Public Assessment Report

Scientific discussion

Daivobet gel

(Calcipotriol and betamethasone)

DK/H/0279/002/DC

This module reflects the scientific discussion for the approval of Daivobet gel. The procedure was finalised at August 15, 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Type of marketing authorisation, main features of disease/condition etc., discussion in CMD

This Decentralised Procedure application concerns an extension to the existing marketing authorisation for Daivobet ointment, containing the same active drug substances in the same concentrations. Daivobet ointment has been approved via MRP DK/H/279/001.
Xamiol gel (DK/H/1405/001/DC) was submitted as a clone to Daivobet gel (DK/H/279/002/DC)
The DCP application was submitted in according to Article 10b of Directive 20001/83/EC (fixed combination) and has been approved August 15, 2008. The Concerned Member States were BE, DE, EL, ES, FI, FR, IE, IS, IT, LU, NL, NO, PT, SE, UK.

The product is indicated for the treatment of scalp psoriasis vulgaris.

II. QUALITY ASPECTS

II.1 Introduction

Pharmaceutical form, formulation, container system, etc.

Daivobet gel is presented in the form of a gel, the D-vitamin analogue calcipotriol monohydrate 50 mcg/g and the potent corticosteroid betamethasone 0,5 mg/g (as dipropionate).

The excipients are:
Paraffin liquid, polyoxypropylene-15 stearyl ether, hydrogenated castor oil, butyl hydroxytoluene, all-rac-alfa-tocopherol and nitrogen.

The container closure system consists of high density polyethylene bottles equipped with a low-density polyethylene nozzle and a high-density polyethylene screw cap.

II.2 Drug Substance

INN; chemical features like chemical class, chirality, manufacturing, specifications, stability

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Daivobet gel are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substances are adequately drawn up.

Stability studies have been performed with the drug substance betamethasone dipropionate. No significant changes in any parameters were observed. The proposed re-test period of 2 years is justified. For calcipotriol a re-test period is accepted and is listed on the presented CEP.

II.3 Medicinal Product

Pharmaceutical development, manufacture of the product, product specification, stability of the product

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on a long range of batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of "*2 years at no special storage condition. Do not refrigerate. Keep bottle in the outer carton. The product should be used within 3 months after first opening*" is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Not applicable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Since this is an extension application and the active ingredients are well-established medicinal substances, non-clinical testing was limited to a comparative mass balance bridging study in rats and minipigs, a 4-week local dermal tolerance study in rabbits, an acute eye irritation test in rabbits and a series of supplementary short-term photosafety studies in hairless mice. Safety tests for hypersensitivity, phototoxicity and photoallergy were performed in humans and are reviewed in the clinical assessment report.

III.2 Pharmacology

No pharmacology studies have been submitted. This is acceptable as the active ingredients have well-established use in the topical treatment of psoriasis, both separately and in combination.

III.3 Pharmacokinetics

Pharmacokinetic studies are limited to mass balance bridging studies following dermal administration of either radiolabelled active ingredient in male and female rats and female minipigs. Two parallel experiments were performed in each model with either ^{3}H-calcipotriol labelled at carbon 1 in the ring structure and unlabelled betamethasone dipropionate or with ^{3}H-betamethasone dipropionate labelled at carbon 1 and 2 and unlabelled calcipotriol. The application rate per cm^2 was approx. 10 mg formulation in rats and 10-17 mg in pigs. Urine and faeces were quantitatively collected for the periods: 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hours post dose. At 168 hours, the animals were killed and a blood sample, the dosed skin, liver and remaining carcass retained for analysis. The samples were subjected to liquid scintillation counting for 5 min. The limit of quantification was 30 c.p.m. above background.

