- Psoriasis vulgaris of trunk and/or limbs amenable to topical treatment
- Disease severity of moderate, severe or very severe
- Aged 18 years or above

Main Criteria for Exclusion:

- Requirement for treatment of more than 30% of body surface area
- Erythrodermic, exfoliative or pustular psoriasis
- PUVA, UVB or systemic antipsoriatic treatment
- Topical antipsoriatic treatment of the trunk or limbs, with the exception of emollients and medications used to treat psoriasis of the skin folds and /or genitals
- Disorders of calcium mbetabolism associated with hypercalcemia
- Pregnancy or breast feeding
- Known or suspected severe renal insufficiency or severe hepatic disorders

Comment: The exclusion of subjects with severe renal insufficiency or severe hepatic disorders was added in Amendment 1 because use of the combination product is contraindicated in such subjects per the Summary of Product Characteristics for the combination product. In a facsimile dated November 29, 2005, the applicant stated that Dutch and Belgian authorities had requested that the contraindication be inserted in place of a "special warnings and precautions for use" statement that read, "Caution should be exercised in patients with severe liver and kidney disease ***due to lack of experience****" (emphasis from the applicant). The applicant states that the request for the contraindication was not based on any clinical findings.*

Safety Assessments: Adverse events, adverse drug reactions and adverse events of concern associated with long term corticosteroid use, adrenal function testing in a subset of subjects (added in Amendment 2; testing was done at two centers). Adrenal function testing was done at baseline, Week 4 and Week 52 (or at end of study in the case of premature withdrawals) and 6 weeks after the study end for subjects who had values of possible clinical significance at the end of study, 24 hour urine sample preceding visit 1 (Week 0), visit 2 (Week 4), visit 4 (Week 12) and 6 weeks after the end of the study for patients who had values of possible clinical significance 6 weeks after the end of the study.

Comment: Additional exclusion criteria applied to subjects enrolled at sites where HPA axis testing was done:

- *Patients who did not have a requirement for treatment of at least 10% of their body surface area*
- *Patients who had clinical signs or symptoms of Cushing's disease or Addison's disease*
- *Topical corticosteroid treatment in the 4 weeks prior to visit 1 apart from WHO Group I/II corticosteroids on the skin folds and/or genitals and/or face and WHO Group I/II/III corticosteroids on the scalp*
- *Use of inhaled cortocsteroids in the 4 weeks prior to visit 1*
- *Systemic corticosteroid treatment in the 12 weeks prior to visit 1*
- *A history of hypersensitivity to ACTH or Synacthen®*
- *A history of allergic disorders (e.g. asthma)*

- *Patients found to have evidence of adrenal suppression of possible clinical significance from the baseline laboratory testing (such subjects were excluded when results were known).*

Efficacy Assessments: Investigator's global assessment of disease severity and patients' global assessment of study treatment

RESULTS

Disposition of Subjects

Randomization for the 634 subjects enrolled in the study was as follows:

- 212 subjects were randomized to the combination group
- 213 were randomized to combination/calcipotriol (4/4 alt.)
- 209 were randomized to combination/calcipotriol (4/48, respectively)

Subjects were enrolled from 67 centers in 10 European countries and Canada.

Reasons for Withdrawal: Randomized Subjects (from Applicant Table 3)

	All Randomized N=634	**Combination** N= 212	**Combination/ Calcipotriol (4/4 alt.)** N=213	**Combination/ Calcipotriol (4/48)** N= 209
Total Number Withdrawn (%)	190 (30.0)	64 (30.2)	56 (26.3)	70 (33.5)
Reason for Withdrawal				
Exclusion criteria emerging during study	10 (1.6)	4 (1.9)	1 (0.5)	5 (2.4)
Lost to follow-up	33 (5.2)	15 (7.1)	8 (3.8)	10 (4.8)
Other reason[1]	17 (2.7)	6 (2.8)	9 (4.2)	2 (1.0)
Unacceptable adverse event	41 (6.5)	14 (6.6)	11 (5.2)	16 (7.7)
Unacceptable treatment efficacy	105 (16.6)	32 (15.1)	31 (14.6)	42 (20.1)
Voluntary	25 (3.9)	6 (2.8)	9 (4.2)	10 (4.8)
Total number of reasons[2]				
Total number (%) attending last possible on-treatment visit[3,4]	445 (70.2)	148 (69.8)	158 (74.2)	139 (66.5)

[1] Excludes subjects described in footnote #4

[2] A single subject could appear in more than one category

[3] Subject 6341 attended Visit 14 and also gave a reason for withdrawal (exclusion criteria emerging) at this visit

[4] Includes subjects who were recorded as withdrawing from the study for "other" reason but who were in the study for at least 52 weeks at their last visit and who completed the study at this time.

In all treatment groups, most withdrawals occurred between visit 3 (week 8) and 6 (week 20): 25 (11.8%) in the combination group, 28 (13.1%) in the combination/calcipotriol (4/4 alt.) group, and 34 (16.3%) in the combination/calcipotriol (4/48 alt.)

Demographic and Other Baseline Characteristics

The mean age of subjects was 48.0 years in the combination group, 49.8 in the combination/calcipotriol (4/4 alt.) and 48.4 in the combination/calcipotriol (4/48). Males were

60.4% of the combination group, 58.7% of the combination/calcipotriol (4/4 alt.) and 64.1% of the combination/calcipotriol (4/48).

Most subjects in all treatment groups had baseline disease of moderate severity at baseline.

Applicant Table 16 Section 14.2.6 of the study report

Baseline Severity	Combination # (%)	Combination/ Calcipotriol (4/4 alt.) # (%)	Combination/ Calcipotriol(4/48) # (%)
Moderate	149 (70.3%)	151 (70.9%)	138 (66.0%)
Severe	56 (26.4%)	58 (27.2%)	63 (30.1%)
Very severe	7 (3.3%)	4 (1.9%)	8 (3.8%)

The extent of disease was recorded only at the two centers where assessment of adrenal function was to be done and only for 19 subjects. The mean extent was 13.1% (range 12-16%) body surface area in the combination group, 17.7% (range: 11-26%) in the combination/calcipotriol (4/4 alt.) group, and 17.8% (10-30%) in the combination/calcipotriol (4/48).

Duration and Extent of Exposure

Mean mount of study medication used per treatment group over the first four weeks of treatment (the only period where all treatment groups used the combination product) was

- the combination group: 99.3g (range: 3.4 to 382.4g),
- the combination/calcipotriol group (4/4 alt.): 99.0g (range: 2.7g to 338.5g),
- the combination/calcipotriol group (4/48): 118.5g (range 2.4g to 389.9g)

Mean weight of study medication used per treatment group over the course of the study was

- the combination group: 898.8g (range: 10.2 to 4347g),
- the alternating combination/calcipotriol group (4/4 alt.): 892.5g (range 15.4g to 4420g),
- the combination/calcipotriol group (4/48): 1044g (range 20.0g to 5008g)

Mean duration of exposure was

- 43.8 weeks (range 0.1 to 60.0) in the combination group,
- 45.3 weeks (range 0.9 to 62.0) in the combination/calcipotriol group (4/4 alt.),
- 42.7 weeks (range 0.1 to 60.9) in the combination/calcipotriol group (4/48).

Adverse Drug Reactions

Adverse drug reactions occurred at the following rates:

- the combination group: 45 (21.7%) had 58 reactions,
- the combination/calcipotriol group (4/4 alt.): 63 (29.6%) had 89 reactions,
- the combination/calcipotriol group (4/48): 78 (37.9%) had 111 reactions

Adverse drug reactions that occurred in 2% or more of subjects were: burning sensation erythema, pruritus, psoriasis, and skin irritation:

	Combination	Combination/ Calcipotriol group (4/4 alt.)	Combination/ Calcipotriol group (4/48)
Burning sensation	3 (1.4%)	8 (3.8%)	10 (4.9%)
Erythema	2 (1.0%)	4 (1.9%)	7 (3.4%)
Pruritus	12 (5.8%)	22 (10.3%)	27 (13.1%)
Psoriasis	11 (5.3%)	8 (3.8%)	14 (6.8%)
Skin irritation	0 (0.0%)	6 (2.8%)	7 (3.4%)

Adverse events that were of concern associated with long-term use of topical corticosteroids were folliculitis, furuncle, skin atrophy, skin depigmentation.

Deaths

No subjects died during the study.

Other Serious Adverse Events

All subjects in this study had some exposure to the combination product.

In the combination group, 17 serious adverse events were reported for 11 subjects. The events were:

- face injury (#6013): A 23-year-old male suffered severe facial wounds in a workplace accident and required hospitalization; he did not complete the study.
- urinary tract infection/convulsion (#6054): A 44-year-old female was hospitalized after 26 weeks in the study due to recurrent urinary tract infection and seizure. She had a suprapubic cather and history of seizures prior to randomization.
- tendon rupture (#6095): A 58-year-old male was hospitalized after 9 weeks in the study due to rupture of left shoulder tendon after a workplace accident.
- bladder neoplasm (#6109): A 74-year-old male was diagnosed with a bladder tumor after 9 days in the study.
- ovarian neoplasm (#6282): A 59-year-old female had an ovarian tumor diagnosed after 5 weeks in the study.
- diverticulum (#6399): A 50-year-old female was hospitalized after 7 weeks in the study and severe diverticulitis was diagnosed.
- hypertension/headache/prostate cancer (#6553): A 58-year-old male was hospitalized due to high blood pressure and headache after 5 weeks in the study. He was diagnosed with prostate cancer after 18 weeks in the study.
- loss of consciousness (#6655): A 69-year-old male fainted after 37 weeks in the study. He was hospitalized overnight for observation. The fainting was thought to be caused by a vasovagal episode or electrolyte disturbance.
- sleep apnoea syndrome (#6690): A 60-year-old male developed sleep apnoea synodrome within a month of starting the study; he completed the trial.
- psoriasis (#6752): A 44-year-old male experienced a "severe" flare of psoriasis after 4 weeks in the study. He continued in the study for an additional 4 weeks before

withdrawing due to this adverse event. He was hospitalized 16 days after discontinuing study treatment, and treatment included crude coal tar and UVB.

