CBG MEB

Public Assessment Report

Scientific discussion

Calcipotriol/Betamethason Sandoz 50 microgram/g + 0.5 mg/g, ointment

(calcipotriol monohydrate and betamethasone dipropionate)

NL/H/3441/001/DC

Date: 20 April 2016

This module reflects the scientific discussion for the approval of Calcipotriol/Betamethason Sandoz 50 microgram/g + 0.5 mg/g, ointment. The procedure was finalised on 14 December 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FAS	Full Analysis Set
ICH	International Conference of Harmonisation
IPGA	Investigator's Psoriasis Global Assessment
MAH	Marketing Authorisation Holder
PASI	Psoriasis Area and Severity Index
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PPGA	Patient's Psoriasis Global Assessment
PPS	Per Protocol Set
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Calcipotriol/Betamethason Sandoz 50 microgram/g + 0.5 mg/g, ointment from Sandoz B.V.

The product is indicated for the topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy in adults.

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

This decentralised procedure concerns a hybrid application claiming similarity with the innovator product Daivobet 50 microgram/g + 0.5 mg/g ointment which has been registered in Denmark by LEO Pharma A/S since 20 March 2001. In the Netherlands this product has been registered under the trade name Dovobet 50 microgram/g + 0.5 mg/g ointment (NL License RVG 27095) since 11 June 2002 through Mutual Recognition Procedure DK/H/0279/001.

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Spain, France, Lithuania, Luxembourg, Latvia, Ireland, Portugal, Slovenia, Sweden and United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as for locally applied and locally acting medicinal products such as ointments bioequivalence cannot be demonstrated trough bioavailability studies. A comparative clinical trial has been performed to demonstrate therapeutic equivalence.
Scientific advice was given by the CHMP in April 2013 concerning the design of the pivotal therapeutic equivalence study.

II. QUALITY ASPECTS

II.1 Introduction

Calcipotriol/Betamethason Sandoz is an off-white ointment and one gram contains as active substance 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate, micronised).

The ointment is packed in Aluminium/epoxyphenol tubes with a polypropylene or polyethylene screw cap. The tubes contain 15 g,30 g, 60 g or 120 g of ointment.

The excipients are: all-*rac*-α-tocopherol (E307), oleyl alcohol, paraffin light liquid and paraffin white soft.

II.2 Drug Substances

The active substances are calcipotriol (as monohydrate) and betamethasone (as dipropionate) and are established active substances described in the European Pharmacopoeia (Ph.Eur.). Calcipotriol monohydrate is a white or almost white crystalline powder, which is practically insoluble in water, freely soluble in ethanol (96%) and slightly soluble in methylene chloride. Calcipotriol monohydrate is dissolved during manufacturing procedure and partially precipitates in the final dosage form. The polymorphic form of precipitated calcipotriol in the final dosage form was confirmed during development. No change in polymorphic form during shelf life is expected, since calcipotriol monohydrate is the more stable form.
The active substance betamethasone dipropionate is a white to almost white, crystalline powder, which is practically insoluble in water, freely soluble in acetone and in methylene chloride and sparingly soluble in ethanol (96%). There is no evidence for crystal polymorphism in the reviewed literature; there is only one crystal form of the substance.

The CEP procedure is used for both active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included. The process of the active substances is assessed by the EDQM in order to grant a CEP.

Quality control of drug substances
The drug substance specifications for both active substances are based on the Ph.Eur. with additional tests in line with CEPs and in-house requirements. The specification is acceptable in view of the various European guidelines. Certificates of analysis have been provided for batches of each active substance, demonstrating compliance with the specifications.