Following topical administration of ^{3}H-betamethasone dipropionate plus calcipotriol formulated as gel or ointment to rats, transdermal absorption of radioactivity accounted for approx. 8% and 9% of the applied dose of ^{3}H, respectively. Following topical administration of ^{3}H-calcipotriol plus betamethasone dipropionate formulated as gel or ointment, absorption was similar in males and females, but differed between the two formulations. Absorption was approx. 19% from Daivobet ointment, but only approx. 10% from the Daivobet gel. The decreased absorption of radioactivity from the gel compared to the ointment was statistically significant. Following topical administration of ^{3}H-betamethasone dipropionate plus calcipotriol formulated as gel or ointment to minipigs, transdermal absorption of radioactivity accounted for approx. 2.6% and 3.5%, respectively. There was no statistically significant difference in the extent of absorption of the test item from the different formulations. Following topical administration of ^{3}H-calcipotriol plus betamethasone dipropionate formulated as gel or ointment, transdermal absorption of radioactivity accounted for approx. 2.4% and 3.5% of the applied dose, respectively. There was no statistically significant difference in the extent of absorption of the test item from the two formulations. The minipig is regarded the better animal model

to investigate absorption through the skin given the similarities of the minipig skin with the human skin. It is therefore concluded that the absorption of the active ingredients from Daivobet gel is similar compared with Daivobet ointment. This was confirmed in humans in clinical trial No. MBL 0404 FR.

III.4 Toxicology

The local tolerability of Daivobet gel was investigated in a 4-week non-occlusive skin irritation test in rabbits and in an acute eye irritation study according to OECD 405. In these studies Daivobet gel caused mild to moderate skin irritation and a slight transient irritation of the eye. These findings are clinically relevant and are included in section 5.3 of the SPC.

Supplementary photosafety studies were carried out because of the results of a 2-year dermal carcinogenicity study and 1-year photo(co)carcinogenicity study of calcipotriol conducted subsequent to the initial approval of Daivobet ointment in the EU in 2001 and submitted to the European authorities in 2006 (MRP No. DK/H/0279/001/II/009). The dermal carcinogenicity study showed no indications of increased carcinogenic risks in mice. In the photo(co)carcinogenicity study, however, there was a statistically significant reduction in the time required for UVR to induce skin tumour formation in male hairless mice. In two supplementary studies, mice of the same strain were treated repeatedly with either calcipotriol solution or calcipotriol/betamethasone gel, followed by UVR exposure and measurement of recognised cellular indicators of skin photocarcinogenicity. These studies showed a similar enhancing effect of calcipotriol alone on the photobiological response of the skin, but indicated no effect of the calcipotriol/betamethasone combination and no evidence of a biologically-important increase in UVR-induced inflammation induced by any of the test article formulations was found. These observations are duly reflected in section 5.3 of the SPC.

All relevant impurities have been qualified in non-clinical and/or clinical studies.

A comprehensive ERA report has been submitted. Although the estimated $PEC_{surfacewater}$ is below the action level for both calcipotriol and betamethasone, the results of a ready biodegradability test (OECD 301F) and the $logK_{ow}$ of calcipotriol (4.68) suggest that the latter should be classified as a PBT/vPvB substance. Therefore, the following statement has been included in section 6.6 (Special precautions for disposal and other handling): Any unused product or waste material should be disposed of in accordance with local requirements.

In conclusion, the MAA for Daivobet gel was considered approvable from a non-clinical point of view

III.5 Environmental risk assessment

The Applicant has performed an assessment of the potential risk to the environment caused by the active substances, calcipotriol monohydrate and betamethasone dipropionate, in the antipsoriatic product Daivobet gel. The report includes an assessment of the potential environmental risks from the use, storage and disposal of the product.

The assessment is made in accordance with the principle of the guideline on the environmental risk assessment of medicinal products for human use.