- pregnancy (#6031): A 30-year-old subject was found to be pregnant after 24 weeks in the study and was withdrawn from the study at that time. She gave birth to a healthy child 33 weeks after withdrawal from the study.
- pancreatitis due to gallstones/acute renal failure/adult respiratory distress syndrome/multi-organ failure (#6874): A 52-year-old male was hospitalized 34 days after the end of the study due to acute pancreatitis secondary to gallstones. He subsequently developed adult respiratory distress syndrome and multiple organ failure. He was recovering after 14 weeks in the hospital.

Comment: Only #6752 (flare of psoriasis) was considered by the investigator to be probably related to study treatment; all other events were considered unrelated to study treatment. The reviewer agrees.

In the combination/calcipotriol group (4/4 alt.), 5 serious adverse events were reported for 5 subjects. The events were:

- arrhythimia (#6111): A 76-year-old male was hospitalized overnight for a cardiac arrhymia of mild severity after 29 weeks in the study.
- headache (#6213): A 38-year-old male was hospitalized for severe headache after 30 weeks in the study; no abnormalities were found; "symptoms" resolved.
- pneumonia ((#6621): A 61-year-old female was hospitalized due to severe pneumonia after 52 weeks in the study; she recovered.
- prostatitis (#6742): A 68-year-old male was hospitalized after 12 weeks in the study with acute prostatits; he recovered.
- myocardial infarction (#6776): A 32-year-old female was hospitalized due to a heart attack after 48 weeks in the study; coronary artery bypass graft was performed; she recovered.

Comment: All events were considered unrelated to study treatment. The reviewer agrees.

In the combination/calcipotriol group (4/48), 17 serious adverse events were reported for 13 subjects. The events were;

- transient ischemic attack, blindness (#6052): A 72-year-old female suffered a cerebrovascular accident after approximately 19 weeks in the study with permanent loss of vision in one eye due to retinal artery occlusion.
- foot fracture (#6076): A 60-year-old male suffered a fracture metatarsus after 39 weeks in the study; the event "resolved."
- pericarditis (#6206): A 72-year-old male was hospitalized after 18 weeks in the study due to severe pericarditis; the event "resolved."
- pulmonary embolism (#6261): A 71-year-old male was hospitalized due to pulmonary embolism after 47 weeks in the study; he recovered.
- weight control (#6310): A 56-year-old female was hospitalized after 14 weeks in the study for repositioning of a gastric ring.

- osteonecrosis (#6317): A 64-year-old female was hospitalized after 8 weeks in the study for surgery for aseptic osteonecrosis of the right ankle; the condition was present prior to randomization; she recovered.
- transient ishaemic attack (#6393): A 58-year-old male was hospitalized due to a transient ischemic attack after 17 weeks in the study; he had a history of same; ultrasound showed carotid stenosis; he recovered.
- psoriasis (#6428): A 44-year-old male was hospitalized after 40 weeks in the study due to a severe psoriasis flare in association with "psychological stress" related to the death of his father. He was hospitalized and ultimately treated with UVB therapy. He was discharged after 34 days, study medication was resumed, and he completed the study with no recurrence of a psoriasis flare.
- dehydration (#6430): A 56-year-old female was hospitalized for dehydration after 32 weeks in the study. The dehydration was attributed to "fluid loss by either viral infection or gastric irritation;" the event resolved.
- hyperthyroidism, phlebothrombosis, atelectasis, pancreatic neoplasm (#6434): A 63-year-old male was hospitalized due to pain in the right chest and shoulder after 36 weeks in the study. He was ultimately diagnosed with thyroid dysfunction and a pancreatic neoplasm. He went on to complete the study.
- colon cancer (#6619): A 64-year-old female was diagnosed with colon cancer between weeks 1 and 4 and was hospitalized for surgical intervention after 5 weeks in the study.
- aortic aneurysm (#6737): A 74-year-old male was diagnosed with an abdominal aortic aneurysm after 17 weeks in the study.
- psoriasis (#6775): A 52-year-old male left the study after 50 weeks of participation at which time he had an "ongoing" adverse event of worsening psoriasis of 23 weeks duration. The extent of psoriasis had increased although the activity of the involved areas had diminished. He was prescribed the combination ointment after discontinuation from the study, improved with subsequent discontinuation of the prescription treatment. Approximately one week later, he began to develop pustules and was ultimately determined to have pustular psoriasis. Treatment included cyclosporine.

Comment: Cases #6428 and #6775 (flare and worsening of psoriasis, respectively) were considered by investigators to be possibly related to study treatment; all other events were considered unrelated to study treatment The reviewer agrees..

Laboratory Data

Laboratory testing of adrenal function was conducted in 19 subjects randomized at two centers: 7 to combination, 6 to combination/calcipotriol (4/4 alt.) and 6 to combination/calcipotriol (4/48).

Comment: Serum cortisol values for this study were reported in nmol/L rather than mcgd/L, the units used in Cortrosyn labeling. Per Section 2.7.4.2.1.5.1 of the Summary of Clinical Safety, the applicant used a conversion factor of 0.036247 to convert nmol/L to mcg/dL (factor was based on the molecular weight of cortisol: 362.4). The clinical pharmacology reviewer confirmed that this conversion factor was acceptable, and it was therefore applied in the Medical Officer's

review of the data from this trial (applicant did the conversion only in the Summary of Safety but not in the study report).

Mean Serum cortisol concentrations for subjects (T30)* Applicant Table 57 Clinical study report

	Combination N=7	Combination/Calcipotriol (4 /4 alt.) N=6	Combination/Calcipotriol (4 /48) N=6
Baseline			
Median	26.3	27.6	28.3
Mean	28.4	27.8	24.8
Min	19.8	22.2	18.0
Max	37.5	33.2	36.5
Week 4			
Median	28.1	29.5	26.2
Mean	27.7	29.5	26.5
Min	23.0	25.0	15.3
Max	31.4	34.5	41.8
Week 52			
Median	24.4	25.1	21.9
Mean	26.4	23.1	22.9
Min	22.9	9.0	15.8
Max	34.2	29.9	31.8

*T30= 30 minute stimulation

The sole criterion of a 30-minute post-stimulation cortisol value > 18 was applied in the determination of adrenal suppression. Based on this criterion, the reviewer considered that two subjects showed evidence of suppression post-treatment:

Subject	Treatment Group	Baseline	Week 4	Week 52	6-week follow-up
6857	combination/calcipotriol (4/4 alt.)	26.8	25.0	9.0	N/A
6866	combination/calcipotriol (4/48)	18.0	15.3	15.8	17.9 and 17.0

Comment: No subjects who received only the combination product showed evidence of HPA axis suppression. One subject (#6866) in the combination/calcipotriol (4/4 alt.) group showed evidence of suppression after four weeks of treatment with the combination product; however, this subject had evidence of suppression at baseline and should therefore not have been enrolled. Repeat testing was not reported to have been done on subject 6857 apparently because the applicant did not consider this subject to have been suppressed (because of the cortisol level at 60 minutes).

A third subject might be considered to have shown evidence suggestive of borderline suppression, since the 30-minute value was 18.1 (therefore, technically > 18):

Subject	Treatment Group	Baseline	Week 4	Week 52
6873	combination/calcipotriol (4/48)	22.2	18.1	21.5

MCB 0202 FR/PC 1644: Repeat insult patch test with Daivobet®/Dovobet® Ointment- A study on the sensitisation potential of Daivobet®/Dovobet® Ointment and the Vehicle when applied on healthy skin in 200 healthy subjects.

Objectives: The objective of this study was to determine the potential of repeated applications of the combination product and its vehicle to induce sensitization to the skin of healthy volunteers.

Design: This was a randomized, double-blind, vehicle-controlled, single-center study with intra-individual comparison.

Methods: Two hundred and twenty subjects were enrolled. Study phases included (in sequence) a three-week induction phase, a two-week rest phase, and a one-week challenge phase. All subjects received both the combination product and its vehicle. Test products were applied to the skin of the back using occlusive dressings.

During induction, a total of 9 applications were made over a 21-day period on Mondays, Wednesdays and Fridays. Sites were assessed prior to each new application of study product. No products were applied during the two-week rest phase. During the challenge phase, study products were applied and left on the skin for 48 hours. Sites were then visually assessed for signs of skin reactions suggesting sensitization. These assessments were done 30 minutes following removal of patches and 24 and 48 hours after removal. The visual scoring of skin reactions were based on a 0 (no erythema) to 4 (severe erythema, edema, vesicles or blisters) scale.

Results: Mean scores for skin reactions increased slightly from Day 10 to Day 22 for combination-treated sites from Day 10 to Day 22 during the induction phase while mean scores for vehicle-treated sites were almost unchanged during the induction. However, most subjects in both treatment groups had scores equal to or below 1 (barely perceptible erythema).

During the challenge phase, mean scores were lower than the maximum values observed during induction for the combination sites while vehicle scores were slightly increased. Assessment for sensitization potential was negative for all subjects.

Conclusions: Under conditions of the study, the combination product showed no potential for sensitization and repeated applications revealed low potential for irritation.

MCB 0203 FR/CPCAD CPC-3169: 21-day cumulative irritation test. Assessment of the local skin tolerability, after repeated application of Daivobet®/Dovobet® ointment [calcipotriol 50 µg/g and betamethasone (as dipropionate) as 0.5 mg/g]

Objectve: The objective of this study was to determine the skin irritation potential of the applicant's combination product and its vehicle ointment after repeated application to the skin of healthy subjects.

Design: This was a randomized, investigator-blinded, vehicle-controlled, single-center study with intra-individual comparison. The study enrolled 32 subjects.