Stability of drug substances
The active substance calcipotriol is stable for 36 months and the active substance betamethasone dipropionate for 5 years, when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. All excipients used are well known. The choices of the packaging and manufacturing process are justified in relation to the innovator product. Comparative data between test and reference product have been provided. Assay of the active substances and alfa-tocopherol, related substances and degradation products were similar.
Comparability of the rheology by viscosity between the test and reference product has been demonstrated.
The only difference between the test and reference product is the solvent used for the dissolution of calcipotriol monohydrate: oleyl alcohol (test formulation Calcipotriol/Betamethasone Sandoz) versus PPG-15 stearyl ether (reference formulation Daivobet). Compatibility with the excipient oleyl alcohol was confirmed on laboratory samples for both drug substances. The concentration of oleyl alcohol in the final product is well within the usual ranges for topical products; according to FDA Inactive Ingredients Guide registered topical product have a maximum of 10% of oleyl alcohol. Due to the difference in composition, pharmaceutical equivalence of the test product with the reference product cannot be assumed. However, based on clinical studies therapeutic equivalence has been demonstrated.

Manufacturing process
The analytical results and in-process-controls prove that the manufacturing process of calcipotriol/ betamethasone ointment is suitable to produce ointment with the desired quality. The validation tests show that the proposed manufacturing is capable of rendering a product with a homogenous distribution of both active substances. The different stages of the manufacture run without noticeable problems and no interruptions or disturbances in the course of the process were observed. The manufacturing process is a non-standard process due to the amount of active substance and the formation of a suspension during the manufacturing process. The process has been adequately validated, including three production scale batches.

Control of excipients
The excipients comply with Ph. Eur. requirements with additional in-house tests to ensure their suitability for the final ointment. The peroxide levels are adequately controlled. These specifications are acceptable.

Microbiological attributes
The manufacturing process is carried out at elevated temperature and no water is present during the manufacturing or in the final ointment. Final ointment is sealed in tubes preventing secondary contamination. The ointment itself is an unsuitable microbial growth medium due to its composition and lack of water. Microbiological attributes are nevertheless monitored by final dosage specification, as per Ph. Eur. requirements.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, description, viscosity, identity and assay of calcipotriol, betamethasone and alpha tocopherol, related substances, minimum fill, peroxide number, particle size, number of particles of calcipotriol and microbiological quality. 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 from four bulk batches filled into several tube sizes from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for four batches in accordance with applicable European guidelines, with fill volume 15 g and 120 g for 18 months (stored at 25°C/60% RH) and 12 months (stored at 30°C/65% RH). An accelerated stability study was not performed as the ointment base melts at the temperature around 40°C, which significantly alters the permeability of the matrix. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the highest and lowest content tubes, no differences were observed between the results from the different tube sizes and the composition per tube is similar. Therefore the bracketing approach is acceptable. No other trends were observed at long term or intermediate conditions.
An in-use stability study and transport stability study were conducted and no trends were observed, all data remained well within the specification. Hence, an in-use period of 1 year is acceptable.
From the photostability study it was demonstrated that the product is sensitive to light and should be stored in the original packaging. Since it is extremely unlikely that any patient would store the ointment elsewhere than in the tube there is no need to additionally specify storage in original package in order to protect from light.
The 2 year shelf-life period, if stored below 25ºC, is acceptable in view of the available stability data.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Calcipotriol/Betamethason Sandoz 50 microgram/g + 0.5 mg/g, ointment has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Calcipotriol/Betamethason Sandoz is intended for substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Calcipotriol/Betamethason Sandoz which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

Calcipotriol and betamethason are well-known active substances with established efficacy and tolerability.

Calcipotriol/Betamethason Sandoz 50 microgram/g + 0.5 mg/g, ointment is a locally applied and locally acting medicine. Therefore, bioequivalence cannot be demonstrated through bioavailability studies. Essential similarity with the innovator product is discussed below.

IV.1 Clinical efficacy

Therapeutic equivalence
For this hybrid application, the MAH has submitted a clinical study to demonstrate therapeutic equivalence between the test product Calcipotriol/Betamethason Sandoz 50 microgram/g + 0.5 mg/g, ointment (Sandoz B.V., the Netherlands) and the reference product Daivobet 50 microgram/g + 0.5 mg/g ointment (LEO Pharma A/S, Denmark). In addition, superiority of the test product to its vehicle (placebo) was tested as a one of the secondary objectives.

The study design, number of groups/patients, primary and secondary endpoints and statistical analysis are according to the recommendation made in the scientific advice by the Committee for Medicinal Products for Human Use (CHMP).