III.6 Discussion on the non-clinical aspects

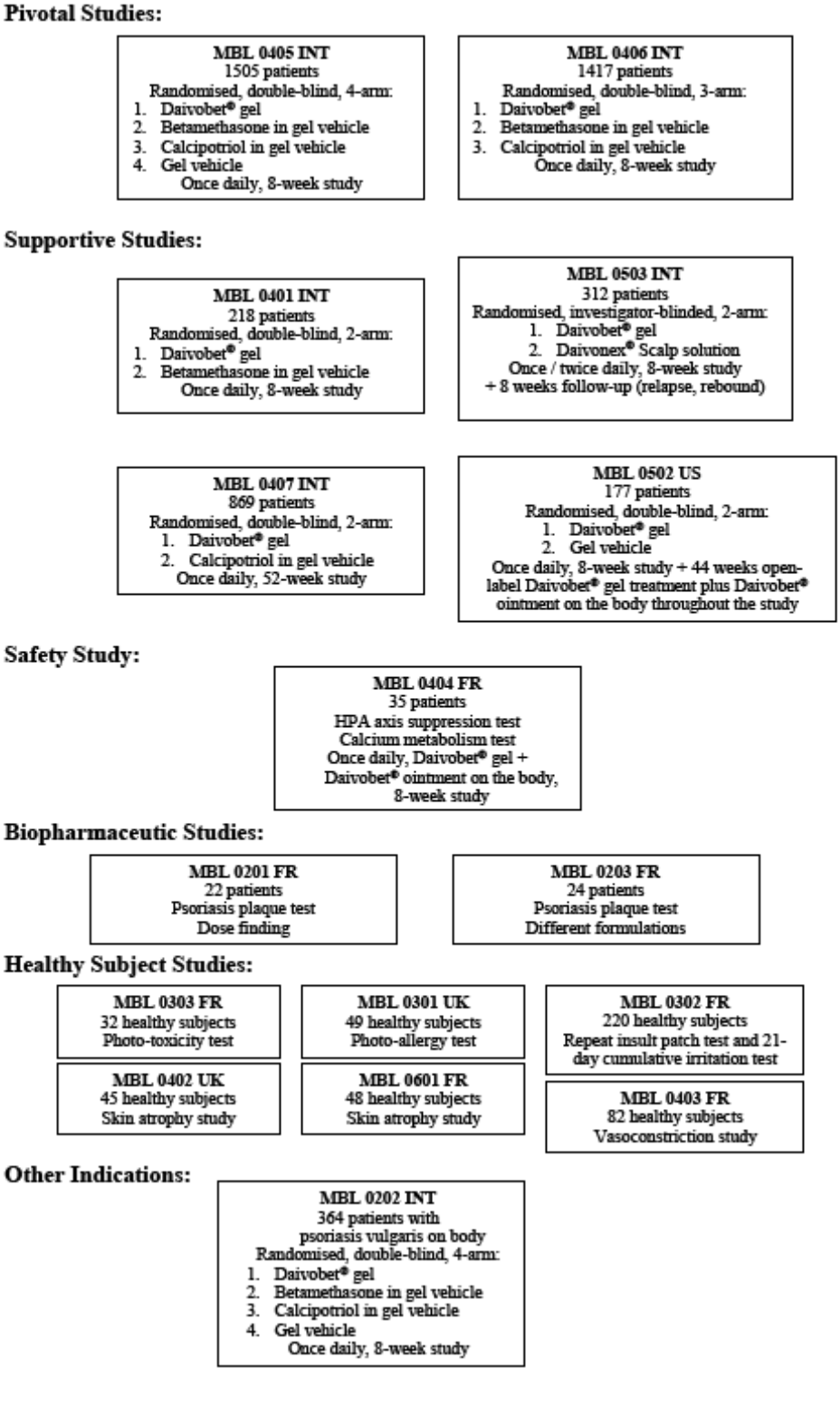
For generics: brief explanation that abridged applications avoid the need for repetitive tests on animals and humans. Reference to the reference medicinal product

Not applicable.

