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APPLICATION NUMBER:

21-852

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA Number	21-852
Stamped Receipt Date(s)	March 9th, 2005;August 11th, 2005, September 21st, 2005, October 31st, 2005, November 21st, 2005 and, November 29th, 2005
Brand Name	Dovobet
Generic Name	Calcipotriene hydrate (0.005%) and Betamethasone dipropionate (—
Reviewer	Abimbola Adebowale Ph.D.
Team Leader	Dennis Bashaw Pharm.D.
OCPB Division	DCPB 3
OND division	HFD-540
Applicant	Parexel International, NC 27713 for Leo Pharmaceutical Products Ltd., Denmark
Relevant IND(s)	62,993
Submission Type; Code	Original NDA; 3S
Formulation	Ointment
Indication	Treatment of Psoriasis Vulgaris in Adults aged 18 years and above

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1. Executive Summary

This application is for the approval of Dovobet® ointment, a fixed combination of calcipotriene hydrate and betamethasone dipropionate. It is intended to be applied as a once daily treatment for up to 4 weeks in adult patients with psoriasis vulgaris. Calcipotriene hydrate has been marketed in the US since 1994 under the trade name Dovonex ® for use as a topical treatment for plaque psoriasis in adults. It is available as an ointment, cream and scalp solution. In contrast to Dovobet which is intended to be applied once daily, Dovonex is currently labeled to be applied twice daily for plaque psoriasis. Betamethasone dipropionate is available on the US market in several topical formulations from various manufacturers, formulated as ointments, creams and lotions. It is currently labeled to be applied once or twice daily for various dermatologic conditions including psoriasis.

The clinical pharmacology and biopharmaceutics data and information included in this submission to support the use of Dovobet ointment in psoriasis vulgaris is discussed in this review.

1.1 Recommendation (s):

The Clinical Pharmacology and Biopharmaceutics data submitted demonstrated that the systemic exposure of betamethasone and calcipotriene following topical application of Dovobet ointment to patients with psoriasis vulgaris was minimal.

For the assessment of the systemic exposure of betamethasone, the hypothalamic-pituitary-adrenal (HPA) axis suppression study demonstrated that after 4 weeks treatment with Dovobet ointment none of the patients demonstrated adrenal suppression under maximal use conditions. However under actual use conditions (i.e. on an as needed basis), there was one patient who was considered suppressed after 4 weeks treatment and another patient after 4 weeks and 52 weeks treatment. Following discussions with the medical reviewer (Dr. B. Carr) it was concurred that the applicant should incorporate this information in their label.

For the assessment of the systemic exposure of calcipotriene, there was no apparent difference in the mean change from baseline for albumin-corrected serum calcium levels obtained before and after treatment with Dovobet ointment. However, the individual data indicated that an increase in albumin-corrected serum calcium was observed in 24 of 1060 (2.3 %) patients treated with Dovobet ointment for 4 weeks. Following discussions with the medical reviewer (Dr. B. Carr) it was concurred that the applicant should incorporate this information on the observed hypercalcemia in their label. .

In addition, the data from the mass balance studies in healthy volunteers indicated that the effect of calcipotriene on the systemic exposure of betamethasone was minimal and vice versa.

Based on the data submitted the applicant has met the requirements outlined in 21CFR 320 and, their application is acceptable from a clinical pharmacology and biopharmaceutics perspective. We recommend that the labeling changes in Section 3 on pages 18-20 be conveyed to the applicant:

1.2 Phase IV Commitments: NA

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The applicant included 8 clinical pharmacology and Biopharmaceutics studies for Dovobet in this submission. Seven studies were reviewed. One study (MCB 9801 NL was not reviewed in detail because the formulation used was not the to-be-marketed formulation). Please note that Dovobet and Daivobet were used interchangeably throughout the study reports. The applicant stated that Dovobet and Daivobet are synonyms. Daivobet is the trade name mainly used in non-English speaking countries.

HPA Axis Study:

The effect of the topical application of Dovobet ® ointment on the HPA axis was evaluated in two studies (MCB 0201 FR and MCB 0102 INT). In study MCB 0201 FR, Dovobet ® ointment applied once daily for 4 weeks was compared with betamethasone applied once daily to patients (N =24, 12 per treatment arm) with psoriasis lesions covering 15 to 30 % of the body surface area. In this study no patients in the Dovobet ® ointment group showed abnormal stimulated serum cortisol levels (i.e. $\leq$ 18 mcg/dL) at 30 minutes post stimulation.

Study MCB 0102 NT which was a sub-study, compared the effects on the HPA axis of three once daily treatment regimens {(Dovobet® ointment once daily for 52 weeks, (n = 7) Dovobet® ointment once daily for 4 weeks/calcipotriol once daily for 4 weeks on an alternating schedule for 52 weeks(n = 6), and Dovobet® ointment 4 weeks/calcipotriol 48 weeks (n=6)} used as required in 19 patients with psoriasis lesions covering 10 % to 30 % of the body surface area. Two patients indicated adrenal suppression. One patient (# 6866) in the Dovobet® ointment 4 weeks/calcipotriol 48 weeks treatment group showed abnormal stimulated serum cortisol levels (i.e. $\leq$ 18 mcg/dL) at 30 minutes post stimulation after 4 weeks and 52 weeks of treatment. The applicant stated that this patient was considered to have borderline adrenal suppression. The second patient (# 6857) in the Dovobet® ointment once daily for 4 weeks/calcipotriol once daily for 4 weeks alternating also showed abnormal stimulated serum cortisol levels (i.e. $\leq$ 18 mcg/dL) at 30 minutes post stimulation after 52 weeks of treatment.

Effects on Calcium Metabolism:
Serum calcium was investigated in three phase III studies with Dovobet® ointment, MCB 9905 INT, MCB 9904 INT, and MCB 9802 INT and, in the HPA axis study MCB 0201 FR as a marker for calcipotriene absorption. Briefly, these studies investigated once daily and twice daily application of Dovobet® ointment for 4 weeks in patients with psoriasis vulgaris. For the three phase III studies there was no difference observed in mean albumin corrected serum calcium from baseline to end of treatment.

However, an examination of the individual data obtained from the three studies indicated that 24 of 1060 (2.3 %) of the patients treated with Dovobet ointment for 4 weeks had an increase in albumin-corrected serum calcium levels. Within this group of 24 patients 9 of 151 (6.0 %) applied the ointment once daily and 15 of 909 (1.7 %) applied the ointment twice daily. This observed hypercalcemia under the proposed conditions of use will be incorporated into the applicant's label.

In study MCB 0201 FR, all serum calcium values were categorized as normal, both at baseline and end of treatment. However, it should be noted that the serum calcium levels in this study were not corrected for albumin.

Mass Balance:
The percutaneous absorption of calcipotriol and betamethasone dipropionate from Dovobet® ointment was investigated in healthy volunteers in a mass balance study (MCB 9901 NL). A single application of ^{3}H radiolabeled Dovobet® ointment was applied to 625 cm^2 of skin for 12 hours. ^{3}H radioactivity was measured in serum, urine, feces and ointment samples as well as in gauzes, gloves, cleaning swabs and shorts using liquid scintillation methods. The total absorption of calcipotriol and betamethasone from Dovobet ointment were 0.15 % and 0.06 % of the given dose.

The percutaneous absorption of calcipotriol (0.1% vs. 1.3 % of the applied dose) from Dovobet® was less than that of the single ingredient product (Dovonex®), and that of betamethasone was also less (0.05 % vs. 0.1 %) in the presence and absence of calcipotriol. However, the differences observed were not statistically significant ($p > 0.05$). Therefore calcipotriol had a minimal effect which is unlikely to be clinically relevant from a safety perspective on the systemic exposure of betamethasone and vice versa.

Vasoconstrictive Action:
Dovobet® ointment can be classified as a potent corticosteroid ointment based on the results of the vasoconstrictive action study. The vasoconstrictive action of betamethasone dipropionate in Dovobet® ointment was assessed in a pharmacodynamic study (MCB 9902) performed in healthy volunteers. In this study, Dovobet® ointment was compared to a marketed product (Diprosone ® ointment, a potent corticosteroid). The 90% confidence interval obtained for the skin blanching response ratio of the two products was 0.81-1.04. Therefore Dovobet® ointment is equivalent to Diprosone® ointment in terms of topical potency as these intervals are within the Agency criteria [0.8, 1.25].

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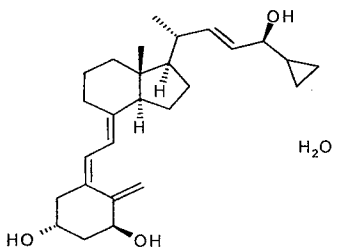
2. QBR

2.1 General Attributes

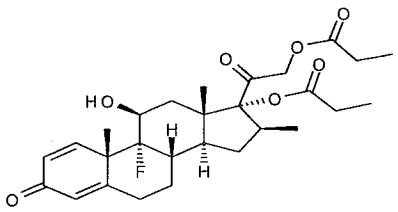
Physicochemical Properties of the active drug substances, calcipotriene hydrate and betamethasone dipropionate in Dovobet® ointment drug product

Calcipotriene hydrate: It is a white to almost white crystalline compound.

Molecular Formula: $C_{27}H_{40}O_3$, H_2O, ***Molecular Weight***: 430.6
Structural Formula:



Betamethasone dipropionate***:*** It is a white to almost white odorless powder
Molecular Formula: $C_{28}H_{37}FO_7$, ***Molecular Weight:*** 504.6
Structural Formula:



Mechanism of Drug Action
Calcipotriene hydrate is a synthetic vitamin D_3 analogue and, betamethasone dipropionate is a synthetic corticosteroid. The possibility of a beneficial effect of combining vitamin D_3 analogues and topical corticosteroids has been suggested because of their different modes of action. It is believed that the vitamin D_3 analogue may reduce the daily amount of steroid used and, the duration of steroid exposure, decreasing the risk of steroid-related adverse effects such as skin atrophy, and telengiaectasia. Likewise, the anti-inflammatory effect of the corticosteroid may serve to decrease the skin irritation frequently associated with the vitamin D_3 analogues.

Calcipotriene:
The mechanism of action of calcipotriene is similar to that of the active form of vitamin D_3, 1, 25 $(OH)_2$ D_3 (calcitriol). Calcipotriene, like calcitriol, acts by binding to the vitamin D receptor and regulating various genes. Calcitriol is known to be involved in the regulation of calcium homeostasis. Additionally, calcitriol has been shown to inhibit proliferation and induce differentiation of keratinocytes, and modulate the immune response in skin tissue.

Calcipotriene is believed to have the same effects as calcitriol on the skin, but with minimal effects on calcium metabolism, possibly due to the fact that it is rapidly metabolized to less active metabolites in the liver.

Betamethasone dipropionate:
Corticosteroids have a broad mechanism of action. They inhibit the synthesis of many inflammatory cytokines, the production of prostaglandins and nitric oxide, and the expression of adhesion molecules. Betamethasone dipropionate is believed to have anti-inflammatory and antipruritic actions that are characteristic of corticosteroids.

Therapeutic Indications and Proposed Dosing Regimen

Dovobet® ointment is indicated for the topical treatment of psoriasis vulgaris in adults aged 18 years and above. It is recommended to be applied to the affected area once daily. The recommended treatment period is 4 weeks. After this period, Dovobet® ointment may be used according to need. There is experience with repeated courses of Dovobet® ointment up to 52 weeks. The maximum weekly dose should not exceed 100 g.

2.2 General Clinical Pharmacology

Q. What were the design features of the clinical pharmacology and clinical studies used to support efficacy and safety?

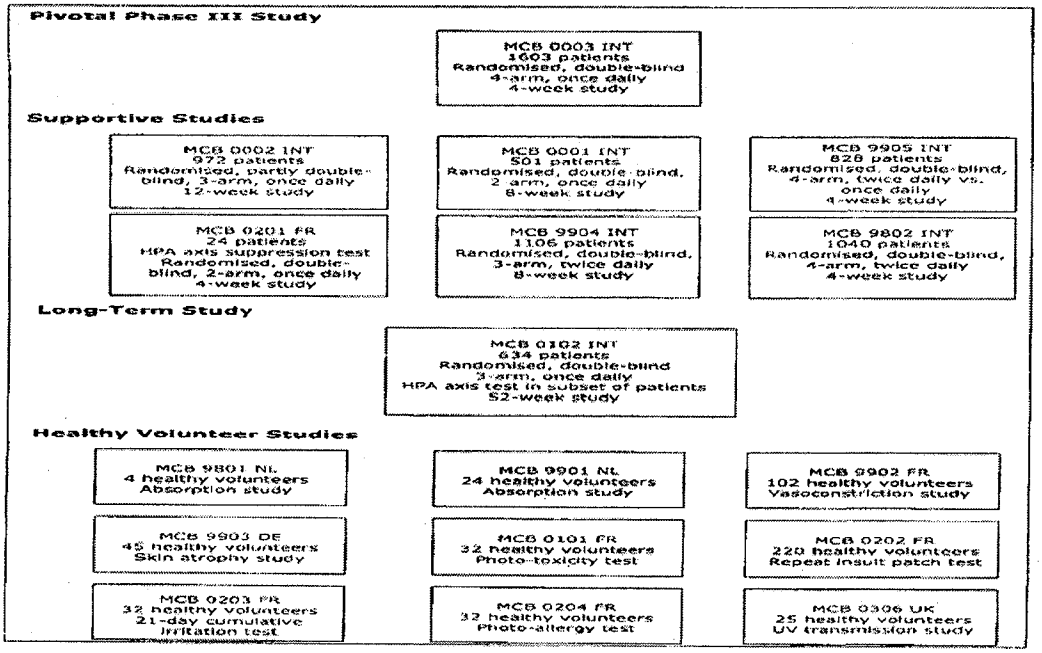
Efficacy

The applicant conducted one pivotal trial, MCB 0003 INT, in support of efficacy. Six additional supportive studies were submitted in support of efficacy, however only four (MCB 0002 INT, MCB 0001 INT, MCB 9905 INT and MCB 0201 FR) of these studies evaluated the sponsor's proposed once daily regimen. The other two studies MCB 9904 INT and 9802 INT evaluated a twice daily dosing regimen.

Safety

The applicant conducted twenty-one studies with Dovobet and included these in the safety database. Only 17 of these studies were considered as being "Core Studies" because the populations in those studies were representative of the applicant's proposed target population and formulation (see table below for study details). The 17 studies consisted of nine Phase 1 studies in healthy volunteers , seven studies used to support efficacy and one long term study (0102 INT) conducted to investigate once daily treatment for up to 52 weeks. The four studies classified as "Non-Core" were either of other topical medications in which Dovobet served as an active comparator or they were conducted in conditions other than psoriasis vulgaris. A summary description of the design features of the 17 clinical studies used to support efficacy and safety is presented in the diagram below.

Figure 1. Overview of the Clinical Development Program for Dovobet® Ointment



Q. What is the basis of selecting the clinical/pharmacodynamic response endpoints?

Clinical End Points

For the pivotal clinical study, the two primary endpoints were as follows:

1. Percentage of patients classified as "controlled disease" (absence of disease or very mild disease according to the Investigator's Global Assessment of Disease Severity IGA) at the end of treatment (i.e. 4 weeks). The IGA was the primary efficacy assessment for the integrated analysis of efficacy (IGA) and the
2. Reduction in Psoriasis Area Severity Index (PASI) score from baseline to end of treatment (i.e. up to 4 weeks)

The Investigator's Global Assessment of Disease Severity (IGA) was made using a 6-point scale as follows:

Scale	Description
Absence of disease	The disease is controlled. No evidence of redness, no evidence of thickness, and no evidence of scaling
Very mild disease	The disease is controlled but not entirely cleared. The overall clinical picture consists of lesions with some discoloration with absolutely minimal thickness, i.e. the edges of the lesion(s) can just be felt.
Mild disease	The overall clinical picture consists of lesions with light red coloration, slight thickness and a fine, thin scale layer.
Moderate disease	The overall clinical picture consists of lesions with red coloration, a moderate thickness and a moderate, somewhat coarse scale layer.
Severe disease	The overall clinical picture consists of lesions with very red coloration, severe thickness and a severe, coarse thick scale layer
Very severe disease	The overall clinical picture consists of lesions with extreme deep red coloration, very severe thickness and very severe, coarse thick scale layer.