The study was conducted in compliance with GCP and relevant guideline from competent authorities ("Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents", CPMP/EWP/239/95 final, psoriasis guideline and scientific advice from the CHMP) as well as published literature were considered when the study was planned. Therefore, the quality and conduct of the study comply with current state of the art standards of clinical trials in psoriasis.

Design
A multi-centre, randomised, double-blind, active- and vehicle parallel-group phase III study was carried out in 443 males and females above 18 years suffering from chronic stable plaque psoriasis.
Each subject received a maximum daily dose of 15 g ointment of one of the 3 formulations (test, reference or placebo product, 4:4:1 ratio). The patients self-administered the products once daily in the evening at approximately the same time of the day for four weeks on the lesions on the trunk, arm and/or legs (not face and scalp). This treatment period was followed by an end-of-treatment examination.
Visits were scheduled at screening (visit 1), randomisation (visit 2), end of week 1 (visit 3), week 2 (visit 4), week 4 or end of treatment (visit 5), and follow-up (visit 6).
The randomization 4:4:1 to treatment with the test or reference product or placebo is as recommended. The study duration was 4 weeks which is adequate for the purpose of demonstrating therapeutic equivalence in plaque psoriasis.

The primary endpoint was considered as: the mean percent change from baseline in modified Psoriasis Area and Severity Index (PASI) score at the end of week 4. The primary endpoint is agreed. Patients with a PASI between 5 and 15 and a body surface area (BSA) of <30% could participate in the study, i.e. patients with mild-to-moderate psoriasis. A modified PASI was used in the study, since the head was not treated with the study medication and was not evaluated in the present study. The modified PASI, i.e. without effect on lesions on the face, was calculated from the area, grade erythema desquamation, and filtration in three parts of the body: trunk, upper and lower extremities. The

modified PASI could range between 0 and 64.8. The fact that a modified PASI was applied is agreed since effect on lesions on the face was to be excluded (in line with the indication of the innovator).
The following efficacy variables were considered as secondary endpoints:

- Mean percent change from baseline in modified PASI score at the end of week 1 and week 2
- Proportion of patients with a reduction in modified PASI score of >75% between baseline and end of week 4 (responders).
- Proportion of patients with a reduction in modified PASI score of >50% between baseline and end of week 4.
- Mean percent change from baseline in IPGA (Investigator's Psoriasis Global Assessment) at the end of week 1, week 2 and week 4.
- Mean percent change from baseline in PPGA (Patient's Psoriasis Global Assessment) at the end of week 1, week 2 and week 4.
- Proportion of patients with controlled disease (defined as "clear" or "almost clear") in IPGA at the end of week 4.
- Proportion of patients with controlled disease (defined as "clear" or almost clear") in PPGA at the end of week 4.
- Mean percent change from baseline in BSA measurement at the end of week 1, week 2, and week 4.

The BSA is part of the PASI and was determined as described above (grade 0 = no involvement, 1 = <10% up to grade 6 = 90% to 100%). The IPGA is an investigator-rated scale used for the determination of the severity and extent of psoriasis (0 = clear to 5 = severe). The patients rated the severity and extent of psoriasis compared to the pre-treatment state (including itching and burning) in the PPGA scale (-1 = worse, 0 = no change to 5 = clear). The secondary endpoints were subjected to descriptive and comparative statistical methods.

The proposed equivalence margin of ±10% of the 95% CI of the mean difference between the test and the reference product for the primary efficacy endpoint has been discussed during the scientific advice and has been accepted by the CHMP. It has also been used in other studies for this condition and it is considered that < 10% difference is not a clinically meaningful difference.
Since the CHMP had expressed the opinion that both Full Analysis Set (FAS) and Per Protocol Set (PPS) analysis will be relevant for assessment, these were provided in the report.

Results
A total number of 444 patients started the double-blind treatment with the study medications: 194 patients were allocated to the test medication (Calcipotriol/Betamethasone Sandoz), 201 patients to the reference drug (Daivobet) and 49 patients to the placebo formulation (test product vehicle). One subject was excluded for FAS analysis (n=443), since post-baseline data was unavailable. For the PPS analysis (n=398), 45 patients were excluded due to major protocol deviations.
The patients analysed were 171 patients treated with test, 186 patients treated with reference and 41 patients treated with placebo.

