studies on a total of 265 patients (Green *et al*., 1994; Klaber *et al.*, 1994) no change in serum calcium was detected. Additionally, the cutaneous solution is used for scalp psoriasis, and therefore it is used on a much smaller area in comparison to ointment or cream formulation.

One member state had a major objection concerning the risk of laryngospasm in children below 2 years, due to one of the excipients (levomenthol). Although this well known safety issue was recognized, there was no sufficient evidence for inclusion of a contraindication. The concentration of menthol is much lower than the therapeutic concentration in antitussiva. Moreover, the calcipotriol 0.05 mg/ml cutaneous solution will not be used in young children because of the later onset of disease and because there is a recommendation in SPC section 4.2 not to use this product in children. The issue is also indirectly covered with the warning in section 4.4 of the SPC. This is similar to the SPC of the innovator and of other topical calcipotriol products. For these reasons a contraindication in children was not considered necessary.

Risk management plan

Calcipotriol was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance calcipotriol. The safety profile of calcipotriol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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

Readability test

A bridging report was provided which for Calcipotriol ointment with the readability test for Calcipotriol ointment (procedures NL/H/729-731/91/DC, NL license RVG 34408-34410). See below for initial readability test.

The package leaflet 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 consisted of 16 questions on the content of the PIL and three questions to obtain feedback on the general layout and appearance of the PIL. A sufficient number of questions have been used testing traceability, comprehension and applicability, *i.e.* can the patient find the information quickly and easily, does he/she understand it and act on it appropriately.
Two test rounds were performed. Adults of either sex were recruited. The demographics, *e.g.* sex, age, occupation and highest educational achievement, of the test population were provided and deemed sufficient.
A first test was performed with 10 participants, leading to the following results: 90.63% of the participants were able to locate the requested information, all of whom were able to give the correct answer. The first round showed that participants experienced some difficulty with two specific questions). In both cases, a recommended change to the questionnaire was given. These recommendations were adopted, together with further minor amendments to the leaflet from the prior round.
The second test was performed with 20 participants. The participants able to locate the information increased to 95.94%, with all participants giving the correct answer. This was attributable to marked improvements in the response to question 2. The recommended change to one question failed to have a significant impact on the participant's ability to find the correct information.
After the second test, no further changes to the leaflet are warranted. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Calcipotriol Sandoz 0.05 mg/ml, cutaneous solution has a proven chemical-pharmaceutical quality and is a hybrid form of Daivonex cutaneous solution. Daivonex is a well-known medicinal product with an established favourable efficacy and safety profile.

Both the reference and current product are locally applied and local acting drugs. 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 multi-centre, double-blind, six week clinical study evaluating the efficacy and safety of Calcipotriol Sandoz and the innovator product, i.e. Daivonex cutaneous solution. Although the study showed some deficiencies (see II.3 Clinical aspects), it was concluded that non-inferiority of Calcipotriol Sandoz 0.05 mg/ml to the innovator product was established, and hence bridging to the Diavonex dossier is justified.
Calcipotriol Sandoz is an aqueous solution for cutaneous use, the same as Daivonex, it contains the same concentration of the same active substance in the same amounts, the same excipients with only minor quantitative differences as the medicinal product currently approved. Although the study showed some deficiencies (see II.3 Clinical aspects), sufficient argumentation has been provided to demonstrate the clinical efficacy of Calcipotriol 0.005% scalp solution which is comparable to the efficacy of the originator and separates from placebo. It was concluded that non-inferiority of Calcipotriol Sandoz 0.05 mg/ml to the innovator product was established

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Calcipotriol Sandoz 0.05 mg/ml cutaneous solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 19 December 2008. Calcipotriol Sandoz 0.05 mg/ml, cutaneous solution was authorised in the Netherlands on 3 February 2009.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from registration to January 2011.

The date for the first renewal will be: 30 September 2011.

There were no post-approval commitments 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
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
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
TSS	Total Signs Score
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
Addition of a batch release site, not including batch control/testing.	NL/H/1266/ 001/IA/001	IA	3-7-2009	17-7-2009	Approval	N
Addition of a secondary packaging site.	NL/H/1266/ 001/IA/002	IA	3-7-2009	17-7-2009	Approval	N