The PASI score is based on the extent and severity of the psoriatic lesions. Extent is recorded as follows: 0=no involvement, 1 = < 10 % 2 = 10-29 %, 3 = 30-49 %, 4 = 50-69 %, 5 = 70-89 %, 6 = 90-100 %. Severity is scored for each symptom of redness, thickness, and scaliness as given below: 0=absent, 1=slight, 2=moderate, 3 = severe and 4 = severest possible. The PASI score is the weighted sum of the extent scores times the corresponding sum of symptoms scores. The computed PASI score ranges from 0 to 64.8, with larger numbers reflecting a worse condition.

Pharmacodynamic Endpoints

The applicant used the effects on calcium homeostasis and, HPA axis suppression for the assessment of systemic absorption of calcipotriene and betamethasone dipropionate respectively, in patients with psoriasis. Because of its pharmacological action on calcium metabolism which is mediated through its binding to vitamin D receptors, serum and urine calcium levels can be used to assess the extent of systemic absorption of calcipotriene.

The pharmacologic basis for HPA axis monitoring as an assessment of betamethasone dipropionate absorption is the suppression of the HPA axis through negative feed-back. This results in a decrease in cortisol response from the adrenals in response to adrenocorticotropic hormone (ACTH) stimulation. Therefore, the extent of systemic absorption of betamethasone dipropionate can be assessed by measuring effects on adrenal function through HPA axis testing using standard

methodology. The applicant also evaluated the vasoconstrictive action (i.e. skin blanching) of betamethasone dipropionate in Dovobet ointment to determine its steroid potency.

Q. What are the characteristics of the exposure-response relationships for efficacy?

The efficacy of Dovobet® ointment once daily (od) was compared with that of Dovobet® ointment twice daily (bid) in study MCB 9905 INT. The primary response criterion in this study was the percentage change in PASI from baseline to end of treatment (up to 4 weeks). The mean percentage change in PASI was -67.7% for Dovobet® ointment od and -72.9% for Dovobet® ointment bid. The difference was statistically significant (P=0.045). To make a more precise estimate of the difference between od and bid application a comparison was also conducted between the pooled treatment groups in the integrated analysis of efficacy. This showed a mean percentage change in PASI of -68.8% for Dovobet® ointment od and -72.8% for Dovobet® ointment bid. The treatment difference was again statistically significant (P=0.015).

However, the applicant stated that from a clinical point of view, a difference in percentage change in PASI of about 5% between treatments cannot be considered clinically relevant; particularly when both treatments have produced a substantial reduction in PASI from baseline. Thus the absence of a clinically relevant difference in efficacy between the two different dosing regimens justified od dosing. It was also believed that the overall benefit/risk ratio should be more favorable with this less frequent application regimen (see medical review for further details).

Q. What are the characteristics of the exposure-response relationships for safety?

Pharmacodynamic Endpoints:

Hypercalcemia is one of the systemic related adverse events (AE) associated with calcitriol and some of its analogues. Therefore, the calcemic activity of calcipotriene was evaluated in a number of studies by measuring albumin-corrected serum calcium. The data in the table below indicates that there was no apparent difference in the mean change from baseline for albumin-corrected calcium between the od and bid dosing regimen (see table below). However, the data should be interpreted with caution due to the imbalance in the sample size.

Table T42: Changes in Albumin-Corrected Serum Calcium from Baseline to End of Treatment: Short-Term Core Studies by 2nd Level Pooled Treatment Group for Dovobet® Ointment, Safety Analysis Set

	Dovobet® ointment od (N=151)	Dovobet® ointment bid (N=909)
Mean value (SD) at baseline (mmol/L)	2.37 (0.09)	2.36 (0.09)
Mean value (SD) at EOT (mmol/L)	2.38 (0.10)	2.36 (0.09)
Actual change[1] (mmol/L)		
Mean (SD)	0.01 (0.08)	0.00 (0.08)
Min, Max	—	—
Ratio[2]		
Mean[3] (SD)[4]	1.00 (3.63)	1.00 (3.71)
Min, Max	—	—
Number of subjects assessed[5]	144	886

SD: Standard Deviation; EOT: End of treatment with Dovobet ointment for study MCB 9904 INT; Min, Max: Minimum, Maximum; 1: Actual change from baseline to EOT; 2: Ratio of EOT value to baseline value; 3: Geometric mean; 4 SD as percentage of mean; 5: Number of subjects for whom both baseline and EOT values were available. Calcium (mmol/L) Reference Range: 2.25 - 2.54 mmol/L

In addition an examination of the individual data indicates that there were 9 of 151 (6.0 %) patients in the od group and 15 of 909 (1.7 %) patients in the bid group who had an increase in albumin-corrected serum calcium levels following treatment with Dovobet ointment (see table below)

Table T44: Shift Table for Albumin-Corrected Serum Calcium: Short-Term Core Studies by 2nd Level Pooled Treatment Group for Dovobet® Ointment, Safety Analysis Set

Category at Baseline	Dovobet® ointment od			Dovobet® ointment bid		
	Category at EOT			Category at EOT		
	Low	Norm	High	Low	Norm	High
Low	0	0	0	1	3	0
Normal	0	132	9	3	847	15
High	0	1	2	0	11	6

Source: Statistical Table 141 (5.3.5.3; M.5, Vol. 67).
Excludes the phase I study MCB 0201 FR
EOT: end of treatment (end of treatment with Dovobet® ointment for study MCB 9904 INT)

Clinical Endpoints:

In Study MCB 9905 INT which compared od and bid application of Dovobet ointment, the percentages of patients reporting adverse events (AE's) were as follows: 26.5 % for Dovobet ® ointment od, 25.1 % for vehicle od, 33.7 % for Dovobet ® ointment bid and 35.2 % for calcipotriol bid. Based on this data it appears there were more AE's associated with the bid dosing compared to the od dosing regimen.

However, the applicant stated that a comparison of the od and bid application in the pooled database indicated that the overall number of patients reporting AEs was similar between Dovobet® ointment od (26.9 %) and bid application (27.4 %), and there was no statistically significant difference (p = 0.79) between the od and bid regimens (see table below):

Table T32: Adverse Events Reported by > 1% of Subjects by Preferred Term: Short-Term Core Studies (treatment up to 12 weeks) by 2nd Level Pooled Treatment Group for Dovobet ® Ointment, Safety Analysis Set

	Number (%) of Subjects with AE	
Preferred Term	**Dovobet® ointment *od*** (N=1539)	**Dovobet® ointment *bid*** (N=909)
Headache	44 (2.9)	25 (2.8)
Pruritus	43 (2.8)	32 (3.5)
Nasopharyngitis	37 (2,4)	19 (2.1)
Influenza	18 {1.2)	5 (0.6)
Psoriasis	18 (1.2)	12 (1.3)
Rash scaly	18 (1,2)	12 (1.3)
Upper respiratory tract Infection	16 (1.0)	4 (0.4)
Back pain	15 (1.0)	6 (0.7)
Folliculitis	6 (0.4)	13 (1.4)
Application site pruritus	3 (0.2)	10 (1.1)
Any adverse event*	414 (26.9)	249 (27.4)

Source: Statistical Tables *56 and 59 (5.3; M, 5, Vol. 65). Data obtained from Study #'s :MCB 0003INT, MCB 0002 INT, MCB 0001 INT, MCB 9905 INT, MCB 0201 FR, MCB 9904 INT, and MCB 9802 INT)

Based on the data in the table above the AEs reported by 1% or more of the subjects in the Dovobet ® ointment were pruritus, psoriasis, rash scaly, headache, and nasopharyngitis. The data also indicates that there were some notable differences between the AE's reported for the od and bid dosing. Only application site pruritus and folliculitis were reported less frequently for od than for bid. While all the other AE's were reported more frequently for od than for bid (see medical review for further details).

Q. What is the systemic exposure of calcipotriene from Dovobet ointment in patients?

The applicant evaluated the systemic exposure of calcipotriene by means of its effect on calcium metabolism. The data indicated that there was no apparent change in mean albumin-corrected serum calcium from baseline to end of treatment for Dovobet ointment. However, individual data indicated that an increase in albumin-corrected serum calcium was observed in 9 out of 151 of the patients treated with Dovobet ointment once daily for 4 weeks.

The applicant evaluated the effects of Dovobet ointment on serum calcium in three Phase III studies (MCB 9905 INT, MCB 9904 INT and MCB 9802 INT). The three studies involved a total of 1060 patients treated with Dovobet® ointment over a period of 4 weeks (151 with od and 909 with bid). The maximum amount of ointment used per week during the 4-week treatment period was ~ 98 g/week. The extent of psoriasis was at least 10 % in one of the regions arms, legs, or trunk. In these studies serum calcium, serum albumin and albumin-corrected serum calcium were measured. Serum calcium was also measured in the HPA axis study MCB 0201 FR in which Dovobet ointment was applied od for 4 weeks to larger surface areas (15 – 30 %) compared to the Phase III studies. A tabular summary of the changes from baseline to end of treatment in the three Phase III studies is inserted below:

Table T2: Changes in Albumin-Corrected Serum Calcium from Baseline to End of Treatment in Studies MCB 9905 INT, MCB 9904 INT and MCB 9802 INT

	Dovobet® ointment (N=1060)	Vehicle (N=316)	Calcipotriol (N=901)	Betamethasone (N=690)
Mean value (SD) at baseline (mmol/L)	2.36 (0.09)	2.36 (0.09)	2.36 (0.08)	2.35 (0.09)
Mean value (SD) at EOT (mmol/L)	2.36 (0.09)	2.36 (0.10)	2.36 (0.09)	2.34 (0.09)
Actual change[1] (mmol/L)				
Mean (SD)	0.00 (0.09)	0.00 (0.09)	0.00 (0.09)	-0.01 (0.08)
Min, Max	—	—	—	—
Ratio[2]				
Mean[3] (SD)[4]	1.00 (3.70)	1.00 (3.78)	1.00 (3.65)	1.00 (3.35)
Min, Max	—	—	—	—
Number of subjects assessed[5]	1030	304	872	659

SD: Standard Deviation; EOT: End of treatment with Dovobet ointment for study MCB 9904 INT; Min, Max: Minimum, Maximum; 1: Actual change from baseline to EOT; 2: Ratio of EOT value to baseline value; 3: Geometric mean; 4 SD as percentage of mean; 5: Number of subjects for whom both baseline and EOT values were available.
Calcium (mmol/L) Reference Range: — — mol/L

The data in the table above shows that there was no apparent change in mean albumin-corrected serum calcium for Dovobet ointment and the 3 other treatments evaluated. Individual changes were minimal (between — and — mmol/L). In addition the mean ratio of end of treatment value to

baseline value was 1.00 and the ratios for individual patients were between [redacted] Dovobet ointment and the 3 other treatments evaluated.

However, an examination of the individual data indicated that 24 of 1060 patients had an increase in albumin corrected serum calcium levels (see table below) and this information will be incorporated into the label.

Table T43: Shift Table for Albumin-Corrected Serum Calcium: Short-Term Core Studies by 1st Level Pooled Treatment Group, Safety Analysis Set

Category at Baseline	Dovobet® ointment			Vehicle			Calcipotriol			Betamethasone		
	Category at EOT			Category at EOT			Category at EOT			Category at EOT		
	Low	Norm	High	Low	Norm	High	Low	Norm	High	Low	Norm	High
Low	1	3	0	1	0	0	2	0	0	0	0	0
Normal	3	979	24	0	286	9	0	834	22	2	638	6
High	0	12	8	0	4	2	0	12	2	0	5	8

Source: Statistical Table 340 (5.3.5.3; M.5, Vol. 67).

Excludes the phase I study MCB 0201 FR.

EOT: end of treatment (end of treatment with Dovobet® ointment for study MCB 9904 INT).

Although the applicant indicated that the percentages of patients with this observed increase is low and therefore did not consider it clinically relevant, the medical reviewer (Dr. B. Carr) believes the information should still be incorporated in the label. This reviewer concurs with her.

In Study MCB 0201 FR (HPA axis study) in which the ointment was applied to larger surface areas, total serum calcium values were categorized as normal (i.e. within the reference range of [redacted] mmol/L), both at baseline and at end of treatment with Dovobet ointment. Although this data indicates that there were no clinically relevant changes in serum calcium, it is mainly supportive because total serum calcium and not albumin-corrected calcium (the more sensitive measure) was assessed.

Q. What is the systemic exposure of betamethasone dipropionate from Dovobet ointment in patients?

The applicant evaluated the systemic exposure of betamethasone dipropionate by means of its effect on the HPA axis. The effects of Dovobet ointment on the HPA axis was evaluated in two studies, MCB 0201 FR and MCB 0102 INT. The results of study MCB 0201 FR indicated that there were no patients with signs of HPA axis suppression after 4 weeks treatment with Dovobet ® ointment once daily. In study MCB 0102 INT two of the patients would be considered suppressed (i.e. a 30 minute cortisol level ≤ 18 mcg/dL) at end of treatment.

In study MCB 0201 FR, 4 weeks application of Dovobet® ointment *od* was compared with betamethasone od in 24 patients with extensive psoriasis lesions (15% to 30% of the body surface area (mean BSA = 22%).

The results indicated that no patients in the Dovobet ® ointment group showed abnormal stimulated serum cortisol levels (i.e. ≤18 mcg/dL @ 30 minutes post-stimulation) after 4 weeks of treatment (see Table T3 below). It should be noted that one patient (#13) in the betamethasone treatment group was considered suppressed by the applicant.

Table T3: Patients with abnormal serum cortisol values in the HPA Axis test. Study MCB 0201 FR

Treatment / Patient No	Baseline (mcg/dL)			After 4 weeks' treatment (mcg/dL)		
	Basal[1]	30-min post Synac-then[2]	30-min rise[3,4]	Basal[1]	30-min post Synac-then[2]	30-min rise[3,4]
Dovobet® ointment						
1	[redacted]					
20						
Betamethasone						
4						
6						
13						
13						
23						

Study MCB 0102 INT compared the effects on the HPA axis of the three *od* treatment regimes [Dovobet® ointment od 52 weeks (n = 7), Dovobet® ointment od 4 wks/calcipotriol od 4 wks alternating (n = 6), and Dovobet® ointment 4 wks/calcipotriol 48 wks (n = 6)] used as required in 19 patients (subpopulation of the patient population) with psoriasis lesions covering 10 % to 30 % of the body surface area (the mean in the three treatment groups were between 13% and 18 %) and a baseline disease severity of at least moderate. Although the ointments were administered as needed in this study, the design is more representative of actual use conditions. The applicant stated that there were three patients who had one or more abnormal results according to the Cortrosyn ® criteria (see table T4 below)

Table T4: Patients with abnormal serum cortisol values, HPA axis substudy of MCB 0102 INT.

Treatment Patient No.	Serum cortisol								
	Baseline			After 4 weeks' treatment			End of treatment (up to 52 weeks)		
	Basal[1]	30-min post Synac-then[2]	30-min rise[3]	Basal[1]	30-min post Synac-then[2]	30-min rise[3]	Basal[1]	30-min post Synac-then[2]	30-min rise[3]
Dovobet[6] ointment od 52 weeks									
[redacted]									

However, according to the Agency criteria for adrenal suppression (i.e. ≤18 mcg/dL @ 30 minutes post-stimulation) two of the patients indicated possible adrenal suppression. One of the patients (#

[redacted]

Reviewer's Comments: ***This reviewer (in concurrence with the medical reviewer) does not agree with the applicant since the Agency criteria which is only the 30-minute value, indicates that both patients are suppressed.***

Q. ***What is the percutaneous absorption of Dovobet ointment?***

Absorption of ^{3}H-radioactivity, as indicated by the recovery of radioactivity in urine and feces, was below 0.5% of the total applied dose for the majority of the volunteers. Sixteen subjects showed virtually no excretion in urine and fifteen showed virtually no excretion of radioactivity in feces. The total absorption of calcipotriol and betamethasone from Dovobet ointment were 0.15 % and 0.06 % of the given dose.

The percutaneous absorption of calcipotriol and betamethasone dipropionate from Dovobet ointment was investigated in healthy volunteers in a mass balance study (MCB 9901 NL). Absorption and excretion balance of ^{3}H- calcipotriol and ^{3}H- betamethasone dipropionate from Dovobet ®ointment and ^{3}H- calcipotriol from Dovonex ®Ointment was assessed after application of radio labeled ointment. A single application of 2.5g of ^{3}H- radio labeled ointment was applied to 625 cm^{2} of skin on the thigh of healthy male volunteers (N = 24) for 12 hours. The subjects were broken into two groups of six subjects (Group I and II) and three groups of four subjects (Group III, IV and V). Subjects in groups I and II were to receive a second application of the same radio labeled ointment on Day 36 after applying unlabeled ointments (Dovonex and Dovobet) for 28 days. ^{3}H- radioactivity were measured in serum, urine, feces, and ointment samples as well as in gauzes, gloves, cleaning swabs and shorts using a liquid scintillation method.