Primary endpoint
The mean percent change from baseline in the modified PASI score at the end of week 4 (visit 5) in the FAS is displayed in the figure below.

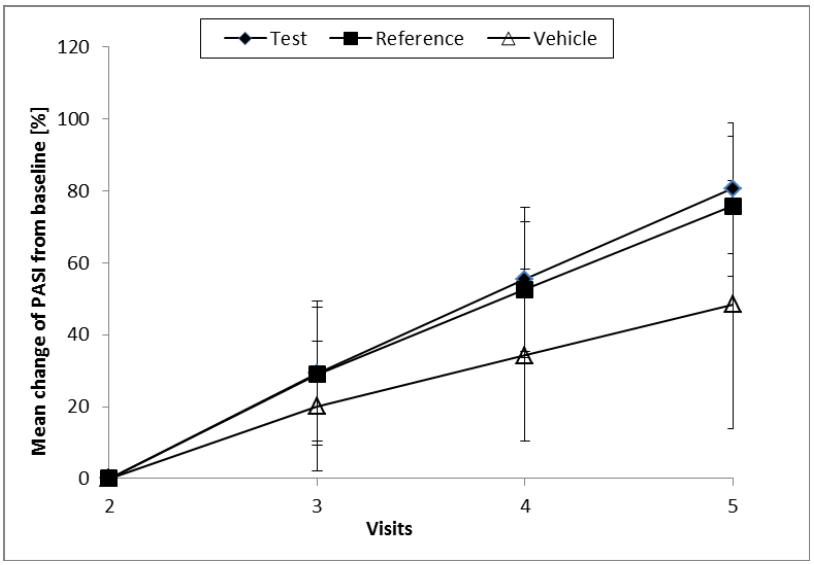

Figure 1: Mean (±SD) percentage change of the modified PASI from baseline to the end of double-blind treatment (FAS with LOCF imputation)

The change on the modified PASI score at week 4 was 80.7% in the test group, 75.7% in the reference group, and 48.4% in the placebo/vehicle group. The confirmatory analysis performed with the FAS showed that the test product is therapeutically equivalent to the reference product Daivobet, according to predefined equivalence margins of ±10% points (95% CI: 0.78-8.78).
Also the analysis of the primary endpoint comparing the test vs. reference treatment, performed in the PPS, showed that the test product is therapeutically equivalent to the reference, as the null hypotheses could be rejected using the equivalence margins of ±10% points (95% CI: 1.69-9.87). The mean percentage change from baseline in the modified PASI score at the end of week 4 (visit 5) is displayed in the figure below, showing a clear separation between the test/reference and placebo group already starting at visit 2.

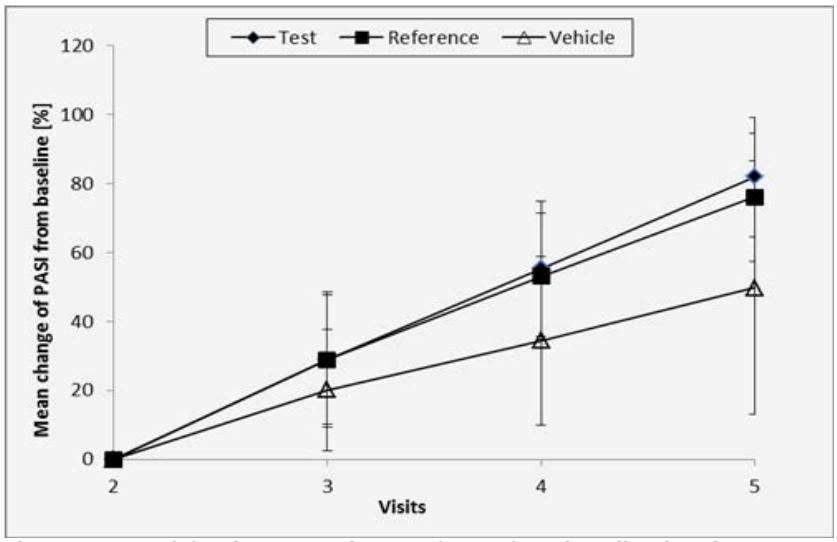

Figure 2: Mean (+/-SD) percent change of PASI from baseline (PPS)