IV. CLINICAL ASPECTS

IV.1 Introduction

An overview of the clinical development programme for Daivobet gel is shown in the figure below:



IV.2 Pharmacokinetics

For this type of topical product containing calcipotriol and betamethasone dipropionate the systemic bioavailability should be assessed using surrogate pharmacological parameters such as the calcium metabolism, with relevance for the D-vitamin component calcipotriol and the hypothalamic-pituitary-adrenal (HPA) axis function with relevance for the corticosteroid component betamethasone dipropionate.

Effect on calcium metabolism

The Applicant has evaluated the effect of Daivobet gel on calcium metabolism and HPA axis in 35 patients with extensive psoriasis on scalp (at least 30% of scalp) and body (15-30% of BSA), who received Daivobet gel concomitant with Daivobet ointment once daily for 8 weeks (study MBL 0404 FR). The treatment was not associated with increase in serum calcium values or 24-hour urinary calcium excretion. In addition, albumin-corrected serum calcium values from 1215 patients in three of the 8 weeks controlled studies (MBL 0405 INT, MBL 0406 INT, and MBL 0502 US) did not show trend of increase during treatment with Daivobet gel.

Effect on HPA axis

The effect of intensive treatment of scalp psoriasis and body psoriasis with Daivobet gel on the HPA axis was similarly evaluated in study MBL 0404 FR according to generally accepted guidelines. Based on the primary response criterion, serum cortisol levels less than 18 mcg/dl 30 minutes after Synacthen injection, a total of 6 of the 32 patients in the per protocol population showed biochemical evidence of a possible weak effect on the HPA axis. An independent evaluation of the result by external experts concluded that the clinical relevance was questioned as the observed changes were small and both pre-stimulation and 60-minutes serum cortisol values were adequate.

IV.3 Pharmacodynamics

Corticosteroid potency

The Applicant has conducted a vasoconstrictor study in 70 healthy adults in order to evaluate the potency of the product relative to a marketed potent corticosteroid Diprosone ointment in controlled study (MBL 0403 FR). The study showed that the vasoconstrictive effect of betamethasone dipropionate in Daivobet gel was inferior to that of Diprosone ointment.

Atrophogenic potential

The atrophogenic potential of Daivobet gel was assessed in 48 healthy adults in a controlled comparative trial against Diprosone ointment after once daily application for 4 weeks (MBL 0402 UK). Daivobet gel induced the same degree of dermal thinning, visually and sonographically as Diprosone ointment.

IV.4 Clinical efficacy

Dose-response studies

The selected concentration of calcipotriol 50 mcg/g and betamethasone 0.5 mg/g (as dipropionate) in the final formulation of Daivobet gel was based on results obtained by in vivo treatment of single psoriasis plaques with various concentrations in a validated model (study MBL 0201 FR, study MBL 0203 FR).

Duration of treatment

The optimal treatment duration with Daivobet gel was assessed in a controlled clinical trial where 218 patients received Daivobet gel or betamethasone dipropionate in the gel vehicle once daily for 8 weeks. A gradual decrease in disease activity was noticed over time with Daivobet gel being significantly more effective than the corticosteroid gel after 8 weeks.

Choice of end points

There are no validated or generally accepted end points in scalp psoriasis. The Applicant has used a Investigator's Global Assessment (IGA) and local skin signs as recommended in the CHMP guideline for topical antipsoriatic agents. As primary end point all pivotal studies used the percentage of patients achieving "clear" or "almost clear" status, also defined as "controlled disease" with either absence of

disease or very mild disease.

IV.5 Clinical safety

Pivotal clinical studies

The Applicant has conducted two active controlled 8-week trials in patients with mild to very severe scalp psoriasis comparing the efficacy and safety of once daily application of Daivobet gel with each of its active components calcipotriol and betamethasone dipropionate in the same vehicle (study MBL 0405 INT and study MBL 0406 INT). In study MBL 0405 INT there was also a vehicle arm included. A total of 2922 patients were randomised and treated in the trials. Both studies demonstrated that Daivobet gel treatment resulted in significantly higher proportion of patients with controlled disease (clear or almost clear) approximately 70%, compared to betamethasone, calcipotriol and vehicle treated patients.