The average total recovery was between 77.4 % (treatment group III) and 87.9 % (treatment group V) of the dose. The vast majority of the radioactivity (77 to 88%) was accounted for by the gauzes used to cover the ointment during the application period and to remove the remainder thereafter.

Q. Were the active moieties in plasma appropriately identified and measured?
Yes, see Section 2.6 for validation methods

2.3. Intrinsic Factors:

Pediatrics:

In this submission, the applicant included a request for a partial waiver of pediatric studies for Dovobet ointment in pediatric patients aged 0-11 years old. For the pediatric patients aged 12-17 years old with psoriasis vulgaris, the applicant agreed to conduct the study, but requested a deferral for the study to be conducted as a post approval commitment. The protocol for this study has been submitted to the IND and it is currently being reviewed by the clinical division.

2.4. Extrinsic Factors

Drug-Drug Interactions:
The applicant did not conduct any drug-drug interaction studies with co-administered drugs since the systemic exposure of calcipotriol and betamethasone dipropionate was minimal. However, studies were conducted to determine if the systemic exposure of each active ingredient in the combination drug product is comparable to that obtained when the active ingredients are administered as single ingredient topical formulations.

How does the systemic exposure of Dovobet ointment compare to that of the currently marketed single ingredient topical formulations?

Effect of Percutaneous Absorption:

In the percutaneous absorption study (#9901 NL) with radio labeled Dovobet ointment in healthy volunteers (see table below) the results indicated that the absorption of calcipotriol from Dovobet ointment was not influenced by the presence of betamethasone dipropionate and vice versa following single and multiple doses (for calcipotriol alone).

Table 2. Excretion of ^{3}H-radioactivity per treatment group as percentage of the dose (mean ± SD, 95% confidence intervals for A^e_{total} only between brackets)

Group	I		II		III	IV	V
Treatment	Dx; ^{3}H-C		Dt; ^{3}H-C+B		Dt; ^{3}H-C (no B)	Dt; C+^{3}H-B	Dt; ^{3}H-B (no C)
Parameter	day 1	day 36	day 1	day 36			
A^e_{urine}	0.9 ± 1.0	0.4 ± 0.4	0.02 ± 0.04	0.05 ± 0.08	0.2 ± 0.1	0.03 ± 0.05	0.1 ± 0.1
A^e_{faeces}	1.4 ± 1.8	0.7 ± 0.6	0.1 ± 0.1	0.1 ± 0.2	0.3 ± 0.3	0.03 ± 0.05	0.03 ± 0.05
A^e_{total}	2.3 ± 2.8	1.1 ± 1.0	0.1 ± 0.2	0.2 ± 0.3	0.4 ± 0.4	0.05 ± 0.1	0.1 ± 0.2
95%CI A^e_{total}	(-0.7 - 5.2)	(0.0 - 2.1)	(-0.1 - 0.3)	(-0.1 - 0.4)	(-0.3 - 1.1)	(-0.1 - 0.2)	(-0.1 - 0.4)

Dx = Daivonex ointment; Dt = Daivobet ointment

C = calcipotriol; B = Betamethasone

The data of the subjects in Groups I and II (day 1) was performed in order to show that that the absorption of calcipotriol from Dovobet ointment (combination) is the same or less than from Dovonex ointment (single ingredient). The mean results show that the absorption of calcipotriol from the Dovonex ointment was higher as compared to the Dovobet ointment. This was mainly due to the contribution of Subject 04, whose absorption (2.8 % in urine and ~5 % in feces) was considerably higher as compared to the other subjects in his treatment group. However, even when the results of this subject are ignored, the absorption of calcipotriol from Dovonex appears to be higher as compared to Dovobet (1.3 % vs. 0.1 %). This would imply a difference in efficacy between the combination product and the single ingredient product. However, based on the positive efficacy results obtained for Dovobet ointment in the clinical trials (see medical review for details) and the fact that this study was conducted in healthy volunteers, this difference is unlikely to be clinically relevant

The data of the subjects in Groups I and II after four weeks administration of the unlabelled ointment indicated that absorption of ^{3}H-labelled calcipotriol from Dovonex and Dovobet after four weeks twice daily application of the respective ointment was similar to the absorption after the single application. In addition the applicant stated that there was no apparent change in the number or nature of reported adverse events (AE's), in the local tolerability assessments or in other safety assessments after the four week treatment as compared to the single dose.

The comparison of the data from treatment group III (application of Dovobet ointment with ^{3}H-labelled calcipotriol, without betamethasone) with treatment group II (day 1, application of Dovobet ointment with ^{3}H-labelled calcipotriol), indicated that betamethasone in Dovobet ointment may influence the absorption of calcipotriol. The absorption of calcipotriol from Dovobet ointment with

betamethasone was higher compared to Dovobet ointment without betamethasone (0 4% versus 0 1%). However, if one takes the variability into account this difference is minimal.

The comparison of the data from the subjects in treatment groups IV and V who received a single application of Dovobet ointment with ^{3}H labeled betamethasone, with or without calcipotriol indicated that calcipotriol in Dovobet ointment does not influence the absorption of betamethasone. In general the total absorption (0.5 ± 0.1 % vs. 0.1± 0.2 %) was comparable when one takes the variability into account.

In addition, although differences to some extent in the absorption of calcipotriol and betamethasone were observed between the treatment groups, these differences were not statistically significant ($p > 0.05$) as shown in the table below. However, it should be noted that the calculated p-values are only exploratory, as the number of subjects in this study were too small to perform formal statistical analysis.

Table 3 Statistical analysis of differences in total ^{3}H-radioactivity excretion

Treatment groups compared	treatments compared	p-value	est. diff	95%CI
Group II day 1 - Group I day 1	Dt, 3H-C+B (day 1) Dx, 3H-C (day 1)	0.0917	-2.1	-4 6 – 0 4
Group II day 36 - Group I day 36	Dt; ^{3}H-C+B (day 36) - Dx, ^{3}H-C (day 36)	0 0507	-0 9	-1 9 – 0 0
Group II day 1 - Group III	Dt, ^{3}H-C+B (day 1) - Dt, ^{3}H-C (no B)	0 1707	-0.3	-0.7 – 0.2
Group IV - Group V	Dt: C+3H-B - Dt, 3H-B (no C)	0 4372	-0 1	-0 2 – 0.1

Dx = Daivonex ointment, Dt = Daivobet ointment
C – calcipotriol, B = Betamethasone

In summary, the systemic absorption of calcipotriol from Dovobet ointment (combination formulation) was comparable to the absorption of calcipotriol from Dovonex ointment (single ingredient formulation) after a single application and multiple applications once daily for 28 days. In addition, betamethasone in Dovobet ointment had minimal influence on the systemic absorption of calcipotriol and vice versa. In general, minimal absorption (≤ 0.5 %) of calcipotriol and betamethasone from Dovobet ointment was observed.

2.5. General Biopharmaceutics

Q. What is the in vivo relationship between the to-be-marketed formulation (TBMF) and the pivotal clinical trial formulation(s)?

The applicant stated that all the batches used in the clinical development of Dovobet ® ointment have been identical to those intended to be marketed, except for the batches used in the phase I studies, where the active substances were radio-labeled (^{3}H). This was confirmed by the chemistry reviewer (Dr. E Pappas). Inserted below is a table showing the quantitative composition of the TBMF of Dovobet ointment.

Composition of Dovobet® Ointment

Name of Components	Quantity per g	Function	Reference to Standards
Drug Substances:			
Calcipotriol (as hydrate)	50 mcg [1]	Drug substance	LEO
Betamethasone dipropionate	0.643 mg [1]	Drug substance	
Excipients:			
[redacted]			
Polyoxypropylene-15 stearyl ether[4]			
[redacted] α-Tocopherol[5] [6]			
[redacted]			
[redacted]			

[redacted]

Q. What is the vasoconstrictive action of Dovobet® ointment?

The data obtained from study #MCB 9902 indicated that Dovobet ointment can be considered as a potent topical corticosteroid ointment based on its vasoconstrictive action. The relative potency of betamethasone dipropionate in Dovobet ointment compared to a marketed product (Diprosone ® ointment) was assessed in a vasoconstrictive assay study (MCB 9902) performed in healthy volunteers.

In the conditions of this study, 32 subjects met the detector criteria and were used to test bioequivalence. The parameter used for the bioequivalence evaluation was the chromameter reading (a*). According to the results obtained with a* data and using the Locke method, the 90 % confidence interval for the skin blanching response ratio (Dovobet ® ointment to Diprosone ® ointment) was (0.81; 1.04). Based on this data, the vasoconstrictive action of betamethasone dipropionate in Dovobet ® ointment was found to be equivalent to Diprosone ® ointment because the 90% confidence interval is within the Agency criteria of [0.8; 1.25]. Therefore Dovobet ointment can be considered to act as a potent corticosteroid like Diprosone ointment.

2.6. Analytical

Q. Were the analytical methods used adequately validated?

The applicant stated that S-cortisol concentrations in serum were determined by a chemiluminiscent immunoassay designed for use on the IMMULITE 2000 automated immunoassay analyzer. Since this is a standard in vitro diagnostic method for determining cortisol levels in clinical laboratories no further assay method validation was necessary.

3. Labeling Recommendation (deletions are strikethroughs and recommendations and additions are underlined text):

CLINICAL PHARMACOLOGY

Dovobet® Ointment:

Dovobet® ointment combines the pharmacological effects of calcipotriene hydrate and betamethasone dipropionate as described below.

Reviewer's Comments: The medical reviewer informed this reviewer that skin atrophy studies are not used to l topical products. Therefore, the proposed label is as follows:

In a vasoconstrictor study, the skin blanching response of Dovobet® ointment was consistent with that of a potent corticosteroid.

Calcipotriene:

Reviewer's Comments: Recommend that the applicant removes all references to the natural since it may not always apply to calcipotriene. Reviewer's proposed label is as follows:

Calcipotriene metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriene are less potent than the parent compound.

Betamethasone dipropionate:

[ ]

Reviewer's Comments: Above label incorporates information on a different indication from what this product is intended for and some of the language included seems redundant. The proposed label is as follows:

Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact-mechanisms of their actions in psoriasis vulgaris are uncertain.

Pharmacokinetics:

Pharmacokinetics:

[ ]

Reviewer's Comments: Recommend deleting the information on calcipotriene since this is redundant and re-wording the information on betamethasone as follows:

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

There are no human data regarding the distribution of corticosteroids to body organs following topical application. Nevertheless, once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids.

Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

[ ]

Reviewer's Comments: This reviewer recommends deleting these statements because this proposed language is not providing information that would be very useful to the health care provider under actual use conditions since the radio labeled studies were conducted in healthy subjects. Also it may be misleading because the Dovonex label states the following " ...approximately 6% (± 3%, SD) of the applied dose of calcipotriene is absorbed systemically when the ointment is applied topically to psoriasis plaques, or 5% (± 2.6%, SD) when applied to normal skin...".

This reviewer proposes including the HPA axis data instead as shown below:

Dovobet ointment was applied once daily for 4 weeks to adult patients (N =12) with psoriasis vulgaris to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. Of eleven patients tested, none demonstrated adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤ 18 mcg/dL.

However in another clinical study of Dovobet ointment, one patient (N =19) demonstrated adrenal suppression.

PRECAUTIONS

General:

Reviewer's Comments: ***Proposed Label by the medical reviewer is as follows:***

Hypercalcemia has been observed with use of Dovobet. If elevation of serum calcium outside the normal range occurs, discontinue treatment until normal calcium levels are restored.

4. Appendix

4.1. Consult Review: None

4.2. Proposed Package Insert

8 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1a

U.S. Patent Nos.: 4,866,048 and 6,753,013.

Manufactured by:
LEO Laboratories Ltd. (LEO Pharma)
Dublin, Ireland

[ ]

4.3. Individual Study Reviews

A. Mass Balance Studies (Percutaneous Absorption)

1. Healthy Volunteers

Study No. **MCB 9901 NL**:

Study Title: Absorption of ^{3}H-calcpotriol and ^{3}H-betamethasone from Daivonex® Leo and Daivobet® Leo Ointment in 24 healthy volunteers

Investigators:

Study Centers:

Studied period (years): August 1999 – October 1999

Objectives: To investigate the absorption and excretion balance of 3H calcipotriol from Daivonex Leo Ointment and 3 H calcipotriol and 3 H betamethasone dipropionate from Daivobet Leo ointment after single application to healthy volunteers.

To investigate the absorption and excretion balance of 3H calcipotriol from Daivonex Leo ointment and Daivobet Leo Ointment after 4 weeks twice daily application of unlabeled Daivonex Leo ointment and Daivobet Leo Ointment

Study Design: Phase I, single-centre, randomized, open, single and multiple (2 application arms) topical administration of 2.5 g 3H radiolabeled ointment to 625 cm^2 of skin on the thigh for 12 hours

Subjects: 24 healthy male volunteers ((21 Caucasians and 3 Asians). Age: 19-45 yrs (mean ±SD: 27.8 ±7.7); Weight: 64.5 -87.0 years (mean ±SD: 76.9 ±6.8).

Test product: Daivonex and Daivobet (per the sponsor, these are equivalent European products) ointment (~2.4-2.5g) with different levels of radioactivity. 0.05 mg/g 3H-calcipotriol (1.51-1.72 MBq/g 3H-radioactivity); 0.643 mg/g 3-H betamethasone dipropionate (1.68 -1.72 MBq/g 3-H radioactivity) [Dosage form/Batch nos.: Ointment/9923016 (Daivonex), L8948; 9922917, 9838381; 9922916, 9923117, 9923216]

Treatments: Two groups of **six** subjects (Groups I and II) and three groups of **four** subjects (Group III. IV and V) were to receive single topical administration of radiolabeled ointment; subjects in Groups I and II were to receive a second administration of the same radiolabeled ointment at day 36; as well as unlabeled Daivonex once daily from day 8 to 36 (28 days).

Group I: Daivonex ointment with 3-H-calcipotriol on days 1 and 36#
Group II: Daivobet ointment with 3-H-calcipotriol and unlabelled betamethasone on days 1 and 36#

Group III: Daivobet ointment with 3H-calcipotriol without betamethasone
Group IV: Daivobet ointment with unlabelled calcipotriol and 3H-betamethasone
Group V: Daivobet Ointment without calcipotriol but with 3H-betamethasone
= twice daily application of unlabelled ointment from day 8 to 35 (28 days)

Pharmacokinetic Sampling:

Blood sampling (7 mLs) ***for total radioactivity*** in serum: pre-dose and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72h and every 24 h thereafter until discharge

Urine sampling ***for total radioactivity***: pre-dose (-12-0 h) and 0-4, 4-8, 8-12, 12-24, and in 24 h intervals until discharge or until 3H radioactivity was below 50dpm/mL

Feces sampling: ***for total radioactivity***: blank and all stools in 24-h pooled fractions until discharge or until 3H Radioactivity was below 75 dpm per 400 mg homogenized feces

* Blood, urine and feces collection was on Days 1 and 36 for Groups I and II.

Safety Assessment: clinical laboratory: 24 h after application; vital signs and ECG: pre-dose and 1 and 24 h after each radiolabeled application; adverse events: daily while in clinic; physical examination: upon each discharge from the clinic; local irritation: before each radiolabeled application and before removal and at 24 h and 72 h after each radiolabeled application

Analytical Methods:

Concentrations of ^{3}H-radioactivity were measured in ointment samples, in serum, urine and feces samples and in gauze, gloves, cleaning swabs and shorts using a liquid scintillation method

Pharmacokinetic Analysis: Serum radioactivity concentrations, excretion profiles in urine and feces, recovery data from excreta and application materials

Statistical Methods: Descriptive analysis. For groups I and II the parameters for Days 1 and 36 were to be compared descriptively.