Methods: Test products were applied under occlusion 15 times for over 21 study days (3 weeks) to two selected test sites on the back of each subject. Clinical assessments for reactions were performed according to a 6-point irritation score, from 0 (no erythema) to 4 (severe erythema, edema, vesicles or blisters) 30-minutes following removal of the patch and prior to application of the next patch.

For each subject, a Cumulative Irritancy Index (CII) was calculated for each of the study products: CII = sum of clinical scores across readings (Days 2-22)/number of readings. A Mean Cumulative Irritancy Index (MCII) was calculated for each product by averaging individual CIIs across subjects. MCIIs were then used to classify each product into an irritancy category ranging from non-irritant to extremely severely irritant.

Results: No test site score higher than 1 (slight erythema with and without edema). MCIIs were higher for the vehicle sites than for combination sites. For the combination product, the MCII was within the classification of "non-irritant." For the vehicle, the MCII was within the classification of "slightly irritant (*sic*)."

Conclusion: Under conditions of the study, the combination product showed low potential to cause irritation.

Comment: Irritant effect from the vehicle is probably calmed by the corticosteroid in the combination product. These results are consistent with those from the induction phase of the contact sensitization study.

MCB 0204 FR/CPCAD CPC-3186: Photo-allergy Test: Assessment of the photosensitization potential of Daivobet®/Dovobet® ointment [calcipotriol 50 µg/g and betamethasone (as dipropionate) as 0.5 mg/g]

Objective: The objective of the study was to evaluate the photosensitization potential of the combination product.

Design: This was a randomized, investigator-blinded, vehicle-controlled, single-center study with intra-individual comparison. The study enrolled 32 subjects.

Methods: The study consisted of three phases: induction, rest and challenge. On Days 1 and 2 of the induction phase, minimal erythema dose (MED) was assessed at six sites on the upper back with UVA and UVB. The two study products were applied under occlusive conditions to two sites on the back for 24 hours, twice weekly for 3 weeks (a third site remained untreated). Twenty-four hours after each product application, irradiation was performed on the test site after patch removal. The irradiation dose was twice the subject's MED during the first week and three times the MED the second and third weeks, using the total spectrum of UV light. Skin reactions were assessed before application of study products and before irradiation. No study products were applied during the two-week rest period. During the challenge phase, two sets of the two

products were applied on four new sites on the back under occlusion for 24 hours. Two untreated but occluded sites were used as well. Only one set of test sites was irradiated with 0.75 MED full spectrum UV light followed by 4 J/cm^2 of UVA light. The non-irradiated sites served as controls for a possible contact sensitization.

All test sites were evaluated 24, 48 and 72 hours after irradiation. Skin reactions and erythema on the test sites were evaluated using a 5-point scale (0= no reaction; 3=severe erythema). Other reactions were also recorded, e.g. papules, vesicles. At 72 hours post irradiation, the investigator assessed the occurrence of possible photosensitization.

Results: All test sites were evaluated as negative for occurrence of photosensitive reactions during the challenge phase at 72 hours.

Conclusion: No photosensitization reaction was seen for the combination product or its vehicle.

MCB 0101 FR: Photo-toxicity study. Assessment of the phototoxic potential of Daivobet®/Dovobet® ointment (betamethasone dipropionate 0.5 mg/g and calicipotriol 50 µg/g)

This was a single-center, randomized, investigator-blinded study with intra-individual comparison of treatments. The study enrolled 32 healthy volunteers (males and females).

Objective: The objective of the study was to evaluate the phototoxic potential of the applicant's combination product

Methodology: The study was of five days duration. On Days 1 and 2, MED was assessed by irradiation of six small test areas on the upper back with UVA and UVB. On Day 1, test chambers with 50 µl of the combination product and vehicle were separately applied in duplicate on designated areas on both sides of the mid back (occlusive application). A third test site had no study product applied. The test chambers were removed on Day 2 (i.e. 24 hours after application), and the test areas on the left side were irradiated with 20 J/cm^2 UVA + 0.75 x MED UVA + UVB. The areas on the right side served as non-irradiated control. All patch sites were evaluated 1, 24, 48 and 72 hours after irradiation. The phototoxicity reaction was assessed for erythema, edema, papules, vesicles on a 6-point scale.

Results: All 32 subjects enrolled completed the study. No phototoxic reactions were observed.

Conclusion: Neither of the test products (combination or vehicle) elicited a phototoxic reaction.

MCB 0306 UK: Daivobet/Dovobet Ointment/ UV Penetration Study in Humans-Detection of Erythema Induced by UV light, A Within Subject Comparison of Investigational Materials Against Untreated Skin

This was a single center, randomized double-blind, active- and vehicle-controlled, intra-individual comparison in 25 healthy volunteers.

Objective: The objective of the study was to evaluate the UV light penetration potential of the combination ointment, the combination ointment vehicle, Dovonex® scalp solution and the scalp solution vehicle. An emollient (Diprobase Cream) was included to demonstrate the UV penetration of a "standard" moisturizer. A "standard" sunscreen 8% Homosalate was included to validate the evaluation of erythema and SPF (assay sensitivity).

Comment: The protocol states that the study the clinical study was being undertaken to learn whether the result of a photocarcinogenicity study conducted with Dovonex solution in hairless mice would be relevant for the evaluation of the potential effect of the combination ointment on ultraviolet-induced tumor formation in humans. To accomplish this, the two drugs and both vehicles were investigated. An enhancing effect could be a function of either active ingredient or either vehicle. It was the applicant's belief that any effect of the combination ointment might be masked by the presence of betamethasone, and that it was therefore necessary to include both vehicles in the study. Section 4 of the protocol states that the information from this study had been requested by the FDA as part of the documentation to be submitted in the marketing application.

Methodology: The MED of untreated skin was determined by exposure to a series of eight UV light exposures within a $50cm^2$ test site on the back. The combination ointment, the combination ointment vehicle, Dovonex® scalp solution, the scalp solution vehicle, "standard" sunscreen and "standard" emollient were randomly assigned to and applied to one of seven new $50cm^2$ test sites on the back. One site was left untreated. Each site was divided into eight sub-sites and exposed to an incremental range of eight UV doses, based on the individual pre-treatment MEDs. Skin reactions were assessed and graded immediately after the pre- and post-treatment UV exposure. Erythema scores were used to calculate the MED and repeat MED for untreated skin, and the MED for treated skin, and based on these values the sun protection factor (SPF) for each investigational product was determined.

Results: Except for the sunscreen, the mean SPF results for all study products was similar (0.98 to 1.18). The mean SPF for the sunscreen was 3.06.

Conclusion: The applicant concluded there was no measurable increase in UV penetration, determined by SPF calculation, after application of any of the investigational materials. They therefore concluded that the application of investigational materials did not induce further UV penetration in comparison with untreated skin. The mean SPF for the 8% homosalate was lower than expected but did demonstrtate protection to UV.

Comment: As the combination ointment contains calcipotriene at the same concentration as in the scalp solution, labeling for the combination product should include cautionary language similar to what is included in the Dovonex labels.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The applicant states that there have been no reports of abuse of the product.

The post-treatment period was not routinely evaluated in the development program. However, in the marketing application, the applicant reports having received 18 post-marketing reports (9 serious; 9 non-serious) describing possible flare of psoriasis after discontinuation of treatment. Cases are described below (Note: bolded cases were reported as serious adverse events):

Flare of Psoriasis After Stopping Combination Treatment

Case #	Dosing/ Treatment Duration	Time to Flare from stop of treatment	Course
102550	Unknown/ 03Sept-30Sept02	3 weeks	Psoriasis returned after 3 weeks
102580	BID*/ 31Jan-14Mar03	1 day	"Mild" disease at treatment onset and cleared; Developed severe, widespread pustular psoriasis 1 day after stopping treatment which resolved with methotrexate.
102587	Unknown/unknown	Unknown	Report re "couple" of patients who had "rebound" after treatment (Note: vague information provided)
102676	7g daily/ 10Dec02-20Jan-03	2 months	Plaque psoriasis at treatment onset; developed pustular psoriasis on 21Mar03; resolved with methotrexate
102925	QD+/42 days	1 week	"Severe rebound" and "exacerbation" one week after discontinuing treatment
103453	?/?	?	Pustular psoriasis after use of the combination; required hospitalization
103602	QD/ 30Dec02-15Dec03	1 week	Was in Long-Term study (0102 INT); discontinued treatment 1st week of Jan.; spreading erythema on 12 Jan with eventual pustules and vesicles; cyclosporin, acyclovir, flucloxacillin started on Jan 16; resolved to "minor" plaques Feb.9
102080	BID/ 12Jun-?Jul02	?2 weeks?	Used betamethasone and polytar liquid on 17Jul; found to have "guttate" lesions on 25 Sept. and previous plaques were worse after stopping combination treatment
102097	BID/ 12Aug-16Sept02	1 week	"Extensive flare-up" within a week of stopping combination; referred for "urgent" UVB phototherapy
102098	BID/ 17Jul-28(?)Aug02	Unclear	"almost clear" on 14Aug and was given to continue combination on remaining lesions; "extensive flare-up" noted on 28Aug; referred for "urgent" UVB phototherapy
102103	240g weekly/ 5 months	Unknown	
102360	?	?	"Rebound effect;" no other information
102408	?	?	"Rebound effect;" no other information
101930	?	3 weeks	Onset of flare 3 weeks after stopping treatment; became erythrodermic;hospitalized;treated with systemic retinoids
103880	Not reported/ ?Jun03-?	6 days	Had chronic plaque disease; Combination was "abruptly" stopped 18May04 for elective surgery; erythrodermic and with pustular psoriasis on 26May04
103963	?/ 30Jan-27Feb04	3 months	Also used "Daktacor" on skin folds and "Psoriderm bath emulsion" when using combination; rebound on 25May that was "much worse;" treated with UVB
103402	?	?	Two males experienced "rebound psoriasis"

Sources: Periodic Safety Update Reports
*BID= twice daily
+QD= once daily

7.1.14 Human Reproduction and Pregnancy Data

Five pregnancies occurred in the development program, two of which occurred in women treated with the combination product:

- One subject in the 52-week study, MCB 0102 INT was found to be 5 to 9 weeks pregnant after 24 weeks of study treatment. She discontinued the study and later gave birth to a healthy child.
- In the ongoing study, MCB 0303 INT, a subject was found to be 10 weeks pregnant after the start of treatment. Follow-up on the outcome of the pregnancy was reportedly not yet available.