Secondary endpoints
The results on secondary endpoints such as “mean percent change from baseline in modified PASI score at the end of week 1 and week 2“ confirmed equivalence of the test and innovator product and superiority to the vehicle early on in treatment. In terms of responder analysis (proportion of patients with a reduction of the modified PASI score of >75% between baseline and the end of week) the results are confirmative as well – with the test product performing better than the reference product.

Therapeutic equivalence is also supported by the results for the mean percentage change from baseline in the IPGA and PPGA at the end of week 1, week 2, and week 4 with no statistically significant difference for comparisons between test and innovator product both on the FAS and PPS analysis, and difference to the vehicle.

Conclusion
Based on the submitted clinical study, therapeutic equivalence was demonstrated between Calcipotriol/Betamethason Sandoz and Daivobet. In addition superiority of the test product to its vehicle has been demonstrated, which was one of the secondary objectives of the study.

IV.2 Clinical safety

With regard to safety, the data do not indicate any new safety concerns. In general the type and frequency of adverse events between current product and active comparator and in the placebo arm are comparable. In fact some adverse events from the skin and subcutaneous tissue disorder group are slightly higher in the active comparator arm. All together the safety data does not indicate relevant differences between test and reference product and hence is supportive that the test and reference products have a comparable safety profile.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Calcipotriol/Betamethason Sandoz.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypercalcaemia - HPA axis suppression - Skin atrophy
Important potential risks	- Potential enhancement of UV radiation induced skin cancer
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Daivobet. Calcipotriol/Betamethason Sandoz 50 microgram/g + 0,5 mg/g, ointment is a locally applied and locally acting product. As there is almost no systemic absorption, bioequivalence cannot be demonstrated through pharmacokinetic studies. The MAH demonstrated through a therapeutic equivalence study the essential similarity regarding the efficacy, safety and tolerability with the reference product. Risk management is adequately addressed. This hybrid formulation can be used instead of the reference product.

V. USER CONSULTATION

The MAH has provided a bridging report for the proposed packet leaflet of Calcipotriol/Betamethason Sandoz 50 microgram/g + 0.5 mg/g, ointment. With regard to content and key messages, the leaflet has been compared to the package leaflet of Daivobet 50 microgram/g + 0.5 mg/g, ointment (innovator leaflet), for which a successful user test has been conducted. The two leaflets are identical in content, differences in the proposed leaflet and the user tested leaflet cross-referenced are to reflect product specific information (only excipients).
Key messages for safe use are identical, the complexity of the message and language used are identical, the target patient population is identical. The format and text headings follow the current QRD template. The format, design and layout of the proposed leaflet is done according to the MAH's

house-style layout, for which successful user tests have been conducted. The bridging is therefore considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Calcipotriol/Betamethason Sandoz 50 microgram/g + 0.5 mg/g, ointment has a proven chemical-pharmaceutical quality and is a hybrid form of Daivobet 50 microgram/g + 0.5 mg/g ointment. Daivobet is a well-known medicinal product with an established favourable efficacy and safety profile.

As Calcipotriol/Betamethason Sandoz is a product for topical use, intended to act without systemic absorption, it is exempted for biostudy. As there is a difference in composition, pharmaceutical equivalence of the test product with the reference product cannot be assumed. A clinical study was therefore submitted, demonstrating therapeutic equivalence to Daivobet.

In the Board meeting of 26 November 2015, the precipitation of calcipotriol was discussed. This may affect the *in-vivo* availability of the active substance. The MAH performed adequate controls and provided sufficient data to ensure consistent drug product regarding calcipotriol precipitation comparable to those used in clinical batches and equivalent to the reference product.

There was no discussion in the CMD(h). The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Calcipotriol/Betamethason Sandoz 50 microgram/g + 0.5 mg/g, ointment with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 December 2015.

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