Results

Pharmacokinetic Parameters:

The mean recovery as a percentage of the total dose, per treatment group in the different matrices and in total is presented in the table below (mean ± SD):

Table 4 Recovery of ^{3}H-radioactivity per treatment group as percentage of the dose (mean ± SD)

Group	I		II		III	IV	V
Treatment	Dx; ^{3}H-C		Dt, ^{3}H-C+B		Dt; ^{3}H-C (no B)	Dt, C+^{3}H-B	Dt, ^{3}H-B (no C)
Matrix	day 1	day 36	day 1	day 36			
Gauzes	78.4 ± 7.6	78.1 ± 4.1	86.3 ± 2.1	81.8 ± 2.9	76.9 ± 2.1	86.1 ± 1.1	87.6 ± 1.2
Gloves	0.04 ± 0.05	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.05 ± 0.1	0.08 ± 0.1	0.05 ± 0.06
Short	0.6 ± 1.0	0.1 ± 0.1	0.0 ± 0.0	0.2 ± 0.3	0.0 ± 0.0	0.08 ± 0.2	0.0 ± 0.0
Urine	0.9 ± 1.0	0.4 ± 0.4	0.02 ± 0.04	0.05 ± 0.08	0.2 ± 0.1	0.03 ± 0.05	0.1 ± 0.1
Faeces	1.4 ± 1.8	0.7 ± 0.6	0.1 ± 0.1	0.1 ± 0.2	0.3 ± 0.3	0.03 ± 0.05	0.03 ± 0.05
Swabs	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.08	0.1 ± 0.08	0.1 ± 0.0	0.03 ± 0.05	0.1 ± 0.08
Total	81.5 ± 5.8	79.7 ± 3.4	86.6 ± 1.9	82.4 ± 2.9	77.4 ± 1.7	86.4 ± 1.1	87.9 ± 1.0

Dx = Daivonex ointment; Dt = Daivobet ointment
C = calcipotriol, B = Betamethasone

The average total recovery was between 77.4 % (treatment group III, day 36) and 87.9 % (treatment group V) of the dose. The vast majority of the radioactivity (77 to 88%) was accounted for by the gauzes used to cover the ointment during the application period and to remove the remainder

thereafter. Virtually no radioactivity was found on the gloves, indicating that the application was complete. For the first period of Subject 03 (treatment group I), 2.6% of the dose was accounted for by the radioactivity in his shorts. Applicant stated that this was the only incidence in which more than a trace of radioactivity (i.e. ≤ 0.7 %) was found in the shorts.

Absorption of 3H-radioactivity, as indicated by the recovery of radioactivity in urine and feces, was below 0.5% of the total applied dose for the majority of the volunteers. Sixteen subjects showed virtually no excretion in urine and fifteen showed virtually no excretion of radioactivity in feces. The total absorption of calcipotriol and betamethasone were 0.15 % and 0.06 % of the given dose from Dovobet ointment. The total absorption of calcipotriol was ~ 50 % higher (2.3 % of the given dose) from Dovonex ointment (N = 6).

The objective of the absorption assessment for Group I and Group II on day 1 was to show that the absorption of calcipotriol in Daivobet is the same or less than in Daivonex and to prove that the toxicological profile of Daivonex also can be used for Daivobet. In treatment group I, all subjects showed absorption to some extent after single application, whereas in treatment group II in three out of six subjects virtually no absorption was observed. The mean results show that the absorption of calcipotriol from the Daivonex ointment was higher as compared to the Daivobet ointment. This was mainly due to the contribution of Subject 04, in which the absorption was considerably higher as compared to the other subjects in his treatment group.
Two subjects in treatment group I (Daivonex ointment) showed relatively high excretion, both before and after the twice daily application of the ointment for 28 days. After the first application of radiolabeled ointment, Subject 04 (Group I) excreted 2.8% of the total applied dose in urine and 5% in feces. After the second application of radiolabeled ointment, he excreted 1.1% of the applied dose in urine, and 1.8% in feces. Subject 05 (Group I) excreted 1.0% of the applied dose in urine and 1.2% in feces, during the first period, and 0.3% in urine and 04% in feces during the second period. However, even when the results of subject 04 (group I) are ignored, the absorption of calcipotriol from Daivonex appears to be higher as compared to Daivobet. It should be noted, though, that the absorption was very low, in general below 1% of the applied dose, for both formulations.

The second absorption assessment of the subjects in Groups I and II at four weeks administration of the unlabelled ointment was performed in order to clarify safety issues. Absorption of 3H-labeled calcipotriol from Daivonex and Daivobet after four weeks twice daily application of the respective ointment was similar to the absorption after the single application. Only in Subject 04, the absorption was considerably lower during the second administration of radiolabeled ointment. In treatment group I, some extent of absorption was observed in five out of six subjects, whereas in treatment group II for four out of six subjects virtually no absorption was observed. There was no apparent change in the number or nature of reported Adverse Events, in the local tolerability assessments or in other safety assessments after the four week treatment as compared to the single dose.

The objective for including treatment group III (application of Daivobet ointment with 3H-labelled calcipotriol, without betamethasone) was to enable a comparison with treatment group II (day 1; application of Daivobet ointment with 3 H-labeled calcipotriol), in order to show that betamethasone in Daivobet ointment does not influence the absorption of calcipotriol. The

absorption of calcipotriol from Daivobet ointment with betamethasone was lower as compared to Daivobet ointment without betamethasone (mean = 0.1 % vs.0.4 %). In one out of four subjects in Group III virtually no absorption was observed. In treatment group III, Subject 14 showed a total excretion of 1%, and Subject 15 of 0.5%.

The subjects in treatment groups IV and V received a single application of Daivobet ointment with 3H-labeled betamethasone, respectively with or without calcipotriol. The aim for including these groups was to show that calcipotriol in Daivobet ointment does not influence the absorption of betamethasone. The overall recovery in these treatment groups was similar. In treatment group IV, three out of four subjects showed virtually no absorption at all. In treatment group V, this was the case for two out of four subjects. In all cases, absorption was below 0.5% of the applied dose.

Statistical analysis was performed in order to compare the absorption, as indicated by total excretion of 3H-radioactivity, (a) In Group I, day 1 versus Group II, day 1, (b) Group I, day 36 versus Group II day 36, (c) Group II, day 1 versus Group III and (d) Group IV versus Group V. No statistical significant differences were observed.

Almost all 3 H-radioactivity levels in serum were below the Lower Level of Quantification, with the exception of some individual values between 24 to 48 h. Only samples from Subjects 04 and 05 showed significant levels of 3H-radioactivity over a prolonged period of time (ranged from 0.0128 to 0.0769 ng equivalent/mL), which corresponds to the amount of radioactivity excreted.

Applicant's Conclusions:
Although differences to some extent in the absorption of calcipotriol and betamethasone were observed between the treatment groups, these differences were small and statistically not significant ($p > 0.05$). In general, only minimal absorption of calcipotriol from Daivonex and Daivobet ointment and of betamethasone from Daivobet ointment was observed. Absorption of calcipotriol from Daivobet ointment did not differ to a large extent from absorption of calcipotriol from Daivonex, neither after single application, nor after twice daily application for 28 days. Betamethasone in Daivobet had no or minimal Influence on the absorption rate of calcipotriol. Calcipotriol in Daivobet had no or minimal influence on the absorption rate of betamethasone.

Safety parameters indicate that all treatments were well tolerated. Application of Daivonex and Daivobet ointment twice daily for four weeks does not result in a decreasing tolerability.

Reviewer's Comments: About 12 to 23 % of the dose was not accounted for. The applicant stated that in part this may be due to the loss of the 3H-label, although absence of 3H radioactivity in serum suggests that virtually no tritiated body water is formed. Another possibility is that the ointment partly remains in the skin and was not systemically available.

The applicant stated that the calculated p-values for the statistical analysis are more exploratory because the number of subjects in this study was too small to perform a formal statistical analysis.

2. Psoriatic Patients

Absorption of calcipotriol from Dovobet ® ointment has not been directly investigated in patients with psoriasis. The applicant stated that results for the absorption of calcipotriol from Dovobet® ointment in healthy volunteers have been compared with those of previous studies conducted with calcipotriol (marketed vehicle) in healthy volunteers and in psoriasis patients in Table T1. In these studies, transdermal absorption was defined in slightly different ways depending on the study design. To compare data from all studies in the following presentation, transdermal absorption was calculated based on the cumulative excretion in urine and feces (percentage of' administered dose). When comparing the results it should be noted that there were also other differences in the methodology, including differences in the amount of radioactivity applied and the length of the follow-up period (i.e. ranged from 6-20 days).

Table T1: Comparison of absorption of calcipotriol from a single dose of Dovobet® ointment or calcipotriol (marketed vehicle)

Study	Number and type of subjects	Treatment	Percutaneous absorption (% of applied dose): Mean (Min-Max)
Dovobet® ointment			
MCB 9801 NL	4 healthy volunteers	^{3}H-calcipotriol and unlabelled betamethasone[1]	0.85
MCB 9901 NL	6 healthy volunteers	^{3}H-calcipotriol and unlabelled betamethasone[1]	0.1
	4 healthy volunteers	^{3}H-calcipotriol[2]	0.4
Calcipotriol (marketed vehicle)			
MCB 9901 NL	6 healthy volunteers	^{3}H-calcipotriol[3]	2.3
DE 127-004	5 healthy volunteers	^{3}H-calcipotriol[3]	3.3
DE 127-005	4 psoriasis patients	^{3}H-calcipotriol[3]	3.8
MC 289	5 psoriasis patients[2]	^{3}H-calcipotriol[3]	0.4

Source: Clinical Study Reports: MCB 9801 NL, MCB 9901 NL (5.3.3.1; M.5, Vol. 2, 3-5) MC 289, DE-127-004 and DE-127-005 (5.3.5.4; M.5, Vol. 79, 79, 80).

1. 2.5 g ointment was applied to an area of 625 cm^2 for 12 hours, covered by gauze or non-occlusive dressing
2. results of the 5 patients who completed the study
3. [redacted] g ointment applied for 8 hours (not covered by gauze or dressing)

Reviewer's Comments: Despite the limitations of this comparison, the data indicates that the absorption of 3H calcipotriol from Daivonex or Dovonex ointment (calcipotriol single ingredient ointment) is comparable in psoriatic patients compared to healthy volunteers when applied at the same dose for the same duration (i.e. excluding Study # MC 289)

B. Human Pharmacodynamic Studies:

1. Effects on the HPA Axis

The two HPA axis tests were performed using synthetic adrenocorticotropic hormone (ACTH) marketed in Europe, Synacthen®, in which the active compound is identical to the US product Cortrosyn® (The equivalency of the two products was reviewed and found acceptable by Dr. T. Ghosh on 05/04/04).

Study #: MCB 0201 FR
Study Title: Effect of calcipotriol/betamethasone dipropionate ointment compared to betamethasone dipropionate ointment on the HPA axis in patients with psoriasis vulgaris
Investigators:
Study Center:
Studied period:
First patient in (inclusion): April 15th, 2003
First study drug administration: April 28th, 2003
Last study drug administration: November 24th, 2003
Last patient out (completion): January 13th, 2004
Clinical Phase of Development: 1
Objectives: To compare the effect of once daily use of calcipotriol/betamethasone dipropionate ointment (Daivobet/Dovobet) with that of once daily use of betamethasone dipropionate ointment (Diprosone®) on the hypothalamic-pituitary-adrenal (HPA) axis in patients with psoriasis vulgaris.
Study Design / Methods: This was a single center, prospective, randomized, active controlled, double-blind, 2-arm, parallel group, 4-week study in patients with psoriasis vulgaris. The duration of the study for *each* patient was approximately 6 weeks, consisting of a 2-week run-in period followed by a 4-week (28 days) treatment phase. A completion visit was performed during the last day of assessment.
In total, the patients had to come to the centre for four visits:

- two visits during the screening phase: Visits 1and 2.
- two visits during the treatment phase: Visit 3 (Day 0) and Visit 4 (Day 28, completion visit). In case of premature withdrawal visit 4 was performed at that time.

Furthermore, a follow-up visit was carried out at the investigator's discretion, 2 weeks after the patient's last visit if a serious adverse event or a non serious adverse event classified as possibly/probably related to the study medication or not assessable was ongoing at visit 4
Patient Population: 24 patients (12 per arm). Female or male patients with psoriasis vulgaris on trunk and/or limbs amenable to topical treatment, with lesions involving between 15 to 30 % of the body surface area on trunk and/or limbs, excluding genitals and inverse areas, at least 18 years old, willing to participate in the study and to give written reformed consent. Patients with a normal HPA axis function defined by:

a serum cortisol concentration, obtained at 30 or 60 minutes after Synacthen® injection, above 18 mcg/dL,
a rise in serum cortisol concentrations from baseline (T=O) to 30 or 60 minutes after Synacthen® injection of at least 7 mcg/dL.

Test product: Daivobet/Dovobet ointment- calcipotriol 50 mcg/g and betamethasone dipropionate 0.5 mg/g (as dipropionate) manufactured by LEO Pharma **applied once daily for 28 days, topically, non-occlusive**. **Batch numbers / Expiry dates:** 031976101 / 05/2005, 021798101 / 04/2004
Reference Product: Diprosone® ointment, betamethasone 0.5 mg/g (as dipropionate), manufactured by Schering- Plough **applied once daily for 28 days topically, non-occlusive**.
Batch numbers/ Expiry dates: 030936101/ 09/2003, 031826101/05/2004
Patients applied the treatments at home once daily from Day 0 to day 28
Criteria for Evaluation:

Primary Endpoint: Adrenal response to Synacthen® stimulation defined as the maximum serum cortisol concentration obtained at 30 or 60 minutes.

Reviewer's Comments:
The Agency criteria of a serum cortisol concentration, obtained at 30 minutes after Synacthen® injection, ≥ 18 mcg/dL (or 500 nmol/L) was used to indicate a normal HPA axis function in this review.

Secondary Endpoints:
Adrenal response to Synacthen® stimulation defined as the maximum rise in serum cortisol concentration from time zero to 30 or 60 minutes after the Synacthen injection. 08:00 a.m. serum cortisol concentration before Synacthen injection. Mean change in PASI from Visit 3 to 4 by treatment group.
The Synacthen® test consisted of blood sampling at 8:00 a.m. (T = 0) for assessment of baseline serum cortisol concentration followed by an intravenous bolus injection of 250 mcg Synacthen ®. New blood samples were taken 30 and 60 minutes later for assessment of the Synacthen ® stimulation serum cortisol concentration. (Note: the FDA criterion is response at 30min only.)
Safety: Adverse events, clinical laboratory testing including serum calcium), reasons for drop out, evidence of adrenal suppression of possible clinical significance as defined in inclusion criterion 3 and exclusion criterion 6, according to the analysis of adrenal function.
Statistical Methods: The following data from the analysis of adrenal function were tabulated for each patient at each visit: (1) Maximum serum cortisol concentrations obtained at 30 or 60 minutes after Synacthen® injection (values above 18 mcg/dL were considered as normal response). (2) The maximum rise in serum cortisol concentrations from time zero to 30 or 60 minutes after Synacthen® injection (an increase in serum cortisol concentrations of at least 7 mcg/dL was considered as normal response). (3) 08:00 a.m. serum cortisol concentration before Synacthen® injection. The above were also summarized by treatment arm using the mean, median, SD, minimum and maximum values. Treatment arms were compared for the above variables using ANCOVA (analysis of covariance) and taking the visit 2 evaluation as covariate.

Adverse events experienced during the course of the study were individually listed, and all adverse events were summarized by treatment group using count and percentage of patients experiencing AEs and number of AEs experienced. All other safety parameters (laboratory test, blood pressure, ECG and physical examination) were listed individually and summarized using appropriate descriptive statistics. PASI data were tabulated for each visit and summarized by treatment arm. The change in PASI score from visit 3 to 4 was compared between treatment arms using a t-test.

Results:

Demographic Characteristics:

		Treatment		
		Daivobet/Dovobet	Diprosone	Total
Age (years)	**N**	12	12	24
	Mean (SD)	45.1 (12 8)	42 8 (11.7)	44.0 (12 1)
	Median	45 0	44.5	45.0
	Min-Max			

Gender	**Female**	N	7	6	13
		%	58 3	50 0	54 2
	Male	N	5	6	11
		%	41.7	50 0	45 8
Ethnic group	**Asian**	N	0	1	1
		%	0	8.3	4.2
	Caucasian	N	12	11	23
		%	**100 0**	**91.7**	**95 8**

Reviewer's Comment: Generally, treatment arms were comparable with regards to demographic characteristics.