Supportive clinical studies

The Applicant has performed one additional 8-week active controlled clinical trial (MBL 0401 INT) assessing the efficiency and safety of Daivobet gel against the active ingredient betamethasone dipropionate in the gel vehicle after once daily application in a total of 218 patients with scalp psoriasis. The study confirmed the high efficacy of Daivobet gel relative to the single components.

Comparative trial against marketed product

The Applicant has conducted a controlled clinical trial assessing the efficacy and safety of Daivobet gel once daily against the marketed Daivonex scalp solution containing calcipotriol 50 mcg/ml twice daily for 8 weeks in 312 patients with scalp psoriasis. Treatment with Daivobet gel resulted in a significantly higher response rate compared to Daivonex scalp solution (controlled disease in 69% vs. 31%, $p<0.0001$). In this study the time to relapse and risk of rebound was estimated in an 8-week follow-up period.

Relapse occurred in 73 (54%) and 10 (35%) of those obtaining controlled disease at week 8 in the Daivobet gel and Daivonex scalp solution groups, respectively. The median time to relapse was 35 days in the Daivobet gel group vs. 58 days in the Daivonex scalp solution group. A rebound phenomenon was described in 2 (1.5%) of the 135 patients in the Daivobet gel group.

Ongoing study

Study MBL 0502 US is an 8-week controlled study assessing the efficacy and safety of Daivobet gel against the vehicle gel after once daily application to 177 Afro-American/Black and Hispanic patients with concomitant use of Daivobet ointment on the body. The 8-week controlled phase is completed confirming the efficacy of Daivobet gel, but the 44-week follow-up phase allowing open-label Daivobet gel plus Daivobet ointment throughout the study was ongoing at the time of review.The study MBL 0502 US was included in the response document of 2 April 2008.

Long-term efficacy and safety study

The Applicant has conducted a controlled double-blind, 2-armed controlled 52-week study assessing the efficacy and safety of Daivobet gel versus calcipotriol in the gel vehicle in 869 patients with scalp psoriasis. Both treatments were used once daily as required. The mean duration of exposure was 44 weeks and 37 weeks in the Daivobet gel and the calcipotriol group, respectively. Acceptable control of the scalp disease was obtained in the majority of patients. No signs of tachyphylaxis were observed.

Other studies

Study MBL 0202 INT is an active and placebo controlled trial of Daivobet gel in patients with psoriasis vulgaris on the body and is therefore not of relevance for this application and will not be

assessed accordingly in this context.

IV.6 Discussion on the clinical aspects

For generics: brief explanation that abridged applications avoid the need for repetitive tests on animals and humans. Reference to the reference medicinal product. For these applications the bioequivalence studies are pivotal and should be described.

Not applicable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Specific obligations, follow-up measures, if applicable

The risk/benefit ratio is considered positive and Daivobet gel is recommended for approval.

V.1 PSUR cyclus

The RMS has recommended the PSUR submission scheme will follow Volume 9A of The Rules Governing Medicinal Products in the European Union starting with 6-monthly PSUR. The applicant has the possibility to apply for 3 years cycles, when the applicant submits the 6-monthly PSUR.

V.2 Outstanding issues

The MAH has made the following commitments:

Commitments:

Area	Description
Quality	**Drug Substance Betamethasone dipropionate** a) The Applicant commits to submit the results on three batches of Betamethasone dipropionate studied at 40°/75% RH ultimo August 2008. The commitment was fulfilled by the submission of data 20 August 2008.
Quality	**Drug Product** B) The Applicant commits to present 24 months stability data for the full scale primary batches when data for at least three of these batches are available. Stability report on the first three batches will be available by 15 October 2008. The result of stability data will be submitted ultimo November 2008. The commitment was fulfilled by the submission of data 15 October 2008.