Two pregnancies occurred in the calcipotriol group:

- One subject was withdrawn from study MCB 0003 INT due to pregnancy after two weeks of treatment. She ultimately gave birth to a healthy baby.
- One subject discontinued study MCB 0002 INT due to pregnancy after 7 weeks of treatment. She had a spontaneous abortion in week 12-13 of the pregnancy, and the investigator considered the outcome not related to study treatment.

The fifth pregnancy occurred in the betamethasone group: a subject in study MCB 9904 was found to be pregnant after 4 weeks of treatment and discontinued the study. She developed polyhydramniosis and delivered 3 weeks prematurely. The baby suffered with neonatal jaundice. The investigator considered the polyhydramniosis and jaundice not related to study treatment.

The applicant has received two spontaneous notifications of use of the combination product during pregnancy:

- MFR 102239: This was a post-marketing report of a case of "mild" hypercalcemia in a breast-fed, premature infant (32 weeks gestation) whose mother had used the combination product for about 6 months prior to delivery (she had extensive psoriasis on the trunk). It is not known whether the baby was in contact with treated areas on the mother's trunk. He was born on [redacted]. He was begun on small amounts of breast milk on December 13 and was being fully breast fed by December 16. He developed hypercalcemia on December 20, 2002. His corrected calcium levels were from 2.7 to 2.9 mmol/L (reference range 2.14-2.52). The hypercalcemia resolved "remarkably quickly" and without treatment. (The mother's case number was 102242).
- MFR 103563: On December 5, 2003, a teenager started using the combination product, calcipotriol ointment, "Excipial U," "Diprosalic," and UVB for psoriasis involving the scalp and body. On February 23, 2004, she informed her physician that she was approximately 9 weeks pregnant. The combination product, calcipotriol ointment, and UVB were discontinued the same day and betamethasone valerate was instituted. No outcome has been reported for this other case.

Comment: Both betamethasone dipropionate and the marketed calcipotriene ointment are Pregnancy Category C. Pregnant and lactating women were excluded from the clinical trials.

7.1.15 Assessment of Effect on Growth

Assessment of effect of the product on growth was not done. However, this section may apply if the combination product is studied in pediatric subjects.

7.1.16 Overdose Experience

The applicant has received one spontaneous notification of an overdose: A 35 year-old-male developed Cushings's syndrome after using 240 gm of the combination product weekly for 5 months for erythrodermic psoriasis. He developed pustular psoriasis after the combination product was discontinued, and he was hospitalized.

7.1.17 Postmarketing Experience

The submission included a summary report of safety data from the post-marketing experience covering the period of April 1, 2001 through March 31, 2004. The applicant estimates that in the three-year period covered by the report, approximately 1,800 subjects received the product in Leo clinical trials, and approximately 500,000 patients received a treatment course of the product world-wide. This estimation was calculated using sales volume data and the assumption that an average treatment course is 75 g per week with a treatment duration of 3 weeks.

The applicant received two reports of "drug exposure during pregnancy" and these are discussed in Section 7.1.14 ("Human Reproduction and Pregnancy Data").

The applicant has received 18 post-marketing reports of flares of psoriasis following discontinuation of treatment since first launch of the product. Nine of these events were reported as serious adverse events (see Section 7.1.13). When reported, the duration of treatment ranged from 3 weeks to 11 months. When reported, the time from discontinuation of treatment to onset of symptoms was between 1 day and 3 months. The events were reported as exacerbation of psoriasis to erythrodermic psoriasis, appearance of pustular psoriasis, and possible guttate psoriasis (one case). "Rebound" was also reported without accompanying details.

An additional 22 post-marketing reports (11 serious) have described possible flares occurring during treatment with the combination product. When reported, the duration of treatment ranged from 1-2 weeks to 16 months. Several of the flares were reported as pustular psoriasis. Information available pertaining to 3 of those subjects is presented in the table below. Flares that occurred during treatment were not separately evaluated or described in the safety reports covering April 1, 2003 to March 31, 2004 and April 1, 2004 to September 14, 2004 because the applicant has added pustular psoriasis to the product information where the combination product is marketed, (Section 2.7.4.5.7 of the Summary of Clinical Safety).

Flare of Psoriasis During Combination Treatment

Case #	Dosing/ Start Date of Treatment	Time to Flare	Course
102236	120g per week/ 01 Nov 02	3 weeks	Developed pustular psoriasis "over" plaques on 20Nov; folliculitis adjacent to plaques; Biopsied 18Dec: "chronic destructive folliculits"
102314	?/ 24 Oct 02		Developed pustular psoriasis "all over back" on 01Dec; combination stopped on 19 Dec; "recovering"

102334	60g per week/ 30 Jun 02	3 weeks	Initial "dramatic" improvement; On 23 July, sudden widespread pustular psoriasis; combination was stopped; eventually treated with methotrexate; pustular psoriasis resolved

Source: Periodic Safety Update Reports

Applicant Table 2 (Volume 90)
Serious Adverse Events-Post-Marketing

MedDRA SOC Preferred Term	Number of Adverse events N=39
Endocrine disorders	
Cushing's syndrome	1
Gastrointestinal disorders	
Nausea	1
General disorders and administration site conditions	
Rebound	3
Asthenia	1
Drug withdrawal syndrome	1
Infections and infestations	
Folliculitis	1
Rash pustular	1
Injury, poisoning and procedural complications	
Blister	1
Medication error	1
Thermal burn	1
Metabolism and nutrition disorders	
Hypercalcemia	1
Musculoskeletal and connective tissue disorders	
Muscle cramp	1
Nervous system disorders	
Convulsion	1
Psychiatric disorder	
Hypomania	1
Respiratory, thoracic and mediastinal disorders	
Apnoea	1
Skin and subcutaneous tissue disorders	
Psoriasis	19
Pemphigoid	1
Rash maculo-papular	1
Vascular disorders	
Vasculitis	1

Applicant Table 1 (Volume 90):
Non-Serious Adverse Events-Post-Marketing

MedDRA SOC Preferred Term	Number of Adverse events N=53
Eye disorders	
Glaucoma	1
General disorders and	

administration site conditions	
Rebound	5
Application site erythema	1
Application site pain	1
Application site vesicles	1
Drug withdrawal syndrome	1
Tachyphylaxis	1
Immune system disorders	
Hypersensitivity	1
Infections and infestations	
Fungal skin infection	1
Rash pustular	1
Injury, poisoning and procedural complications	
Blister	2
Drug exposure during pregnancy	2
Investigations	
Blood glucose fluctuation	1
Blood glucose increased	1
Musculoskeletal and connective tissue disorders	
Myalgia	1
Nervous system disorders	
Burning sensation	2
Skin and subcutaneous tissue disorders	
Psoriasis	14
Pruitius	5
Dermatitis exfoliative	2
Erythema	2
Dermatitis	1
Ecchymosis	1
Eczema	1
Hypertrichosis	1
Pruritus generalized	1
Skin depigmentation	1
Skin irritation	1

Listing of Post-Marketing Serious Adverse Events by Primary System Organ Class [+]

Case #; Age/Sex	Preferred Term	Dose	Treatment Dates	Adverse Event Onset/Severity*	Outcome
Endocrine Disorders					
102103; 35/M	Cushing's syndrome	240g/week	01Jan02-?	01Jan02/mod.	Recovered/resolved
Gastrointestinal disorders					
102433;63/F	Nausea	?	12Jan-14Jan03	13Jan03	Recovered/resolved
General disorders and administration site conditions					
102433;63/F	Asthenia	?	12Jan-14Jan03	13Jan03	Recovering/resolving
102580;30/F	Rebound effect	2 applications	31Jan-14Mar03	15Mar03	Recovered/resolved
102925;/?	Drug withdrawal syn.	Once daily	?	?	Unknown
103880;58M	Rebound effect	?	01Jun03-01May04	26May04/sev.	Recovering/resolving
103963;34M	Rebound effect	1 application	30Jan-27Feb04	25May04	Not recovered/not resolved
Infections and infestations					
102236;45/M	Folliculitis	120g/week	01Nov-20Nov02	20Nov02	Recovering/resolving
102433;63/F	Rash pustular	?	12Jan-14Jan03	13Jan03	Recovering/resolving
Injury, poisoning and procedural complications					
102103;35/M	Mediacation error	240g/week	01Jan-?	01Jan02	?
102433;63/F	Blister	?	12Jan-14Jan03	13Jan03	Recovering/resolving
103791;/?	Thermal burn	?	?	?	?
Metabolism and nutrition disorders					
102239;2/M	Hypercalcemia	?	01Jun-30Dec02	20Dec02	Recovering/resolving
Musculoskeletal and connective tissue disorders					
102433;63/F	Muscle cramp	?	12Jan-14Jan03	13Jan03	Recovering/resolving
Nervous system disorders					
102239;2/M	Convulsion	?	01Jun-30Dec02	20Dec02	Recovered/resolved
Psychiatric disorders					
101886;?/M	Hypomania	?	01Aug-01Aug02	01Aug02	Recovering/resolving
Respiratory, thoracic and mediastinal disorders					
102239;2/M	apnoea	?	01Jun-30Dec02	20Dec02	Recovered/resolved
Skin and subcutaneous tissue disorders					
101930;63/F	Psoriasis	?	?-07Jul02	28Jul02	Recovering/resolving
102103;35/M	Psoriasis	240g/week	01Jan02-?	01Jan02	?
102146;60/M	Pemphigoid	?	11Jun-20Oct02	01Sep02	Recovering/resolving
102236;45/M	Psoriasis	120g/week	01Nov-20Nov02	20Nov02	Recovering/resolving
102314;40/F	Psoriasis	?	24Oct-19Dec02	01Dec02	Recovering/resolving
102334;62/M	Psoriasis	60g/week	30Jun-23Jul02	23Jul02	Recovered/resolved
102349;?/M	Rash maculo-papular	?	?	?	Unknown
102520;57/U	Psoriasis	10g	01Nov-01Dec02	01Dec02	Recovering/resolving
102538;70M	Psoriasis	?	01Jan02-30Jan03	01Jan02	Not recovered/ not resolved
102550;61M	Psoriasis	?	03Sep-30Sep02	20Oct02/mod.	Not recovered/ not resolved
102580;30F	Psoriasis	2 applications	31Jan-14Mar03	15Mar03	Recovered/resolved
102676;53F	Psoriasis	7g	10Dec02-20Jan03	21Mar02 sev.	Recovered/resolved
102706;70M	Psoriasis	14g	28Jan-25Feb03	25Feb03/mild	Recovered/resolved
102707;40F	Psoriasis	7g	08Oct-02Nov02	08Oct02/mod.	Recovered/resolved
102925;?/?	Psoriasis	Once daily	?	? /sev.	Unknown
102955;41/F	Psoriasis	?	20Feb-16Aug03	01Mar03/sev.	Not recovered/ not resolved
103063;56/M	Psoriasis	2 DF	01Mar-01Jun03	01Jan03/sev.	Unknown
103453;?/?	Psoriasis	?	?	?	?
103671;?/?	Psoriasis	?	?	?	?
103880;58/M	Psoriasis	1 DF	01Jun03-01May04	26May04/sev.	Recovering/resolving
103856;51/M	Vasculitis	?	06Nov-24Nov03	24Nov03/mod.	Recovered/resolved