Baseline Characteristics

Percentage of Psoriasis involving the body

		% of psoriasis involving the body				
		N	Mean	Median	SD	Minimum	Maximum
Daivobet/Dovobet	Visit 1	12	22.1	22.0	5.4		
	Visit 3	12	22.6	22.0	5.0		
Diprosone	Visit 1	12	23.5	22.5	5.2		
	Visit 3	12	23.8	24.5	5.8		
Total	Visit 1	24	22.8	22.0	5.3		
	Visit 3	24	23.2	22.5	5.3		

Patients in the Dovobet (mean (SD) =215.8 ± 96.8g, range = — g) and Diprosone (mean (SD) =207.4 ± 86.7g, range = — treatment arms used comparable amounts throughout the 4 weeks of study participation. Mean amount applied per week was 58.7 ± 23.6 and 55.2 ± 20.3g respectively.

Reviewer's Comments: The percentage of body surface area on trunk and/or limbs presenting lesions induced by the psoriasis varied from 15 to 30 % with a similar distribution in the two treatment arms. The average percentage body surface involvement was 22.1 and 23.5 in the Dovobet and the Diprosone treatment arm respectively.

Adrenal Function Tests: ***Serum Cortisol Levels:***
In the Synacthen® test performed at Visit 2 (before treatment), four patients presented abnormal baseline morning serum cortisol levels. This is summarized in table 4 below.

Table 4: Abnormal baseline cortisol levels and corresponding Synacthen® test results at Visit 2

				Serum cortisol level (mcg/dL)		
Patient No.	**Gender**	**Treatment group**	**Baseline** [a]	**30 minutes post Synacthen® test** [b]	**Maximum (60 minute level) post Synacthen® test** [b]	**Maximum rise post-Synacthen® test** [c]
10	**Male**	Diprosone®	—	—	—	—

11	**Female**	Diprosone®
13	**Female**	Diprosone®
21	**Male**	Daivobet/Dovobet

L. lower than normal range: **H.** higher than normal range
[a] normal range [b] normal range >= 18; [c] normal range >=7

As shown in Table 4, Visit 2 (i.e. before any treatment application), four patients presented abnormal basal serum cortisol levels. All these abnormal values were ascribed to the individual level of stress of the patients and were considered as not clinically significant by the investigator. However, all 24 patients presented a normal maximum rise in serum cortisol level to Synacthen® stimulation (i.e. at least 7 mcg/dL) and all but one patient (who had a maximum serum cortisol level, cg/dL, just below the reference limit /dL) had a normal maximum serum cortisol level after Synacthen®stimulation. Thus all 24 patients were considered to have a normal adrenal function at baseline and were considered eligible for the study.

At Visit 4, after 4 weeks of study treatment, the Synacthen test was performed for 23 patients (***Applicant stated that Patient 16 in the Dovobet treatment arm did not have the second Synacthen test at Visit 4 because he had the flu).***

Table 5: Individual results from the Synacthen® test results at Visit 2 and 4

Treatment	Patient number	Gender	Serum cortisol level (mcg/dL)					
			Before synacthen		T30		T60	
			Visit 2	Visit 4	Visit 2	Visit 4	Visit 2	Visit 4
Daivobet/ Dovobet	1	Female						
	2	Female						
	3	Female						
	7	Female						
	9	Male						
	12	Female						
	14	Female						
	16	Male						
	19	Male						
	20	Female						
	21	Male						
	22	Male						
Diprosone	4	Male						
	5	Male						
	6	Male						
	8	Male						
	10	Male						
	11	Female						
	13	Female						
	15	Male						
	17	Female						
	18	Female						
	23	Female						
	24	Female						

L: lower than reference range: Serum cortisol before synacthen < 10 mcg/dL; Serum cortisol after synacthen < 18 mcg/dL, Serum cortisol after synacthen < 7 mcg/dL. H: Higher than reference range: Serum cortisol before synacthen > 22.4 mcg/dL, BLQ: Below limit of quantitation.

Reviewer's Comments: Patient No. 13 had a baseline cortisol level that was < 10 mcg/dL (as per protocol) at week 4 and BLQ at week 2 and should not have been considered eligible for the study. Also the stimulated serum cortisol level obtained 30 minutes (Agency Standard) post-stimulation was < 18 mcg/dL indicating adrenal suppression following topical administration of diprosone ointment.

There were nine patients who had abnormal results for one or more of the measurements. These patients are shown in Table 6 below:

Table 6: Individual abnormal basal cortisol levels and Synacthen® test results at Visit 4

Patient No.	Gender	Treatment group	Serum cortisol level (mcg/dL) Basal[a]	30 minutes post Synacthen® test [b]	Maximum (60 minutes) post Synacthen® test [b]	Maximum rise post Synacthen® test[c]
3	**Female**	**Daivobet/Dovobet**				
4	Male	Diprosone®				
7	**Female**	**Daivobet/Dovobet**				
10	Male	Diprosone®				
13	***Female***	***Diprosone®***				
15	Male	Diprosone®				
21	**Male**	**Daivobet/Dovobet**				
23	Female	Diprosone®				
24	Female	Diprosone®				

L. lower than normal range; H. higher than normal range
[a] normal range [illegible]; [b] normal range >= 18; [c] normal range >=7

Applicant's Discussion

In the Daivobet/Dovobet treatment arm there were no cases of adrenal suppression. Three patients (# 3, 7 and 21) had basal serum cortisol levels below the lower reference limit, but all three had a normal response to Synacthen® stimulation.

In the Diprosone® treatment arm there was one patient (# 13) with signs of adrenal suppression, which was reported as a serious adverse event (SAE). At Visit 4 the basal serum cortisol level was below the limit of quantification, with a stimulated serum level of [illegible] g/dL. A repeated Synacthen test after 36 days showed the basal serum cortisol level [illegible] cg/dL) and the maximum (60 minutes) stimulated level [illegible] cg/dL) still to be low. This patient is still being followed-up. In the Diprosone® treatment arm there were also three patients (# 15, 23 and 24) with basal serum cortisol levels below the lower reference limit but all three had a normal response to Synacthen® stimulation. For one of these patients (# 23) the low level of the basal value caused it to be reported as an AE, and this patient is still being followed up. One patient (# 4) in the Diprosone® treatment arm had a rise in serum cortisol below the lower reference limit, which was probably explained by a stress-induced high basal level, in addition, one patient (# 10) had high basal serum cortisol levels, but the response to stimulation was normal.

In summary, according to the investigator's evaluation of the results of the Synacthen® test there were no patients among the 11 patients in the Daivobet/Dovobet treatment arm and one patient out

of 12 in the Diprosone ® treatment arm for whom the test indicated adrenal suppression that was described as an SAE (serious adverse event).

Sponsor's Conclusion:
No cases of possible HPA axis suppression were reported for Daivobet/Dovobet. Both treatments were shown to be effective and safe in the treatment of patients with extensive lesions of psoriasis vulgaris.

Reviewer's Comments: Based on the Agency standard (30-minutes post stimulation) patient there were actually two patients (# 13 and 23) with post-stimulation cortisol levels < 18 mcg/dL in the diprosone treatment arm. The applicant is currently following both patients up because the repetition of the Synacthen test 36 days later still indicated adrenal suppression. The applicant has not presented data in this submission that demonstrates recovery of the HPA axis in these patients. By reference, for patient # 13, applicant stated that patient # 13 was still being followed up 5 months after the end of treatment, as her adrenal function had not returned to normal. Study was completed in January 2004, so 5 months would be around June 2004, the report should have been included in this submission (the medical reviewer is currently following up on this).

Serum Calcium Results
All serum calcium values were categorized as normal, both at baseline and at end of treatment (see table below)

Plasma ionogram : cations - Calcium (mmol/l) - Reference ranges :

		Observed values				
		N	Mean	Median	SD	Minimum Maximum
Daivobet/Dovobet	Visit 1	12	2.507	2.500	0.051	
	Visit 4	12	2.425	2.420	0.085	
Diprosone	Visit 1	12	2.512	2.515	0.055	
	Visit 4	12	2.436	2.435	0.072	

Study #: MCB 0102 INT
Study Title: Repeated courses of calcipotriol/betamethasone dipropionate in psoriasis vulgaris/
International Coordinating Investigator:
Study Center (s):

Studied period: 23-Aug-2002 to 20-Apr-2004
Clinical Phase of Development: Phase III
Objectives: To determine the safety and efficacy of the following in the treatment of patients with psoriasis vulgaris: 52 weeks of Dovobet treatment; 52 weeks of alternating 4 week periods of

Dovobet treatment and calcipotriol ointment; 4 weeks of Dovobet treatment followed by 48 weeks of calcipotriol treatment.

Study Design/ Methods: An international, multicenter, prospective, randomized, double-blind, 3 arm, parallel group, 52 week safety study. Patient with psoriasis vulgaris were randomized in a 1:1:1 ratio to one of the three treatment groups described above. Every 4 weeks investigators assessed adverse events and the global disease severity on a 6 category scale (disease absent to very severe), and patients assessed study treatment as either satisfactory or not satisfactory. Adrenal function testing was performed at week 0, 4, 12, and end of study in patients at two UK centers. The following table summarizes the additional study procedures for patients at centers UK068 and UK164:

Visits	**-1[a]**	**1**	**2**	**3**	**4**	**5 to 13**	**14**	**Follow - up [c]**
Weeks	**-4[a]**	**0**	**4**	**8**	**12**	**16 to 48**	**52**	**+ 6 weeks [c]**
Washout of topical corticosteroid treatment	*							
Adrenal function testing (blood & urine)		*	*				*[b]	*
Adrenal function testing (urine only)					*			

a) If required for washout of topical corticosteroid treatment.
b) Or at end of study in case of premature withdrawals
c) If required for patients with evidence of adrenal suppression of possible clinical significance

Patient Population: 636 enrolled, 634 randomized: 212 to the combination group, 213 to the combination/calcipotriol (4/4 alt.) group and 209 to the *combination/calcipotriol* (4/48) group. All randomized patients were included in the ITT- analysis set, 626 patients were included in the safety analysis set: 207 in the combination group, 213 in the combination/calcipotriol (4/4 alt.) group and 206 in the combination/calcipotriol (4/48) group.

Diagnosis and Main Criteria for Patient Selection; Patients ≥ 18 years of age with a diagnosis of psoriasis vulgaris of the body of at least moderate severity and amenable to topical treatment were selected. Patients with any of the following were excluded: more than 30% of body surface area affected; erythrodermic, exfoliative or pustular psoriasis; concurrent use of anti-psoriatic treatments (systemic, topical or UV); disorders of calcium metabolism; other skin conditions present on psoriatic areas of the body.

Test product: Dovobet (calcipotriol 50mcg/g + betamethasone dipropionate 0.5mg/g) ointment applied once daily as required. Lot numbers: 021228101, 021798101 and 031976101.

Reference Product: Dovonex (Calcipotriol 50 mcg/g) ointment applied once daily as required. Lot numbers: 021228201 and 040576101

During the whole study, the mean weight of study medication used per patient was 898.8g in the combination group, 892.5g in the combination/calcipotriol (4/4 alt.) group, and 1044.0g in the combination/calcipotriol (4/48) group.

Criteria for Evaluation:

Efficacy: The investigators' global assessment of disease severity (with disease absent, very mild or mild being considered as 'satisfactory') and the patients' global assessment of study treatment (secondary response criteria).

Safety: Adverse drug reactions of any type and adverse events of concern associated with long term topical corticosteroid use where relationship to study medication was at least a reasonable possibility as identified by an independent Adjudication Panel (primary response criteria) and

adverse events of any type, weight of study medication used, reasons for withdrawal and results of adrenal function tests (secondary response criteria).

Adrenal Function tests performed:

Synacthen ® test

This test was performed at week 0 (visit 1), week 4 (visit 2), at the end of the study (week 52 [visit 14 or earlier] or at the time of premature withdrawal) and, in those patients where the end-of-study laboratory values showed evidence of adrenal suppression of possible clinical significance, 6 weeks after the end of the study.

A 5mL sample of venous blood was drawn at 09.00am, and then 250 microgram tetracosactide (Synacthen®, Alliance Pharmaceuticals, 250 micrograms [as acetate] /mL) injected intravenously as a bolus dose. Two further 5mLvenous blood samples were drawn 30 and 60 minutes after injection. Serum cortisol concentrations were determined for each blood sample.

ACTH (adrenocorticotrophic hormone) test

This test was performed at week 0 (visit 1), week 4 (visit 2) at the end of the study (week 52 [visit 14 or earlier] or at the time of premature withdrawal) and, in those patients where the end-of-study laboratory values showed evidence of adrenal suppression of possible clinical significance, 6 weeks after the end of the study.

A 3mL sample of venous blood was drawn at 09.00am prior to the Synacthen® injection. The plasma ACTH concentration of this sample was determined.

24 hour urinary free cortisol and creatinine

Patients collected a 24 hour urine sample over the 24 hour period preceding visit 1 (week 0), visit 2 (week 4), visit 4 (week 12), the end-of-study visit and, in those patients where the end-of-study laboratory values showed evidence of adrenal suppression of possible clinical significance, 6 weeks after the end of the study.

Urinary concentrations of cortisol and creatinine in this sample were determined, and the 24 hour production of urinary cortisol and creatinine calculated using the concentration and the urine volume collected.

Analysis of adrenal function

The following were tabulated and summarized by treatment group and center for each patient in the safety analysis set at centers UK068 and UK164 at each laboratory assessment visit:

- Serum cortisol concentration prior to Synacthen® injection and 30 and 60 minutes afterwards (as noted earlier, the FDA utilizes the 30min determination, only in its evaluation.)
- Change in serum cortisol concentration from time zero to 30 and 60 minutes after Synacthen ® injection
- Urinary cortisol product on over 24 hours
- Plasma ACTH concentration prior to Synacthen ® injection

- Urinary creatinine production over 24 hours

In this study the serum cortisol values were given in nmol/L. The applicant used a conversion factor of 0.036247 to convert these values to mcg/dL. The conversion factor was derived from the molecular weight of cortisol (= 362.47).

Reviewer's Comments: If one applies this conversion factor to the normal level of 18 mcg/dL = 496.6 nmol/L ~ 500 nmol/L). This is value currently stated in the CIAS draft guidance, so this conversion factor is acceptable.

Patients were classified as to whether or not they had evidence of adrenal suppression of possible clinical significance by the Consultant Fndocrinologist and this was tabulated at each laboratory assessment visit by treatment group and center. A narrative was written for each patient.

Results: The medical reviewer is currently reviewing the safety and efficacy results. This review will mainly focus on the results generated for the adrenal function tests at the two UK sites.

Applicant's Discussion:

Nineteen patients underwent laboratory testing of adrenal function, 7 in the Dovobet alone group, 6 in the combination/calcipotriol (4/4 alt.) group and 6 in the combination/calcipotriol (4/48) group. There were three patients who had one or more abnormal results according to Cortrosyn® criteria during the study (Table T4 below).

Table T4: Patients with abnormal serum cortisol values. HPA axis substudy of MCB 0102 INT.

Treatment Patient No.	Serum cortisol								
	Baseline			After 4 weeks' treatment			End of treatment (up to 52 weeks)		
	Basal[1]	30-min post Synac-then[2]	30-min rise[3]	Basal[1]	30-min post Synac-then[2]	30-min rise[3]	Basal[1]	30-min post Synac-then[2]	30-min rise[3]
Dovobet® ointment od 52 weeks									

Applicant's Discussion:

One patient in the Dovobet® ointment 52 wks group (No. 6864) had normal results at baseline and after 4 weeks' treatment. At end of treatment (52 weeks) this patient had a rise from 0 to 30 minutes below 7 mcg/dL (, corresponding to cg/dL). However, this patient had a high level of serum cortisol mol/L, corresponding tc icg/dL) before Synacthen® stimulation, and the result was not evaluated as adrenal suppression.

Reviewer's Comment: I agree with the applicant since patient meets the Agency criteria.

One patient in the Dovobet® ointment 4 wks/calcipotriol 4 wks alternating group (No. 6857) had normal results at baseline and after 4 weeks' treatment. At end of treatment (52 weeks) this patient had a 30-minute level below 18 mcg/dL (nol/L, corresponding tc cg/dL), which was below the basal level of 354 nmol/L (mcg/dL), resulting in a negative rise. However, this patient had an adequate value at 60 minutes iol/L, corresponding to mcg/dL) and the result was therefore not evaluated as adrenal suppression.

Reviewer's Comment: I do not agree with the applicant. Based on the Agency standard (i.e. 30 minute level) this patients' data indicates adrenal suppression at the end of 52 weeks of treatment.

One patient in the Dovobet® ointment 4 wks/calcipotriol 48 wks group (No. 6866) had basal and 30 minute values just below the normal limit at baseline. At the 4-week and 52-week tests the 30-minute levels were below 18 mcg/dL. mol/L, corresponding to mcg/dL, respectively). At baseline and at week 4 the values were not considered to indicate adrenal suppression as the 60-minute values were adequate (mol/L, corresponding tc and icg/dL, respectively) but at week 52 (after 48 weeks of calcipotriol treatment) the patient was assessed to have borderline adrenal suppression. At follow-up the 30-minute value was still low (orresponding to ~ /dL), but the 60-minute value was adequate nol/L, corresponding tc mcg/dL)

Reviewer's Comments: I do not agree with the applicant. Based on the Agency standard (30-minute levels), this patient's data indicates adrenal suppression after 4 weeks and 52 weeks of treatment with Dovobet.

Study # MCB 9905 INT:
Study Title: Calcipotriol/betamethasone once and twice daily in psoriasis vulgaris.
International Coordinating Investigator:
France
Study Center (s): Patients were recruited from 51 centers in

Studied period: The first patient entered the study on 18 January 2000 and the last patient visit was on 2 August 2000.
Clinical Phase of Development: Phase III
Objectives: To compare the clinical efficacy, in terms of the percentage reduction in Psoriasis Area and Severity Index (PASI) from baseline to end of treatment:

- combination of calcipotriol plus betamethasone dipropionate in new ointment vehicle used once daily versus the new ointment vehicle,

- combination of calcipotriol plus betamethasone dipropionate in new ointment vehicle used once daily versus calcipotriol (Daivonex®/Dovonex®) ointment alone used twice daily,
- combination of calclpotriol plus betamethasone dipropionate in new ointment vehicle used once daily versus combination of calcipotriol plus betamethasone dipropionate in new ointment vehicle used twice daily,

In patients with psoriasis vulgaris after 4 weeks treatment.

Study Design/ Methods: An international, multicenter, prospective, randomized, double-blind, vehicle controlled, 4 arms, parallel group study comparing up to 4 weeks treatment of psoriasis vulgaris with either:

i. calcipotriol 50 mcg/g (as hydrate) plus betamethasone 0.5mg/g (as dipropionate) in a new ointment vehicle used once daily (evening) and new ointment vehicle used once daily (morning),

or

ii. calcipotriol 50mcg/g (as hydrate) plus betamethasone 0.5mg/g (as dipropionate) in a new ointment vehicle used twice daily, or

iii. calcipotriol 50mcg/g (as anhydrate) in the currently marketed ointment vehicle (Daivonex®/Dovonex®) used twice dally,

or

iv. new ointment vehicle used twice daily

Patients were assessed on inclusion and after l, 2 and 4 weeks of treatment.

Diagnosis and Main Criteria for Patient Selection; Outpatients aged 18 years or above, of either sex who had a clinical diagnosis of psoriasis vulgaris, with at least 10% extent in one or more body regions were included in the study (i.e. a minimum PASI score for extent of 2 and at least one body region), thickness and scaliness scores was required.

Test product: Dovobet (Calcipotriol 50 mcg/g (as hydrate) plus betamethasone 0.5mg/g as dipropionate) ointment [Batch Number: 9930583, Expiry Date: October, 2000]. The mean (SD) amount of medication used per week was 20.9 (13.0) g [range = _ —_ for once daily and 43.0 (27.6) g [range = ' —_ for twice daily use.

Reference Product (s): There were two reference products; calcipotriol 50mcg/g (as anhydrate) ointment (Daivonex®/Dovonex®), [Batch Number 9930581, Expiry Date: September, 2001] and new ointment vehicle [Batch Number 992788201, 992798301, 992798303, Expiry Date October 2001 and May 2002 respectively]. The mean (SD) amount of medication used was 44.2 (27.4) g [range = —_ for calcipotriol.

Criteria for Evaluation:

Efficacy: The primary response criterion was the percentage change in PASI from baseline to end of treatment. Extent and severity of psoriasis were recorded at every visit (Weeks 1, 2, and 4) using PASI. A target lesion was selected at visit 1 and assessed for redness, thickness and scaliness at each visit. The overall efficacy assessment was recorded by the investigator and the patient at each visit.

Safety: Adverse events, reasons for withdrawal from the study and any changes in the laboratory parameters from visit 1 to end of treatment were analyzed. Blood samples were taken at visit 1 and at end of treatment to check albumin corrected serum calcium. Adverse events were recorded at visit 2, 3 and 4. The ratio of end of treatment value to baseline value was calculated for each laboratory parameter. Estimation was based on logarithmic transformed data. The geometric mean

ratio and standard deviation (SD) of mean as a percentage of the mean were calculated using the following formulae:

Geometric mean of ratio = exp [mean (log (ratio))] (1)

And,

SD as a percentage of the geometric mean = 100 x {exp (SD (log (ratio)))-1]. (2)

Reviewer's Comments: Calculation for SD is not clear

Summary Results: This reviewer will only be discussing results of the serum calcium data in this review. Please see medical review for a detailed review of the efficacy and safety data from this study.

Patients Studied: Eight hundred and twenty eight patients were randomized: 152 in the combination (calcipotriol plus betamethasone dipropionate) once daily group, 237 in the combination (calcipotriol plus betamethasone dipropionate) twice daily group, 231 in the calcipotriol group and 208 in the vehicle group. The mean age of patients was 49 years old and 64 % were males. The mean duration of psoriasis was 18.3 years and the mean baseline score of PASI was 10.5.

Laboratory Examination:

Thirty seven patients were excluded from all tabulations of laboratory data: Seven patients failed to provide blood samples at visit 4. Twenty nine patients withdrew before visit and had no end of treatment laboratory examination. For one patient, no blood sample was taken at visit 1.

The geometric mean ratio for each of the laboratory parameters was close to one, indicating that the mean values at the end of treatment were similar to those at baseline (Table 45). The minimum and maximum changes indicate there were no individual clinically important changes.

Table 45 : Ratio of laboratory parameters at end of treatment to visit 1

Laboratory parameter Ratio of end of treatment value to baseline value	Combination once/day (n=151)	Combination twice/day (n=235)	Calcipotriol (n=227)	Vehicle (n=208)
Albumin				
Mean1	0.99	0.99	0.98	0.99
SD2	5.61	5.36	5.89	5.40
Minimum	—	—	—	—
Maximum				
Number	144	226	216	198
Calcium				
Mean1	1.00	1.00	1.00	1.00
SD2	3.74	3.91	4.34	4.12
Minimum	—	—	—	—
Maximum				
Number	144	226	216	198
Calcium (albumin adjusted)				
Mean1	1.00	1.00	1.01	1.00
SD2	3.63	3.84	4.22	[illegible]
Minimum	—	—	—	—
Maximum				
Number	[illegible]	226	216	198

1) Geometric mean.
2)Standard deviation of mean as a percentage of the mean.

Each laboratory parameter was categorized as 'low "," normal", or "high", with respect to their corresponding reference range and any change between categories summarized in "shift tables". Most patients had "normal", values for each laboratory parameter at baseline and at end of treatment.

In the Dovobet once daily group, 9 (6.4%) of the 141 patients with a "normal" albumin corrected serum calcium value at baseline, had a "high" value at end of treatment compared to 5 (2.3%) of the 218 patients in the Combination twice daily group, 13 (6.1%) of the 213 patients in the Calcipotriol group, and 7 (3.6%) of the 193 patients in the vehicle group.

Applicant's Conclusions
The geometric mean ratio of the end of treatment values to the baseline values for albumin corrected calcium was 1.00 for the Dovobet (combination) ointment used once daily, Vehicle and Combination used twice daily groups and, 1.01 for the Calcipotriol group. Therefore no mean change in albumin corrected calcium was seen. There were no clinically important changes in any albumin corrected serum calcium values during the study in individual patients in all groups.

Study # MCB 9904 INT
Study Title: Calcipotriol/betamethasone versus calcipotriol alone versus betamethasone alone in psoriasis vulgaris.
International Coordinating Investigator:

Study Center (s):

Studied period: The first patient entered the study on 8th December, 1999 and the last patient visit was on 22nd June 2000.
Clinical Phase of Development: Phase III
Objectives: To compare the clinical efficacy, in terms of the percentage reduction in PASI, of the fixed combination with calcipotriol ointment alone, and with betamethasone dipropionate ointment alone in patients with psoriasis vulgaris after up to 4 weeks treatment.
Study Design/ Methods: An international, multicenter, prospective, randomized, double-blind, 3 arms, parallel group study divided into two phases. Phase I, the double-blind study medication phase, lasted up to 4 weeks. During this phase, patients with psoriasis vulgaris were randomized to treatment as follows:

i. calcipotriol 50 mcg/g (as hydrate) plus betamethasone [redacted] (as dipropionate) in a new ointment base

or

ii. calcipotriol 50mcg/g in the currently marketed ointment base (Daivonex®/Dovonex®) used twice dally,

or

iv. betamethasone 0.5 mg/g (as dipropionate) in a currently marketed ointment base (Diprosone ®)

After completion of this phase, all patients entered Phase 2 and received open-label treatment with calcipotriol 50 mcg/g ointment (Daivonex®/Dovonex®) for 4 weeks.
Patients whose psoriasis cleared before the end of Phase 1 entered Phase 2 at this time. Patients who cleared during Phase 1 were instructed to use this treatment only if required. Patients were

assessed on inclusion and after 1, 2 and 4 weeks in Phase 1 and after 1 and 4 weeks in Phase 2. Phase 1 lasted up to 4 weeks. Phase lasted 4 weeks.

Diagnosis and Main Criteria for Patient Selection; Patients aged 18 years or above, of either sex who had a clinical diagnosis of psoriasis vulgaris, with at least 10% of arm, and/or 10 % of trunk, and/or 10 % of legs. For the target psoriatic lesion, a minimum PASI score of one for each of the redness, thickness and scaliness scores was also required.

Test product: Calcipotriol 50 mcg/g (as hydrate) plus betamethasone 0.5mg/g (as dipropionate) [Batch Number: 9930584, Expiry Date: October, 2001].

Reference Product (s): There were two reference products; calcipotriol 50mcg/g (as anhydrate) ointment (Daivonex®), [Batch Number 9930582, Expiry Date: September, 2001] and betamethasone dipropionate ointment (manufactured by Schering-Plough Ltd.) [Batch Numbers 00 047 81 01, 993348201, 993348101, Expiry Dates: July 2000, May 2000 and May 2000 respectively].

Dosing Regimen: All ointments were applied twice-daily. Maximum usage was 100g/week. The ointment was applied to the affected skin area and gently rubbed in.

Criteria for Evaluation:

Efficacy: The primary response criterion was the percentage change in PASI from baseline to end of treatment visit for Phase 1. Extent and Severity of psoriasis were recorded at every visit using the PASI. Investigators selected a target lesion at visit 1 and at each visit assessed redness, thickness and scaliness of this lesion on a 9 point scale from absent to very severe. At weeks 1, 2 and 4 in Phase 1, investigators and patients recorded the overall efficacy assessment on a 6 point scale: worse, unchanged, slight improvement, moderate improvement, marked improvement, clearance.

Safety: Adverse events were recorded at all visits after visit 1. Blood samples were taken at visit 1 and at end of Phase 1 to check albumin corrected serum calcium. Albumin corrected serum calcium (mmol/l) was calculated as: (total serum calcium (mmol/l) + [0.02 x (40-serum albumin (g/l)]). The ratio of end of treatment value to baseline value was calculated for each laboratory parameter (albumin, calcium and corrected calcium). Estimation was based on logarithmic transformed data. The geometric mean ratio and standard deviation (SD) of mean as a percentage of the mean were calculated using the following formulae:

Geometric mean of ratio = exp [mean (log (ratio))] (1)

and,

SD as a percentage of the geometric mean = 100 x [exp (SD (log(ratio)))-1]. (2)

Reviewer's Comments: Calculation for SD is not clear

Summary Results: This reviewer will only be discussing results of the serum calcium data in this review. Please see medical review for a detailed review of the efficacy and safety data from this study.

Patients Studied: 1106 patients were included in the randomized patient population (372 to combination, 369 to calcipotriol, and 365 to betamethasone dipropionate). The Phase 2 population consisted of 1020 patients for efficacy and safety analysis (344 combination, 332 calcipotriol, 344 betamethasone dipropionate). At baseline the mean age was 47.6 years combination, 47.6 years calcipotriol, 46.0 years betamethasone dipropionate). The proportion of male patients was 58.1 % combination, 60.4 % calcipotriol, and 60.8 % betamethasone dipropionate. The mean age of patients was 49 years old and 64 % were males. The mean duration of psoriasis was 19, 18.6 and 17.7 years for combination, calcipotriol and betamethasone dipropionate respectively.

Laboratory Examination:

Twenty seven patients were excluded from all tabulations of laboratory data due to failure to provide samples or insufficient samples.

The geometric mean ratio for each of the laboratory parameters was close to one for all treatment groups, indicating that the mean values at the end of Phase 1 treatment was similar to those at baseline (Table 65).

There was one patient in the combination group whose corrected calcium value at the end of Phase 1 was $\geq$ 10% higher that that at baseline, compared to one patient in the calcipotriol group and no patients in the betamethasone group. For the one patient in the combination group, the corrected calcium value at the end of Phase 1 was still within the reference range. For the one patient in the calcipotriol group, the corrected calcium value at the end of Phase 1 was slightly above the upper limit of the reference range, at ___ mmol/l (upper limit of reference range =2.54mmol/l).

Table 65: *Ratio of laboratory parameters at the end of Phase 1 treatment to baseline: safety population*

Laboratory parameter Ratio of end of Phase 1 treatment value to baseline value	Combination (n=370)	Calcipotriol (n=366)	Betamethasone (n=365)
Albumin			
Mean[1]	1.00	0.99	0.99
SD[2]	6.00	5.30	5.58
Minimum	—	—	—
Maximum			
Number	361	357	356
Calcium			
Mean[1]	1.00	0.99	0.99
SD[2]	4.09	3.72	3.96
Minimum	—	—	—
Maximum			
Number	361	357	356
Corrected calcium			
Mean[1]	1.00	1.00	0.99
SD[2]	3.48	3.22	3.33
Minimum	—	—	—
Maximum			
Number	361	357	356

1) Geometric mean.
2) Standard deviation of mean as a percentage of the mean.

Most patients had 'normal' values for each laboratory parameter at baseline and at end of Phase 1 treatment. In the combination group, six (1.7%) of the 354 patients with a 'normal' albumin corrected serum calcium value at baseline, had a 'high' value at end of Phase 1 treatment compared to seven (2.0%) of the 350 patients in the calcipotriol group and three (0.9%) of the 351 patients in the betamethasone group.

One of the five patients in the combination group with a 'high' albumin corrected serum calcium value at baseline, had a 'normal' value at end of Phase 1 treatment compared to five of the six patients in the calcipotriol group and one of the five patients in the betamethasone group.
Applicant's Conclusions: The geometric mean ratio of the end of Phase 1 treatment values to the baseline values for albumin corrected serum calcium was 1.00 for the combination and calcipotriol treatment groups and 0.99 for the betamethasone dipropionate group. Therefore no mean change in albumin corrected serum calcium was seen. There were no clinically important changes in any albumin corrected serum calcium values during the study in individual patients in the combination group.