[+]**Source: Applicant Table (Vol.90, Section 5.3.6)** *when reported; mod.=moderate; sev.=severe

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In the Short-Term Core Studies, 2, 448 subjects were exposed to at least one application of the combination product.

7.2.1.1 Study type and design/patient enumeration

Tables of the safety analysis set are presented below:

Applicant Table T2: Number in Safety Analysis Set by Study Grouping

	Combination	Vehicle	Calcipotriol	Betamethasone
Short-term Core Studies				
Once daily	1539	154	1302	486
Twice daily	909	316	1895	678
Total	2448	470	3197	1164
Healthy Volunteer Studies				
Single application	155	0	4	16
3-to 4 week studies	335	0	6	0
Total	490	0	10	16
Non-Core Studies				
Psoriasis	45	0	0	0
Contact dermatitis	23	0	0	0
All Studies*	3477	470	3203	1164

* All Studies= Short-Term Core Studies, Long-Term Core Study (first 4 weeks only), Healthy Volunteer Studies (excluding single application) and Non-Core Studies

Applicant Table T3: Number in Safety Analysis Set Long-Term Core Study

	Combination once daily for 52 wks	Combination/calcipotriol once daily, alternating 4-wk periods	Combination once daily for 4wks/calcipotriol once daily for 48 wks
Long-Term Core Study	207*	213	206

*212 were randomized; however 5 subjects provided no safety data

7.2.1.2 Demographics

Demographic and other baseline characteristics data for the safety population are presented in the following tables.

Baseline Disease Characteristics (Applicant Table T18)

	Combination N=2448	Vehicle N=470	Calcipotriol N=3197	Betamethasone N=1164
PASI: n (%)				
0-6	512 (20.9)	103 (21.9)	657 (20.6)	251 (21.6)
6.1-12	1266 (51.8)	251 (53.4)	1624 (50.8)	582 (50.0)
>12	668 (27.3)	116 (24.7)	913 (28.6)	330 (28/4)
Total	2446 (100.0)	470 (100.0)	3194 (100.0)	1163 (100.0)
Investigator's global assessment of disease severity*				
Mild	116 (14.7)	28 (18.2)	195 (13.9)	88 (18.6)
Moderate	717 (63.5)	97 (63.0)	898 (64.0)	297 (62.7)
Severe	221 (19.6)	28 (18.2)	275 (19.6)	85 (17.9)
Very severe	26 (2.3)	1 (0.6)	36 (2.6)	4 (0.8)
Total	1130 (100.0)	154 (100.0)	1404 (100.0)	474 (100.0)

* Investigator's global assessment of disease severity* at baseline was recorded only in studies MCB 003 INT and MCB 0002 INT

Demographic and Other Baseline Characteristics: Short-Term Core Studies (Applicant Table T18)

	Combination N=2448	Vehicle N=470	Calcipotriol N=3197	Betamethasone N=1164
Age				
Median (years)	48.0	48.0	48.0	47.0
Mean (years)	48.2	48.2	47.9	47.2
SD	14.6	14.3	14.8	14.7
Min, Max (years)	15, 97	18, 87	18, 90	17, 89
Age Group				
≤ 35 years	519 (21.2)	100 (21.3)	712 (22.3)	293 (25.2)
36-50 years	860 (35.1)	153 (32.6)	1114 (34.8)	379 (32.6)
51-64 years	675 (27.6)	156 (33.2)	869 (27.2)	330 (28.4)
≥ 65 years	394 (16.1)	61 (13.0)	502 (15.7)	162 (13.9)
Sex				
Male	1494 (61.0)	282 (59.8)	1938 (60.6)	702 (60.3)
Female	954 (39.0)	189 (40.2)	1259 (39.4)	462 (39.7)
Race				
White	2077 (96.9)	350 (96.7)	2802 (97.0)	826 (97.1)
Black	11 (0.5)	0 (0.0)	18 (0.6)	4 (0.5)
Asian	43 (2.0)	5 (1.4)	59 (2.0)	19 (2.2)
Other	13 (0.6)	7 (1.9)	10 (0.3)	2 (0.2)
Duration of Psoriasis				
Median (years)	16.0	17.0	16.0	15.0
Mean (years)	18.9	18.1	18.9	18.7
SD	13.4	12.5	13.4	13.5
Min, Max (years)	0.0, 70.0	0.0, 62.0	0.0, 70.0	0.0, 75.0
PASI				
0-6	512 (20.9)	103 (21.9)	657 (20.6)	251 (21.6)
6.1-12	1266 (51.8)	251 (53.4)	1624 (50.8)	582 (50.0)
>12	668 (27.3)	116 (24.7)	913 (28.6)	330 (28.4)
Investigator's Global Assessment of Disease Severity				
Mild	166 (14.7)	28 (18.2)	195 (13.9)	88 (18.6)
Moderate	717 (63.5)	97 (63.0)	898 (64.0)	297 (62.7)
Severe	221 (19.6)	28 (18.2)	275 (19.6)	85 (17.9)
Very Severe	26 (2.3)	1 (0.6)	36 (2.6)	4 (0.8)

7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure to the combination product is presented in the tables below.

Duration of Exposure: Short-Term Core Studies (Modified Applicant Table T9)

	Combination once daily N= 1539	Combination twice daily N= 909
Duration of Exposure: n (%)		
1 day	2 (0.1)	3 (0.3)
2-7 days	11 (0.7)	23 (2.5)
1-2 weeks	17 (1.1)	18 (2.0)
2-3 weeks	17 (1.1)	11 (1.2)
3-4 weeks	929 (60.4)	647 (71.2)
4-5 weeks	235 (15.3)	183 (20.1)
5-6 weeks	19 (1.2)	18 (2.0)
6-7 weeks	7 (0.5)	3 (0.3)
7-8 weeks	221 (14.4)	1 (0.1)
8-9 weeks	72 (4.7)	2 (0.2)
9-10 weeks	6 (0.4)	0 (0.0)
10-11 weeks	1 (0.1)	0 (0.0)
11-12 weeks	1 (0.1)	0 (0.0)
> 12 weeks	1 (0.1)	0 (0.0)
Mean exposure (weeks)	4.8	3.9

Total Dose and Mean Daily Dose: Short-Term Core Studies (Applicant Table T13)

	Combination once daily N= 1539	Combination twice daily N= 909
Total Dose (g)		
Median	92.2	130.4
Mean	117.3	152.3
SD	94.6	101.8
Min, Max	0.0, 551.8	0.0, 387.9
Number	1417	814
Mean daily dose (g)		
Median	3.0	4.7
Mean	3.6	5.5
SD	2.8	3.7
Min, Max	0.0, 14.3	0.0, 25.0
Number	1417	814

SD: Standard Deviation
Min., Max.: Minimum, Maximum

Duration of Exposure: Long-Term Core Study (Modified Applicant Table T14)

	Combination once daily for 52 wks N= 207	Combination/calcipotriol once daily (4/4 alt.) N=213
Duration of Exposure:	**n (%)**	
1-4 weeks	4 (1.9)	4 (1.9)
4-8 weeks	5 (2.4)	5 (2.3)
8-12 weeks	4 (1.9)	4 (1.9)
12-16 weeks	6 (2.9)	10 (4.7)
16-20 weeks	7 (3.4)	6 (2.8)
20-24 weeks	4 (1.9)	4 (1.9)
24-28 weeks	8 (3.9)	3 (1.4)
28-32 weeks	6 (2.9)	4 (1.9)
32-36 weeks	5 (2.4)	7 (3.3)
36-40 weeks	4 (1.9)	2 (0.9)
40-44 weeks	3 (1.4)	1 (0.5)
44-48 weeks	4 (1.9)	3 (1.4)
48-52 weeks	46 (22.2)	54 (25.4)
> 52 weeks	101 (48.8)	105 (49.3)
Mean exposure (weeks)	44.8	45.2

Comment: Subjects from two of the three treatment arms would be potentially relevant to the assessment of the long-term safety of the applicant's product: subjects who received the combination product once daily for 52 weeks and subjects who alternated use of the combination ointment and calcipotriol every four weeks over the course of 52 weeks (the third treatment arm used the combination product for four weeks then calcipotriol for 48 weeks). The following table is based on information that the applicant presented in Section 2.7.4.1.2.2.2 of the Summary of Clinical Safety:

Treatment Group	***# who received ≥ 28wks of treatment***	***# who received ≥ 48wks of treatment***
Combination for 52 weeks	*169*	*147*
Combination/calcipotriol (4/4 alt.)	*176*	*159*
Total	[redacted]	[redacted]

Thus, the reviewer concludes that 345 subjects have been exposed to the applicant's product for six months, and 147 subjects have been exposed to the product for approximately 52 weeks. These numbers are in line with the recommendations in the ICH E1A guideline for approximate numbers of subjects at the time points of six months and one year for assessment of long-term safety. The reviewer does not agree with the applicant that [redacted] subjects were exposed to their product for o [redacted] (they propose this number in their draft labeling), since over the course of a year, subjects in the combination/calcipotriol (4/4 alt.) group would have used each product for a total of approximately six months.

7.2.2.3 Literature

The applicant included reference articles in the submission. Since the application was submitted, the applicant has increased the frequency of search of worldwide databases from monthly to weekly. Also see Section 8.6.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects have been exposed to the applicant's product in the clinical trials and in the market environment to permit some assessment of the safety and efficacy of a once-daily, four-week treatment regimen. Inclusion of a vehicle arm in several studies permitted comparison to the background event rate in the study populations.

In the development program, the designs of the short-term studies generally appeared to be adequate to answer certain critical questions pertaining to local tolerance of the applicant's product. Safety assessments permitted some evaluation of systemic tolerance of the combination product as relates to the known class effects of each active ingredient. Collection of adverse event data permitted some assessment of systemic and local tolerance of the combination product. Also, systemically, the potential for the product to impact calcium metabolism and the HPA axis were assessed, and locally, the potential for the product to be associated with local adverse events was assessed, including specifically as relates to the corticosteroid component of the product. Additionally, the applicant conducted the full battery of formal topical safety studies, and the numbers in each study were in line with those recommended.

Systemic safety monitoring appeared to place less emphasis on the assessment of the potential for the product to impact clinical and metabolic parameters beyond calcium metabolism and HPA axis suppression, and the potential for the product to impact the HPA axis was assessed only to a limited extent. Specifically, HPA axis testing under maximal use conditions was done only in 11 subjects (a 12^{th} subject did not have post-treatment testing done). Over the entire clinical development program, comprehensive safety monitoring (including routine labs, ECG's, vital signs) appears to have been done in only 12 subjects with psoriasis.

There is also a body of information available from the post-marketing arena from use of the combination product, as well as for the active ingredients marketed individually.

It is the opinion of the reviewer that the long-term safety of the combination product has not been adequately assessed. While sufficient numbers may have been exposed to the product for the requisite time periods as recommended in the ICH E1A guideline, the reviewer does not consider the safety monitoring to have been sufficiently comprehensive in the long-term safety study to assess the tolerance of long-term use of the combination product. Deficiencies include,

- Calcium metabolism was not assessed.
- HPA axis function was not adequately assessed.
- Routine safety laboratory testing was not done.
- Weights and vital signs were not done.
- ECG's were not done.

The study populations were not sufficiently reflective of the U.S. population, and the applicant has previously agreed to address this in Phase 4. In the development program, limited information was obtained regarding use of the product in non-Caucasians. This could have

particular implications for the U.S. population given the incidence of occurrence of hypertension and diabetes in certain groups and the potential for the applicant's product to have systemic effects which could impact conditions such as these. Also, the extent to which local adverse event might be seen could differ, e.g. higher rates of hypopigmentation. Depending on the design, a Phase 4 study could provide the applicant the opportunity to obtain additional safety information regarding long-term use. Additional safety information about short-term use, e.g. HPA axis testing, could also be obtained in Phase 4.

No post-treatment assessments appear to have been conducted in the development program (except for follow-up of adverse events), and post-marketing reports suggest that development of pustular psoriasis post-treatment may be seen (this event was also reported during treatment). Labeling will reflect the occurrence of this event.

Labeling will reflect the exclusion of patients with known or suspected hypercalcemia, pregnant and lactating women. Subjects with "severe" renal and hepatic insufficiency were excluded from the long-term study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Individually, calcipotriol and betamethasone dipropionate have long marketing histories in the United States. The pharmacologic and toxicologic properties of calcipotriol were extensively studied during its development, and, per the applicant, betamethasone dipropionate has been shown to have "metabolic, pharmacological and toxicological effects typical for corticosteroids" (Non-clinical Overview). Additionally, there is a long history of in-human use for betamethasone dipropionate. The applicant's approach to non-clinical testing relied in part on studies conducted with the individual ingredients. The applicant's product contains the actives in the same concentrations as found in the individually-marketed products, and systemic exposure to each active from the combination product is similar to that from the active ingredients are applied individually. Additionally, the applicant conducted select safety studies with the combination product, including repeat-dose toxicity, and absorption, distribution, metabolism and excretion studies.

7.2.5 Adequacy of Routine Clinical Testing

See Section 7.2.3.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The applicant indicates that the metabolism of each active ingredient and the combination have been studied in human liver homogenates.

The applicant has evaluated how the active ingredients interact with each other, but not how the product interacts with other drugs. The applicant considers the risk of systemic interaction with other drugs to be "negligible" for reasons that include (Section 2.4.2.4 of the Non-clinical Overview):

- less than 1% of applied doses of the active ingredients is systemically absorbed when the combination ointment is topically applied to healthy human skin.

- both ingredients are rapidly metabolized

Comment: It is not clear that results pertaining to systemic absorption from studies conducted on healthy skin would apply to subjects with psoriasis.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant's efforts to detect specific adverse events that are predictable on the basis of the drug classes of each active ingredient were adequate in the Short-Term studies, as pertains to local tolerance, collection of adverse event data, and the potential for the product to impact calcium metabolism. However, the development program placed less emphasis on assessing the systemic tolerance of the product as pertains to the corticosteroid component. Except for 12 subjects in study MCB 0201 FR, safety assessments in subjects with psoriasis did not include routine laboratory monitoring (hematology, chemistries, urinalysis), vital signs, weights or ECG's.

The long-term study did not assess the potential of the product to impact calcium metabolism, or the potential for systemic corticosteroid effects apart from HPA axis suppression, e.g. blood pressure, weights, glucose levels, and the reviewer considers these to be deficiencies of the long-term study. Adverse events suggestive of systemic effects of either active ingredient did not appear to occur at increased frequency with the applicant's product when compared to other study arms; however, these findings are not a substitute for laboratory data.

7.2.8 Assessment of Quality and Completeness of Data

See Sections 7.2.3 and 7.2.7.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted a 120-Day Safety Update on July 5, 2005. The submission also included a Periodic Safety Update Report for the period 01 April 2004 to March 2005. The Safety Update contained safety data from ongoing nonclinical studies and information from the post-marketing experience (obtained between September 15, 2004 and April 9, 2005, the cut-off date for the update). The applicant also performed a search of the clinical literature for new safety information.

One study was ongoing at the lock date: MCB 0303 INT was a double-blind study that evaluated the combination product and Diprosone® ointment for treatment of pustulosis palmoplantaris. The study enrolled 428 subjects. Subjects received study treatment twice daily for eight weeks (the last subject's final visit was April 28, 2004). All serious adverse events from this study that were reported to the applicant during the study and the required follow-up period were included in the original submission of the NDA, and none occurred in the combination group.

One clinical study was initiated after the cut-off date for the safety update: MCB 0402 INT is a 12-week, Phase 4 study which evaluates the safety and efficacy of three once daily treatment regimens in subjects with psoriasis vulgaris:

- 4 weeks of the combination ointment followed by 8 weeks of Dovonvex® cream
- 4 weeks of the combination ointment followed by 8 weeks of Dovonvex® cream on weekdays and the combination product on weekends
- 4 weeks of the combination ointment followed by 8 weeks of Dovonvex® cream vehicle.

The study is being conducted in Europe and Canada and has enrolled 293 of the 1020 subjects planned.

Non-Serious Adverse Drug Reactions

A total of 16 spontaneously-reported case reports for 23 adverse drug reactions were received during the period covered by the update. Four cases were consumer reports. Thirteen cases reported 17 reactions coded as "Skin and subcutaneous tissue disorders," and the most frequent reaction under this system organ class was coded as "exacerbation of psoriasis." The events are summarized in the following table:

Applicant Table 2: Spontaneously Reported, Non-Serious Adverse Drug Reactions, Post-marketing

System Organ Class Preferred Term	# of Subjects with Adverse Drug Reaction
Any adverse drug reaction	23
Skin and subcutaneous tissue disorders	
Psoriasis	4
Pruritus	2
Rash	2
Rash pruritic	1
Rash generalized	1
Erythema	1
Photosensitivity reaction	1
Skin discoloration	2
Dermatitis allergic*	1
Dermatitis contact	2
Nervous system disorders	
Burning sensation	3
Psychiatric disorders	
Insomnia	1
Renal and urinary disorders	
Renal calculi	1
General disorders and application site conditions	
Application site burning	1

*the applicant considered this case non-valid as there was no identifiable patient.

Two will be discussed briefly:

- MFR 104346: A 41-year-old male patient had been treated with the combination product in excess of one year reportedly without any problems. During a period of widespread psoriasis, he self-treated with two applications per day. He noticed changes in his sleep

pattern after a few days. He reduced the use of the product to only small areas and his sleep pattern returned to normal.