Study # MCB 9802 INT
Study Title: Calcipotriol/betamethasone in plaque psoriasis (psoriasis vulgaris)
International Coordinating Investigator:
Study Center (s):

Studied period: The first patient entered the study on 25th, February, 1999 and the last patient visit was on 29 July, 1999 giving a study duration of 22 weeks. The study duration ranged from 8 weeks in
Clinical Phase of Development: Phase III
Objectives: To compare the clinical efficacy of calcipotriol plus betamethasone dipropionate in the new vehicle with the vehicle alone, betamethasone in the new vehicle and calcipotriol in the new vehicle, all applied twice daily in patients with psoriasis vulgaris after up to 4 weeks treatment.
Study Design/ Methods: An international, multicenter, prospective, randomized, double-blind, vehicle controlled, 4 arms, parallel group study comparing up to 4 weeks treatment of psoriasis vulgaris with either:
i. calcipotriol 50 mcg/g (as hydrate) plus betamethasone 0.5mg/g (as dipropionate) in a new ointment base,
or ii. calcipotriol 50mcg/g (as hydrate) in a new ointment base
or iii. betamethasone 0.5 mg/g (as dipropionate) in the new ointment base
or iv. new ointment base
Patients were assessed on inclusion and after l, 2 and 4 weeks of treatment.
Diagnosis and Main Criteria for Patient Selection; Patients aged 18 years or above, of either sex who had a clinical diagnosis of psoriasis vulgaris, affecting at least 10% extent of arms, and/or of trunk and/or of legs, were included in the study.
Test product: Calcipotriol 50 mcg/g (as hydrate) plus betamethasone 0.5mg/g (as dipropionate) in a new ointment vehicle [Batch Number: 9838381, Expiry Date: December, 2000]
Reference Product (s): Calcipotriol 50mcg/g (as anhydrate) ointment in the same ointment base as the combination [Batch Number 9838182, Expiry Date: December, 2000], betamethasone 0.5 mg/g in the same ointment base as the combination product [Batch Number 9838181, Expiry Date: December, 2000], and ointment vehicle of the combination product [Batch Number 983638101, Expiry Date: December, 2000].
Dosing Regimen: The ointment was applied twice-daily. The ointment was applied to the affected skin area and gently rubbed in.
Criteria for Evaluation:

Efficacy: The primary response criterion was the percentage change in psoriasis area and severity index (PASI) from baseline to end of treatment. Extent and severity of psoriasis were recorded at every visit (Weeks 1, 2, and 4) using PASI. A target lesion was selected at visit 1 and assessed for redness, thickness and scaliness at each visit. The overall efficacy assessment was recorded by the investigator and the patient at each visit.

Safety: Blood samples were taken at visit 1 and at end of treatment to check albumin corrected serum calcium. Adverse events were recorded at visit 2, 3 and 4. The ratio of end of treatment value to baseline value was calculated for each laboratory parameter (serum albumin, serum calcium and albumin corrected serum calcium).

Summary Results: This reviewer will only be discussing results of the serum calcium data in this review. Please see medical review for a detailed review of the efficacy and safety data from this study.

Patients Studied: 1040 patients were randomized in the randomized population: 307 in the combination group, 311 in the calcipotriol group, 313 in the betamethasone group and 109 in the vehicle group. At baseline the mean age was 47.5 years combination, 46.3 years calcipotriol, 47.2 years betamethasone dipropionate and 47.8 years vehicle). The proportion of male patients was 57.0 % combination, 59.2 % calcipotriol, and 58.5 % betamethasone dipropionate and 59.6 %vehicle. The mean duration of psoriasis was 19.2, 18.1 and 18.9 years and 18.2 years for combination, calcipotriol, betamethasone dipropionate and vehicle respectively.

Laboratory Examination:

Twenty-five patients were excluded from all tabulations of laboratory data due to failure to provide samples (23 patients), insufficient samples (1 patient), no request form (1 patient). The ratio of end of treatment value to baseline value was calculated for each laboratory parameter.

The geometric mean ratio for each of the laboratory parameters was close to one, indicating that the mean values at the end of treatment were similar to those at baseline (Table 48).

Table 48: *Ratio of laboratory parameters at end of treatment to visit 1*

Laboratory parameter Ratio of end of treatment value to baseline value	Combination (n=304)	Calcipotriol (n=308)	Betamethasone (n=313)	Vehicle (n=108)
Albumin				
Mean[1]	1.00	0.99	1.00	0.99
SD[2]	4.85	5.33	4.93	4.44
Minimum				
Maximum				
Number	299	300	303	106
Calcium				
Mean[1]	1.00	1.00	1.00	1.00
SD[2]	4.08	3.99	3.83	3.79
Minimum				
Maximum				
Number	299	299	303	106
Calcium (albumin adjusted)				
Mean[1]	1.00	1.00	1.00	1.00
SD[2]	3.88	3.60	3.47	3.40
Minimum				
Maximum				
Number	299	299	303	106

1) Geometric mean.
2) Standard deviation of mean as a percentage of the mean.

Most patients had 'normal' values for each laboratory parameter at baseline and at end of treatment. In the combination group, four (1.4%) of the 293 patients with a 'normal' albumin corrected serum calcium value at baseline, had a 'high' value at end of treatment compared to two (0.7%) of the 293 patients in the calcipotriol group, three (1.0%) of the 295 patients in the betamethasone group, and two (1.9%) of the 104 patients in the vehicle group.
In the combination group, three of the five patients with a 'high' albumin corrected serum calcium value at baseline, had a 'normal' value at end of treatment compared to four of the five patients in the calcipotriol group, four of the eight patients in the betamethasone group, and one of the two patients in the vehicle group.

Reviewers Comments: Overall the mean albumin adjusted serum was comparable between treatments and between od and bid dosing. However, the individual data indicated that hypercalcemia was observed in some patients following treatment with Dovobet ointment once daily for 4 weeks as per the intended label. Although the applicant states that the percentage of patients observed with hypercalcemia is low, the information should still be incorporated into the label.

Effects of in Calcipotriol Ointment on Calcium Metabolism
Applicant did not determine calcium levels in urine following topical administration of Dovobet ointment in any of the studies provided in this submission. This information was basically extrapolated from the previous studies conducted with calcipotriol ointment alone.
The applicant stated that data on 24-hour urinary excretion obtained for Dovonex ointment (single ingredient formulation) are relevant when evaluating absorption of calcipotriol from Dovobet ointment (combo formulation) because the absorption of calcipotriol from the two products can be considered to be similar when based on an overall evaluation of the radio labeled absorption study (MCB 9901 NL). Also, it is believed that increased urinary excretion of calcium could be an early and more sensitive sign of increased absorption than total serum calcium.

Urinary excretion of calcium was investigated in four clinical studies (MC 489, MC 9301 INT, DE-127-018 and DE-127-006) with the currently marketed Dovonex ointment in patients with plaques psoriasis. *These studies were not reviewed in detail because they were not conducted with Dovobet ointment.*

In these 4 studies the applicant stated that although urinary excretion of calcium showed some variation over time in most of the studies, no trend of increased urinary excretion during treatment and no difference between Dovonex and the comparator treatments was observed at the proposed dosing regimen (less than 100g/week).
Sponsor's Conclusions: When used in doses of less than 100 g per week, calcipotriol from Dovonex ointment did not show an effect on calcium metabolism. In two other studies in the literature, using doses of 200-360g per week (representing at least twice the recommended maximum dosage), there were significant increases in serum calcium and urinary excretion of calcium.

Vasoconstriction Study

Study # MCB 9902 FR

Title of study: In vivo bioequivalence study of betamethasone dipropionate in Daivobet® ointment (LEO) to Diprosone® ointment according to the FDA guideline for vasoconstrictor bioassay
Investigator:
Study Center(s):
Studied Period: Pilot Part: First subject in: July 30th, 1999; last subject out: August 13th, 1999
Pivotal Part: First subject in: September 30th, 1999; last subject out: December 17th, 1999
Objectives: The aim of this study was to document the bioequivalence of betamethasone dipropionate in Daivobet® ointment, containing calcipotriol (50 mcg/g) plus betamethasone dipropionate (0.5 mg/g) (LEO) test product), and Diprosone® ointment containing betamethasone dipropionate (0.5 mg/g) (Schering-Plough) (reference product) according to the FDA guidelines on vasoconstrictor bioassay for topical corticosteroids.

Methodology / Study design: This was a randomized, double-blind, single centre, bioequivalence study according to the FDA guidelines on vasoconstrictor bioassay for corticosteroids in healthy subjects. The study was conducted in two parts: The pilot part and the pivotal part allowed documentation of the bioequivalence of the test product to the reference product. Both the pilot and pivotal parts of the study were conducted in "responder" subjects. The present report gives the results of the pilot part only. A second manuscript reports the methodology and the results of the pivotal part.

The Pilot Part

Objective: To determine the dose-duration/response relationship of the reference product, thus providing ED50, D1 and D2 to be used in the pivotal part as well as an estimate of the number of subjects expected to meet the D1/D2 ratio of AUC values in the pivotal part ("detector" subjects, i.e. subject whose AUC at D_2 was at least equal to 1.25 times the AUC at D_1 and both AUC < 0 (i.e. negative), D_1 being the dose-duration corresponding to 0.5 times ED50, D2 the dose-duration corresponding to 2 times and ED50 the dose-duration of the reference product at which the effect was half-maximal.
Study Design: Single center, randomized, double-blind study
Study Population: 12 healthy subjects (responders) aged between 18 and 45 years of age. All subjects who withdrew had to be replaced. A responder was defined as a subject who shows a response (i.e. vasoconstriction) when dosed with the reference product. The responder was selected by applying the reference product under non occlusive conditions for duration of 4 hours, on each ventral upper arm and a visual reading of the application site 14 hours after removal. Responders are subjects who showed a change in the chromametric a* value (difference from untreated skin) of 0.5 or more and a visual reading of 1 or more on non-occluded skin.
Reviewer's Comment: Guidance recommends that assessment should be done 2 hrs following drug product removal. However, the applicant was still able to observe skin blanching in subjects and choose responders despite readings being taken at a longer period of time after removal.
Test Sites: Twelve test sites located on the forearms, equally divided between the two forearms, each 1.55 cm in diameter, separated at least 2.5 cm center to center and no closer than 3 to 4 cm to the antecubital fossa or to the wrist were delineated using a circular template. Eight of the sites were randomized to receive one of the dose-durations (corresponding to durations of 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 hours). The remaining four sites served as untreated sites.

Treatments: Only the Reference product, Diprosone® ointment, (betamethasone dipropionate 0.5 mg/g) [Schering-Plough Laboratories; Batch No: 98A09-01 BE-98-BDPA-01] was applied during the pilot part of the study.

A single application of 10 microliter was administered under non-occlusive conditions on eight dose-duration sites on the ventral forearms (corresponding to durations of 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 hours) with applications done at ***staggered times but with synchronized removal.*** At the end of the application period the drug product was removed using water and a mild soap. Two untreated sites on each forearm served as the control. Treatment was followed up to 24 hours after application.

Selection of Dose: The dose of 10 microliter of reference or test product corresponds to 5.3 mg/cm^2. This dose was chosen based on results from previous similar studies.

Criteria for Evaluation: Efficacy: Skin blanching (vasoconstriction) was assessed using the chromametric a* value (primary) and the visual scoring (secondary) at each test site at baseline (within one hour before the application of the longer dose-duration site), at removal (0 hr), then 1, 2, 4, 6, 9, 17, 20 and 24 hours after drug removal.

Reviewer's comments: Currently for bioequivalence studies, the Office of Generic drugs (OGD) believes that the chromameter possesses greater sensitivity to skin blanching than does visual estimation and recommends the former as the method of choice.

Visual Scoring:

The visual scoring scale was as follows:

0: modified skin, 1: blanching barely visible, 2: clear blanching, 3: intense blanching, 4: blanching considered to be maximal

Chromametric Measurements:

The chromameter used was the [redacted], with an opening diameter of [redacted] mm. Three measurements were taken in the center of each site.

Validation of Assay Precision

Validation of intrasport and interspot precision of the assay methodology was documented in six first "responder" subjects who were selected to participate in the pilot study. Four untreated control sites on each ventral arm were selected. Four chromameter readings of each site were made within a one hour period (intervals of 0, 20, 40, 60 minutes). Each of these chromametric measurements was a mean of 3 individual recorded measurements. The same chromameter was used for all the vasoconstrictor bioassays performed during the clinical study on betamethasone dipropionate in Daivobet ® ointment.

Table: Means of the Percentage of Change from the First Measurement by Site

	H20			H40			H60		
Sites	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
ZONE 1	6	2.54	6.58	6	-2.23	4.74	6	1.03	6.56
ZONE 2	6	3.93	7.32	6	0.35	4.20	6	1.76	6.35
ZONE 3	6	1.95	5.73	6	-0.08	6.97	6	2.60	9.51
ZONE 4	6	3.01	9.00	6	0.37	6.84	6	2.66	7.06
ZONE 5	6	3.77	4.96	6	0.76	7.37	6	4.23	7.25
ZONE 6	6	4.48	8.34	6	3.79	5.93	6	4.23	9.10
ZONE 7	6	5.77	7.10	6	3.63	5.56	6	5.51	7.85
ZONE 8	6	3.75	4.68	6	1.89	6.47	6	4.96	4.29

The table above shows that the percentage of change from the first measurement by site is ≤ 5.77 %. Based on this data, the applicant concluded that the percentage variation was low and thus, the precision of measurement was reproducible.

Safety: Adverse events were recorded when reported spontaneously by the subject or observed by the investigator.

Data Analysis: Chromameter Data: The chromameter data of each skin blanching response versus time profile was adjusted for the baseline value at that site. Each baseline-adjusted active drug site was corrected for the mean of the two baseline-adjusted untreated control sites on the arm. The AUC (0-24) was computed using the trapezoidal rule for each baseline-adjusted, untreated control site-corrected dose-duration. The dose-duration response data was fitted using all observations of all individual subjects simultaneously. The ED_{50} and Emax values for the data pooled from 12 subjects were then calculated using non linear least squares regression (proc NLIN SAS). The D_1 and D_2 values were then determined.

The AUC (0-24) data for the 12 subjects for each treatment duration were fitted simultaneously to the following equation:

$E = Emax*D / (ED50 + D)$ ***[E = effect, the AUC for a given dose; Emax = maximum observed effect; D = Dose, the duration of application of cream; ED50 = the dose that causes a half-maximal effect]***

Visual Scoring Data: For each vasoconstriction time profile, the area under the curve was computed using the trapezoidal rule. The dose-duration-response data was fitted as described above. The ED_{50}, D_1 and D_2 were then determined.

Results of the Pilot Part:

Table 3: **Demographics**

Characteristics		**N (%) or Mean ± SD (range)**
Number of subjects		12
Gender	Male	6 (50%)
	Female	6 (50%)
Race		all 12 were Caucasian
Age		26.8 ± 4.9
Weight (kg)		61.7 ± 13.8
Height (cm)		168.3 ± 7.5

Selection of Responders:

The mean blanching scoring evaluated visually was 1.4 ± 0.5 (min-max 1-2). Seven subjects had a blanching barely visible score (=1) and 5 subjects had a clear blanching score (=2). Based on the FDA guidance all subjects are responders because they showed a visual reading of at least one unit.

Efficacy:

Table 16.5.1.4: Detector Subjects

Subject number	ED50 ,min;	D1 (hr)	D2 (hr)	Estimated AUC at D1	Estimated AUC at D2	Ratio of the AUCs	Detector Subjects
1	1.06311	0.53155	2.12621	-8.3512	-6.7598	0.8094	
2	1.06311	0.53155	2.12621	-8.0933	-8.8970	1.0993	
3	1.06311	0.53155	2.12621	2.3483	-24.5194	-10.4414	
4	1.06311	0.53155	2.12621	-2.5168	-15.4958	6.1569	Yes
5	1.06311	0.53155	2.12621	-20.2584	-28.2982	1.3969	Yes
6	1.06311	0.53155	2.12621	-10.9436	-17.8850	1.6343	Yes
7	1.06311	0.53155	2.12621	-29.1269	-57.2365	1.9651	Yes
8	1.063]1	0.53155	2.12621	-19.2172	-30.4373	1.5839	Yes
9	1.06311	0.53155	2.12621	-3.3519	7.5783	-2.2609	
10	1.06311	0.53155	2.12621	-5.4485	-52.4518	9.6268	Yes
11	1.06311	0.53155	2.12621	-19.1343	-29.1701	1.5245	Yes
12	1.06311	0.53155	2.12621	-8.9384	-34.1922	3 8253	Yes

Applicant's Efficacy Conclusions: According to the results obtained with the visual scoring and the chromameter a* parameter, betamethasone dipropionate (Diprosone ®) produced a dose-duration dependent vasoconstriction. The calculated parameters ED_{50}, D1 and D2 were available to perform the pivotal part and were as follows: ED_{50} was 1.06 hour (63.78 minutes) D1 = 0.53hour (31.89 min) and D2 = 2.12 hour (127.57 min).
Thus for practical reasons, ED50 was chosen as 1hr 04 minutes (64 minutes), D1 = 32 minutes and D2 = 2h 08 minutes (128 minutes).
Furthermore, based on these results, 8/12 (67 %) of the subjects were "detectors" so it was decided to include 90 subjects in the pivotal part to obtain 40 to 60 'detector' subjects.
Safety: Applicant stated that the vital signs and laboratory tests were not modified and no adverse event related to the investigational drug was reported.