- MFR 10206: A male patient (age unknown) was treated with the combination product for six weeks. He complained about loin pain when he returned to his treating physician for evaluation. He was diagnosed as having a renal calculus. No further information was given.

Comment: A causative role for the applicant's product cannot be definitively spoken to in either of these reports. However, insomnia and renal calculi can develop in the setting of hypercalcemia. The twice daily application to "widespread" areas of involvement could have resulted in sufficient systemic exposure to result in hypercalcemia with insomnia manifesting as a symptom of that. It is unclear whether an exposure of six weeks duration would be sufficiently long to allow for development of renal calculi.

Deaths and Other Serious Adverse Drug Reactions

There were no spontaneous notifications of deaths during treatment with the combination product. However, one patient died post-treatment due to heart disease and septicemia which were reportedly "not at all related" to psoriasis or the combination product:

A male of unknown age [redacted] reportedly due to heart disease and septicemia. He had self-reported swelling, muscle atrophy, alopecia and erythema to Leo in November 2003 (see Table 3 below). Death and hospitalization were said to not be related to psoriasis of the combination ointment. Concomitant to the combination ointment were betamethasone and clobetasone butyrate. The patient reportedly had a history of poor/noncompliance and self-medication.

Comment: The constellation of signs and symptoms could be suggestive of systemic corticosteroid effects. Swelling, muscle atrophy and alopecia raise the possibility of cushingoid syndrome. Septicemia could occur secondary to immunosuppression.

Four serious case reports were received and covered eight adverse reactions. These events are summarized in the table below (includes self-reported events from the patient who died).

Applicant Table 3: Spontaneously Reported, Serious Adverse Drug Reactions

System Organ Class Preferred Term	Reporter	Age/ Sex	Dates of therapy	Date of onset; Outcome
General Disorders and administration site conditions				
Swelling*	Consumer	?/M	01Nov03-?	01Sept04; unknown
Musculoskeletal and connective tissue disorders				
Muscle atrophy*	Consumer	?/M	01Nov03-?	01Sept04; unknown
Skin and subcutaneous tissue disorders				
Eczema	HCP+	68/F	10Sept-10Oct04	10Oct04; Recovered
Psoriasis	HCP+	67/M	01Oct-01Nov04	14Oct04; Recovering
Psoriasis	HA^	49/M	01Aug04-?Jan05	11Jan05; Recovered
Alopecia*	Consumer	?/M	01Nov03-?	01Sept04; Unknown
Erythema*	Consumer	?/M	01Nov03-?	01Sept04; Unknown

Respiratory, Thoracic and Mediastinal Disorders				
Respiratory distress	HA^	49/M	01Aug04-?Jan05	[redacted], Not recovered

*MFR 104176:
+Health care professional
^Health Authority

In the Safety Update, the applicant stated that weekly literature searches are performed in several internationally recognized databases, including Medline, Embase, Biosis. In the period since the lock date of the NDA and the cut-off date of April 9, 2005, the applicant reports no "relevant" case reports or studies were published.

Comment: The Safety Update did not raise any new safety concerns.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The development program evaluated three general categories of adverse events as pertains to the active ingredients in the combination product: the potential for local adverse events (particularly as relates to the corticosteroid component), the potential for effects on calcium metabolism, and the potential for HPA axis suppression.

Local Adverse Events

The potential for development of local adverse events would particularly relate to the corticosteroid component, and the adverse event profile for topical corticosteroids is well-established. The marketed calcipotriol ointment is labeled as sometimes causing irritancy. Also see Section 7.1.5.5.

Local Events Possibly Related to Use of Topical Corticosteroid: Short-Term Studies (Source: Table 76 Integrated Summary of Safety)

	Number (%) of subjects with Adverse Event			
	Combination N=2448	**Vehicle N=470**	**Calcipotriol N=3197**	**Betamethasone N=1164**
Any Adverse Event				
Preferred Term				
Skin atrophy	3 (0.1)	0 (0.0)	2 (0.1)	2 (0.2)
Telangiectasia	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ecchymosis	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Purpura	1 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Skin hypopigmentation	5 (0.2)	0 (0.0)	3 (0.1)	2 (0.2)
Skin hyperpigmentation	3 (0.1)	0 (0.0)	3 (0.1)	1 (0.1)
Rash pustular	4 (0.2)	0 (0.0)	4 (0.1)	1 (0.1)
Skin folliculitis	16 (0.7)	3 (0.0)	5 (0.2)	4 (0.3)
Furuncle	0 (0.0)	1 (0.2)	4 (0.1)	0 (0.0)
Celliuitis	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Papilloma	1 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)

Total Dose of Combination Product: Long-Term Core Study (Modified Applicant Table T16)

	Combination once daily for 52 wks N= 207	Combination/calcipotriol 4/4 (alt.) N= 213	Combination/calcipotriol 4/48 N= 206
Total Dose of Combination Ointment (g)			
Median	596.4	344.4	84.0
Mean	911.9	477.7	118.9
SD	856.9	461.1	101.0
Min, Max	22.3, 4347.3	0.0, 2403.7	2.4, 389.9
Number	161	187	198

SD: Standard Deviation
Min., Max.: Minimum, Maximum

Healthy Volunteers in 3-to 4-Week Studies

The number of subjects exposed to the combination product was 355 and the mean duration of exposure was 3.5 weeks.

Non-Core Studies

The number of subjects exposed to the combination product was 45 in the psoriasis studies and 23 in the contact dermatitis study. The mean duration of exposure was 2.7 weeks and 1.2 weeks, respectively.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Post-marketing data were reviewed and are discussed in other sections of the review (see Sections 7.1.13, 7.1.17, 7.2.2.2 and 7.2.9). The package inserts for the approved calcipotriene ointment and betamethasone dipropionate ointment were reviewed.

7.2.2.1 Other studies

The applicant indicated that all clinical studies that they conducted which evaluated the combination ointment were included in the Summary of Clinical Safety (Section 2.7.4.1.1.2). The application did not provide safety data from any other clinical studies.

7.2.2.2 Postmarketing experience

Marketing of the combination product was first launched in Denmark in October 2001. Per the applicant, the product has since been launched in most European countries, Asia, South America and Canada. The application included Period Safety Update reports covering the period of April 1, 2001 through March 31, 2004. Additionally, the applicant provided post-marketing data in a Safety Update submitted July 5, 2005. Also see Sections 7.1.13, 7.1.17 and 7.2.9.

Modified Applicant Table 78: Treatment-Related Adverse Events Occurring in ≥ 1% of Subjects: Short Term Studies

	Number (%) of subjects with Adverse Event			
	Combination N=2448	**Vehicle N=470**	**Calcipotriol N=3197**	**Betamethasone N=1164**
Any Adverse Event	145	57	374	55
Preferred Term	**#of subjects (%)**			
Pruritus	67 (2.7)	34 (7.2)	159 (5.0)	15 (6.1)
Rash scaly	30 (1.2)	1 (0.2)	40 (1.3)	0 (0.0)
Application site pruritus	13 (0.5)	6 (1.3)	23 (0.7)	1 (0.4)
Erythema	12 (0.5)	5 (1.1)	47 (1.5)	5 (2.0)
Skin irritation	9 (0.4)	4 (0.9)	55 (1.7)	3 (1.2)
Psoriasis	8 (0.3)	2 (0.4)	22 (0.7)	6 (2.4)
Burning sensation	6 (0.2)	5 (1.1)	28 (0.9)	2 (0.8)

Effects on Calcium Metabolism

The reviewer's assessment of the calcium data is presented in the following table (also see Section 7.1.7):

Reviewer's Table of Subjects with Corrected Calcium Levels Outside of Upper Limit at End of Treatment

Study	**Combination once daily**	**Combination twice daily**	**Calicpotriol twice daily**	**Betamethasone twice daily**	**Vehicle**
9905	9/141 (6.4)	5/218 (2.3)	13/213 (6.1)	n/a	5/193 (2.6)
9904	n/a	7/354 (2.0)	7/350 (2.0)	3/351 (0.9)	n/a
9802	n/a	4/293 (1.4)	2/293 (0.7)	2/295 (0.7)	2/104 (1.9)
Total	9/141 (6.4)	16/865 (1.8)	22/856 (2.6)	5/646 (0.8)	7/297 (2.4)

Comment: Hypercalcemia can be seen with use of the combination product.

HPA Axis Testing

No subjects treated with the combination product showed evidence of HPA axis suppression in study MCB 0201 FR. One subject in the combination/calcipotriol group (4/4 alt.) showed evidence of suppression at 52 weeks of treatment in the long-term safety study. Also see Section 7.1.12.

Comment: HPA axis suppression can be seen with use of the combination product. The potential of the product to cause HPA axis suppression has not been adequately evaluated.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The applicant's pooling strategy for the Short-Term Core Studies was acceptable. This grouping included seven studies in which subjects with psoriasis vulgaris received treatment with the combination product once or twice daily for up to 8 weeks. Most of the studies evaluated durations of exposure to the applicant's product of once daily for 4 weeks. Only one study (MCB 0002 INT) evaluated an 8-week exposure, and two studies (MCB 9904 INT and MCB 9802 INT) evaluated twice daily treatment. The applicant also repeated some analyses by groups pooled according to frequency of treatment with the combination product, i.e. once or twice daily, and this pooling strategy was also acceptable.

Comment: The approach to pooling of these studies was acceptable because it also reflects tolerance to more frequent and longer exposures than what the applicant proposes. It was appropriate that data from the healthy volunteer studies were not included in this pooling as it is not clear that absorption and/or tolerance (systemic or local) would be the same for healthy skin compared to skin affected by psoriasis.

7.4.1.2 Combining data

The pooling was accomplished by combining of the numerator events and denominators for the selected studies.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Dosing regimens for the applicant's product have been once daily and twice daily. Duration of dosing has generally been for 4 weeks. Dosing duration with the combination product was 4 weeks for the subjects who received twice daily treatment.