Pivotal Part

Objective: To demonstrate the bioequivalence of the test and reference products
Study Design: Single center, randomized, double-blind study
Study Population: 90 healthy subjects (responders) aged between 18 and 45 years of age. All subjects who withdrew had to be replaced. Selection of the responders was done using the same procedure as that of the pilot study.
Test Sites: Sixteen test sites (8 per arm) located on the forearms, equally divided between the two forearms, each 1.55 cm in diameter, separated at least 2.5 cm center to center and no closer than 3 to 4 cm to the antecubital fossa or to the wrist were delineated using a circular template. For each arm, the allocation sites were randomly assigned to one of the following 4 designs:

Design 1

RIGHT ARM		LEFT ARM	
Z1	NT	Z9	NT
Z2	ED_{50} Ref	Z10	ED_{50} test
Z3	ED_{50} test	Z11	ED_{50} Ref
Z4	D_1 Ref	Z12	D_2 Ref
Z5	NT	Z13	NT
Z6	ED_{50} Ref	Z14	ED_{50} test
Z7	ED_{50} test	Z15	ED_{50} Ref
Z8	D_2 Ref	Z16	D_1 Ref

Design 2

RIGHT ARM		LEFT ARM	
Z1	D_2 Ref	Z9	D_1 Ref
Z2	NT	Z10	NT
Z3	ED_{50} Ref	Z11	ED_{50} test
Z4	ED_{50} test	Z12	ED_{50} Ref
Z5	D_1 Ref	Z13	D_2 Ref
Z6	NT	Z14	NT
Z7	ED_{50} Ref	Z15	ED_{50} test
Z8	ED_{50} test	Z16	ED_{50} Ref

Design 3

RIGHT ARM		LEFT ARM	
Z1	ED_{50} test	Z9	ED_{50} Ref
Z2	D_1 Ref	Z10	D_2 Ref
Z3	NT	Z11	NT
Z4	ED_{50} Ref	Z12	ED_{50} test
Z5	ED_{50} test	Z13	ED_{50} Ref
Z6	D_2 Ref	Z14	D_1 Ref
Z7	NT	Z15	NT
Z8	ED_{50} Ref	Z16	ED_{50} test

Design 4

RIGHT ARM		LEFT ARM	
Z1	ED_{50} Ref	Z9	ED_{50} test
Z2	ED_{50} test	Z10	ED_{50} Ref
Z3	D_2 Ref	Z11	D_1 Ref
Z4	NT	Z12	NT
Z5	ED_{50} Ref	Z13	ED_{50} test
Z6	ED_{50} test	Z14	ED_{50} Ref
Z7	D_1 Ref	Z15	D_2 Ref
Z8	NT	Z16	NT

Treatments: Test Product: Daivobet® ointment (calcipotriol 50 mcg/g with betamethasone dipropionate 0.5 mg/g) [Leo Pharmaceutical Products, Ltd; Batch No: 9838381] and the **Reference Product:** Diprosone® ointment, (betamethasone dipropionate 0.5 mg/g) [Schering-Plough Laboratories; Batch No: 98A09-01 BE-98-BDPA-01] was applied.
A single application of 10 microliter of the test and reference product was applied under non-occlusive conditions were applied according to the following dose-durations for each arm:

- Two sites were untreated
- Two sites received the test product for 1hr 04 minutes (ED 50)
- Two sites received the reference product for 1hr 04 minutes (ED 50)
- One site received the reference product for 32 minutes (D1)
- One site received the reference product for 2hr 08 minutes (D2)

These applications were performed at ***staggered times but with synchronized removal.*** At the end of the application period the drug product was removed using water and a mild soap.
Selection of Dose: The dose of 10 microliter of reference or test product corresponds to 5.3 mg/cm^2. This dose was chosen based on results from previous similar studies.
Criteria for Evaluation: For the **Efficacy** (vasoconstriction) and **Safety** (adverse events), this was the same as the pilot study with the following exception:
Skin blanching (vasoconstriction) was assessed using the chromametric a* value (primary) and the visual scoring (secondary) at each test site at baseline (within one hour before the application of the longer dose-duration site), at removal (0 hr), then 2, 4, 6, 8, 10, 12, 19 and 24 hours after drug removal.
Data Analysis:
Chromameter Data: Same as the pilot study with the following additions

- The 90 % confidence interval was calculated for the ratio of the average AUC response of the test product and the reference product using Locke's method

- The bioequivalence assessment was based only on AUC values computed at the dosing duration corresponding approximately to ED50, on "detector subjects". However, the data of "non detectors" was also documented in this report

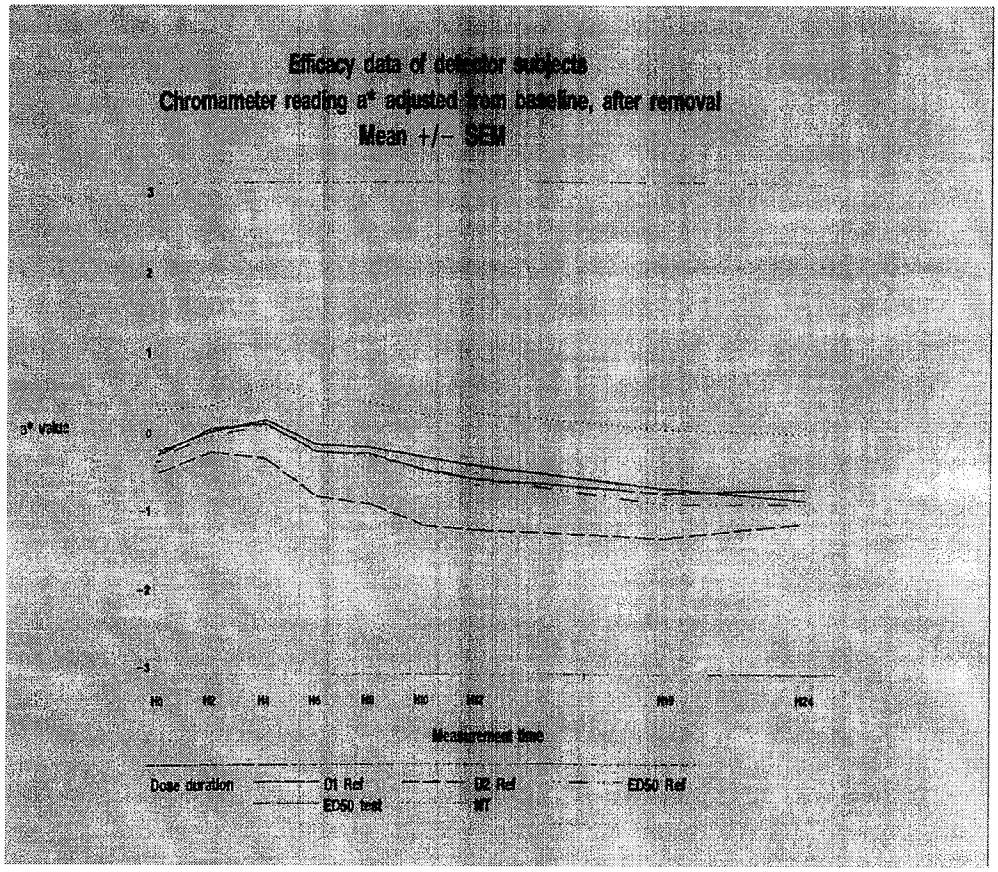
Visual Scoring Data: Same as the pilot study and removal times are the same as described above for the chromameter readings.

Results of the Pivotal Part:
Table 3: Demographics

Characteristics		**N (%) or Mean ± SD (range)**
Number of subjects		90
Gender	Male	37 (41)
	Female	53 (59)
Race		all 12 were Caucasian
Age		26.0 ± 0.6
Weight (kg)		64.2 ± 1.4
Height (cm)		170.9 ± 1.0

The data of 4 subjects (# 7, 8, 36 and 39) were excluded from the chromametry measurements analysis due to technical problems and were judged non evaluable for the efficacy analysis.
Protocol Deviations: There were a number of time deviations (up to 37 minutes) from the scheduled times for about 17 subjects. The applicant stated that the theoretical times were replaced by the real time of measurements for the calculation of AUC for these subjects.
Selection of Responders:
The mean blanching scoring evaluated visually was 1.1 ± 0.0 (min-max 1-2). Seventy nine subjects had a blanching barely visible score (=1) and 10 subjects had a clear blanching score (=2). The blanching score data was missing for one subject. Based on the guidance 89 subjects are responders because they showed a visual reading of at least one unit.

Efficacy:
Primary Efficacy Parameter: chromametric a* Parameter
The Figure below shows the mean chromameter data a* over the time course. For each dose-duration, a* decreased from 4 hours to 24 hours with a maximal at 19 hours approximately. The maximal obtained was between — at the greater dose-duration (D2 ref). The profiles of the curves at ED_{50} for the reference and the test products were similar and very close. These 2 curves were comprised between D_1 and D_2.



Secondary Efficacy Parameter: Visual Scoring

In comparison, an evaluation of the mean visual score versus time indicated that skin blanching increased during 19 hours approximately for each dose-duration with a maximal blanching score obtained at 10 hours. The maximal mean score obtained was 1 at the greater dose-duration (D2 ref).

Statistical Analyses: Thirty two out of the eighty nine responders met the detector criteria. They were included for the BE determination. Inserted below is the table showing the listing of detectors.

Subject number	D1 Ref	D2 Ref	AUC at D2/AUC at D1
6	-21.6003	-42.3045	1.9585
9	-5.4579	-14.8996	2.7299
14	-7.9833	-13.6883	1.7146
18	-6.4292	-8.0975	1.2595
25	-5.7546	-16.6238	2.8888
31	-13.1633	-16.9300	1.2861
33	-17.3525	-25.2658	1.4560
34	-20.3725	-25.9517	1.2739
40	-10.1363	-55.5029	5.4757
42	-1.6121	-19.5929	12.1538
43	-11.3667	-34.4200	3.0282
45	-11.1796	-23.3246	2.0864
47	-23.1921	-30.1388	1.2995
48	-18.0725	-25.4517	1.4083
49	-13.6829	-29.3387	2.1442
52	-2.1642	-23.1342	10.6896
54	-19.7563	-35.8904	1.8167
55	-16.2671	-24.5087	1.5066
56	-16.3900	-41.1942	2.5134
57	-15.5133	-28.2650	1.8220
60	-9.4968	-18.7564	1.9750
64	-10.4867	-14.2717	1.3609
65	-27.7567	-35.4875	1.2785
67	-31.8743	-43.0961	1.35207
70	-5.9488	-37.4946	6.30293
71	-14.2103	-30.7009	2.16047
74	-35.8408	-63.6475	1.77584
83	-4.8446	-7.0654	1.45842
85	-39.2625	-63.2333	1.61053
87	-29.4721	-41.8096	1.41862
88	-8.2996	-40.4596	4.87489
89	-5.7983	-10.6575	1.83803

D1 Ref=0.5 [D1 Ref(right arm)+ D1 ref(left arm)]
D2 Ref=0.5 [D2 Ref(right arm)+ D2 ref(left arm)]
A subject is detector if the ratio is >=1.25

Reviewer's Comments: Guidance recommends 40 to 60 evaluable subjects i.e. subjects who meet the "responder" and "detector" criteria. However, in this case thirty-two subjects were considered acceptable to still provide the required statistical power based on the sponsor's calculations.

Determination of Bioequivalence:

The results of the BE estimated using the Locke's method is summarized in the table below:

Table 4: Results of bioequivalence

Treatment	N	Mean	Variance	Covariance	G(*)	90% CI lower bound	90% CI upper bound
ED50 Ref	32	-18.01	140.25	103.81	0.04	0.81	1.04
ED50 test	32	-16.51	118.74				

G *: calculated parameter by the Locke's method, see in Appendix 16.1.9.

As the calculated parameter G was inferior to 1, the study met the bioequivalence requirements and the 90% confidence interval could be calculated.

Applicant's Efficacy Conclusions: In the conditions of this study, 32 subjects met the detector criteria and were used to test bioequivalence. According to the results obtained with a* data and using the Locke method, the interval for the skin blanching response ratio (Daivobet ® ointment to Diprosone ® ointment) is (0.81; 1.04) and within the reference interval of [0.8; 1.25] as defined by the applicable FDA guideline, thus the test product can be considered as bioequivalent to the reference product.

Safety: Applicant stated that five adverse events were reported in three subjects. Four of them (headache, abdominal pain, diarrhea and nausea) occurred after product application and the remaining one was reported during screening. These adverse events were judged to be unlikely related to the investigational product. (This is currently being reviewed by the medical reviewer).

Reviewer's Comments: The pivotal study report shows that 32 subjects (35.5 %) out of 90 were "detectors" therefore approximately 65 % of all subjects who participated in the study could not differentiate D1 (32 minutes) application from D2 (128-minute) application. The applicant did not provide any explanation for this difference.

OCPB Filing form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-852	**Brand Name**	Dovobet ® Ointment
OCPB Division (I, II, III)	DPE-III	**Generic Name**	Calcipotriene hydrate (0.005%) and Betamethasone dipropionate (C[redacted]
Medical Division	HFD-540	**Drug Class**	Corticosteroid
OCPB Reviewer	Abi Adebowale	**Indication(s)**	Treatment of Psoriasis Vulgaris
OCPB Team Leader	Dennis Bashaw	**Dosage Form**	Ointment
		Dosing Regimen	Apply to the affected area once daily. The recommended treatment period is 4 weeks. After this period, Dovobet® ointment may be used according to need. The maximum daily dose should not exceed 100 g.
Date of Submission, Filing Date	March 9th, 2005 April 19th, 2005	**Route of Administration**	Topical
Estimated Due Date of OCPB Review	November 18th, 2005	**Sponsor**	Leo Pharmaceuticals Products
PDUFA Due Date	January 9th, 2006	**Priority Classification**	4S
Clinical Division Due Date	November 30th, 2005	**IND Number**	62,993

Clin. Pharm. and Biopharm. Information

Background and Introduction: Dovobet ointment is being proposed for the treatment of psoriasis vulgaris in adults aged 18 years and older. It is a combination of two currently approved active ingredients (Calcipotriene hydrate and Betamethasone dipropionate).

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			Included within the study reports
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	1		Study MET/03/01 (In vitro metabolism) in non clinical section
Blood/plasma ratio:				
Plasma protein binding:	X	1		Study 35-86/02 (Binding of calcipotriol to human serum) in non clinical section
Studies using other Human Biomaterials				Report No. 36-94/09 (metabolism of calcipotriol in human skin) in non clinical section
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3		MCB 9801 NL (3 H calcipotriol from calcipotriol ointment) and MCB 9901 NL (3 H calcipotriol and 3H betamethasone from Dovobet ointment) DE 127-004 (percutaneous absorption of 3H-calcipotriol ointment)
multiple dose:				
Patients-				
single dose:	X	1		DE 127-005 (percutaneous absorption of 3H-calcipotriol ointment in psoriatic patients)
multiple dose:		8		MCB 0201 FR and MCB 0102 INT (both HPA axis function evaluations and calcium metabolism) MC 9301 INT, MC 189, MC 389, MC 0290/GP89, DE 127-018 and DE 127-002 (used a calcipotriol ointment only and measured only calcium metabolism)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD (HEALTHY OR PATIENTS):				

Phase 1 or 2:				
Phase 3:				
PK/PD (HEALTHY OR PATIENTS):				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	3		MCB 9905 INT, MCB 9904 INT, MCB 9802 INT for calcium metabolism only following the use of Dovobet ointment
Population Analyses -				
Data rich:	x			
Data sparse:	x			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		MCB 9902 FR (vasoconstrictor assay)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	16			

Fileability and QBR comments

	"X" if yes X	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	**NA**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	Does betamethasone affect the systemic exposure of calcipotriene and vice versa when used in combination?	
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale 04/18/05 Filing Form** **Abi Adebowale 11/17/05 (Full Review)**	
Secondary reviewer Signature and Date	**Filing form was signed off by Ray Baweja (04/18/05) the Acting TL at the time.** **Dennis Bashaw**	

CC: NDA 21-852, HFD-850 (P.Lee), HFD-540 (F.Curtis), HFD-880 (D. Bashaw, J. Hunt)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Abi Adebowale
12/20/2005 01:27:09 PM
BIOPHARMACEUTICS

Dennis Bashaw
1/5/2006 11:55:00 AM
BIOPHARMACEUTICS