Adverse Events Reported by ≥ 1% of Subjects by Preferred Term: Short-Term Core Studies (Applicant table T32)

Preferred term	Number (%) of Subjects with Adverse Event	
	Combination Ointment once daily N= 1539	Combination Ointment twice daily N= 909
Any adverse event	**414 (26.9)**	**249 (27.4)**
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)

Lesional/Perilesional Adverse Events Reported by ≥ 1% of Subjects by Preferred Term: Short-Term Core Studies (Applicant table T33)

Preferred term	Number (%) of Subjects with Adverse Event	
	Combination Ointment once daily N= 1539	Combination Ointment twice daily N= 909
Any adverse event	115 (7.5)	98 (10.8)
Pruritus	40 (2.6)	29 (3.2)
Rash scaly	18 (1.2)	11 (1.2)
Folliculitis	4 (0.3)	10 (1.1)
Application site pruritus	3 (0.2)	9 (1.0)

7.4.2.2 Explorations for time dependency for adverse findings

Clinical evaluations and laboratory testing for systemic effects were generally timed to permit comparison of end-of-treatment results to baseline results. Some studies included interval clinical assessments.

7.4.2.3 Explorations for drug-demographic interactions

There was no consistent pattern of differences in the incidence of adverse events for the combination ointment across different age groups. Pertaining to the reporting of all adverse events and lesional/perilesional adverse events, more females reported adverse events than males in all treatment groups. The numbers of non-Caucasian subjects were too low to adequately explore adverse event rates in these subgroups.

7.4.2.4 Explorations for drug-disease interactions

The applicant assessed drug-disease interactions by baseline disease severity. For all treatment groups, the rate of lesional/perilesional adverse events increased with increasing baseline disease severity in the Short-Term Core Studies.

7.4.2.5 Explorations for drug-drug interactions

The applicant investigated adverse event rates for subjects using betablockers, topical corticosteroids, nasal or inhalation steroids, and other topical antipsoriatics. No clear trends were observed.

7.4.3 Causality Determination

The pharmacologic effects of each of the active ingredients are well-established, making a causal relationship somewhat easier to suspect.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Initially, the applicant evaluated twice daily usage of the product; however, little difference in efficacy was seen with twice daily dosing when compared to once daily. Additionally, the safety profile favored once daily dosing.

8.2 Drug-Drug Interactions

Per Section 2.7.4.5.3.2 of the Summary of Clinical Safety, no formal drug interaction studies have been conducted.

8.3 Special Populations

There are no special dosing recommendations for demographics based on the clinical trial data. Tolerance of the product has not been adequately evaluated with coexisting states such as hepatic or renal insufficiency. The product has not been evaluated in the pediatric population or in pregnant or lactating women.

8.4 Pediatrics

At the guidance meeting held on June 9, 2003, the applicant proposed to submit a request for [redacted] of pediatric studies. However, the Agency advised that since psoriasis does occur in the pediatric age group, a partial pediatric waiver would seem more appropriate and recommended that the product be studied in subjects 12 years and older.

The marketing application included a request for a partial waiver of pediatric studies in subjects aged 0 to 11 years, including newborn infants, infants and toddlers and children. The rationale was stated to be that the product was not considered to be safe in this age group. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk than adults of systemic adverse effects when they are treated with topical medication.

A deferral was issued for study of the product in the age group of 12 to 17 years, and a partial waiver was issued for study of the product in the age group of 0 through 11 years.

On March 24, 2005, the applicant submitted a proposed pediatric study request to IND [redacted]. They proposed to:

[redacted]

8.5 Advisory Committee Meeting

This section is not applicable.

8.6 Literature Review

Per the original submission of the NDA, the applicant performs monthly literature searches in international databases, e.g. MEDLINE, EMBASE. If any possibility of an adverse event was found, the complete article was requested for review. A literature search conducted by the applicant on October 5, 2004 revealed no published cases of adverse events in subjects treated with the combination product, other than those that occurred in the applicant's own clinical trials (and included in the marketing application under current review).

8.7 Postmarketing Risk Management Plan

For the United States market, the applicant states that they will classify spontaneous reports of suspected adverse drug reactions (sADRs) according to CIOMS agreed definitions where possible with active follow-up of the reactions according to CIOMSV criteria.

The applicant will use templates so that each medical assessment, based on CIOMS V guidelines, will include (when such information is available):

- the temporal relationship to the sADR
- biological plausibility of the actives as a cause
- time of onset and progression of the adverse reactions including outcome
- confirmation of diagnosis of the sADR

combination was superior to each monad and to vehicle as assessed by the Investigator's Assessment of Global Severity and by the percentage change in PASI.

In support of efficacy, the applicant submitted data from four additional studies that included treatment arms in which subjects with psoriasis vulgaris received once daily dosing of the combination product for four weeks (as was evaluated in MCB 0003 INT, the pivotal trial). These studies were also conducted in Europe and Canada and were part of the database on which the applicant relied to support approval of marketing overseas. While, the supportive trials differed in certain design elements, such as the comparators, the inclusion and exclusion criteria were essentially the same as in the pivotal trial. All of the trials assessed efficacy by the percentage change in PASI. The PASI results from these additional studies were generally consistent with those from the pivotal study and with each other, and the reviewer considers the results to be supportive of efficacy. One of the trials also included an assessment by a static investigator's global assessment, and the combination product was superior to the comparator.

No new safety concerns were raised in the development program. In the development program, the designs of the short-term studies generally appeared to be adequate to answer certain critical questions pertaining to local tolerance of the applicant's product. Safety assessments permitted some evaluation of systemic tolerance of the combination product as relates to the known class effects of each active ingredient. Collection of adverse event data permitted some assessment of systemic and local tolerance of the combination product. Also, systemically, the potential for the product to impact calcium metabolism and the HPA axis were assessed, and locally, the potential for the product to be associated with local adverse events was assessed, including specifically as relates to the corticosteroid component of the product. Additionally, the applicant conducted the full battery of formal topical safety studies, and the numbers in each study were in line with those recommended.

Laboratory monitoring appeared to place less emphasis on the assessment of the potential for the product to impact clinical and metabolic parameters beyond calcium metabolism and HPA axis suppression, and the potential for the product to impact the HPA axis was assessed only to a limited extent. Specifically, post-treatment HPA axis testing under maximal use conditions was done only in 11 subjects (a 12th subject did not have post-treatment testing done). Over the entire clinical development program, comprehensive safety monitoring (including routine labs, ECG's, vital signs) appears to have been done in only 12 subjects with psoriasis.

There is also a body of information available from the post-marketing arena from use of the combination product, as well as for the active ingredients marketed individually.

It is the opinion of the reviewer that the long-term safety of the combination product has not been adequately assessed. While sufficient numbers may have been exposed to the product for the requisite time periods as recommended in the ICH E1A guideline, the reviewer does not consider the safety monitoring to have been sufficiently comprehensive in the long-term safety study to assess the tolerance of long-term use of the combination product. Deficiencies include,

- Calcium metabolism was not assessed.
- HPA axis function was not adequately assessed.
- Routine safety laboratory testing was not done.
- Weights and vital signs were not done.
- ECG's were not done.

9.2 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that the application be approvable. The approvable recommendation is pending the applicant's agreement to withdraw proposed marketing of the product in — tube sizes. The recommended maximum dosage of their product is 100 gm per week. Packaging of the product in amounts that exceed the recommended maximum weekly usage is not acceptable, as it would make product available to patients in amounts that, if used, would put them at increased risk for side effects. Therefore, tube sizes should not exceed 100 gm.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The applicant will need to extend their post-marketing surveillance program to the United States (See Section 8.7). Adverse events of particular interest would be those that suggest possible systemic effect(s) from the product, as a function of systemic exposure to either of the two active ingredients. Such events would include those that suggest that calcium metabolism and/or the hypothalamic-pituitary-adrenal (HPA) axis have been impacted. Local adverse events would also be of interest and would include those related to use of a topical corticosteroid, such as telangiectasias, atrophy, hypopigmentation, etc.

9.3.2 Required Phase 4 Commitments

There are no clinical Phase 4 commitments, other than the deferred pediatric study under PREA for the treatment of psoriasis vulgaris in pediatric patients ages 12 to 17. A clinical study is ongoing in the United States and was designed to ensure enrichment of enrollment of minorities (few minorities were enrolled in the studies conducted in Europe and Canada).

9.3.3 Other Phase 4 Requests

The sponsor has committed to conduct the following non-clinical studies post-approval of the NDA:

5. Evaluation of the carcinogenicity of calcipotriene (this matter is currently being evaluated by the sponsor as a post-approval commitment to NDA 20-273).
   Final Report Submission: July 1, 2006.
6. Evaluation of the carcinogenicity of betamethasone dipropionate in mice. The sponsor should submit a protocol for this study with appropriate supporting documents for evaluation by the executive carcinogenicity assessment committee of CDER following approval of NDA 21-852.
   Protocol Submission: October 1, 2006
   Study Start: July 1, 2007
   Final Report Submission: October 1, 2010

7. Evaluation of the carcinogenicity of betamethasone dipropionate in rats. The sponsor should submit a protocol for this study with appropriate supporting documents for evaluation by the executive carcinogenicity assessment committee of CDER following approval of NDA 21-852.
   Protocol Submission: October 1, 2006
   Study Start: July 1, 2007
   Final Report Submission: October 1, 2010
8. Evaluation of betamethasone dipropionate for effects upon female fertility, including prenatal and postnatal function.
   Study start: July 1, 2006
   Final Report Submission: December 31, 2007

9.4 Labeling Review

Please see Section 10.2.

9.5 Comments to Applicant

There were no clinical comments for the applicant.

19 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1a

REFERENCES

[1] Lebwohl M. A clinician's paradigm in the treatment of psoriasis. J Am Acad Dermatol 2005;53:S59-69.
[2] Lebwohl M, Suad A. Treatment of psoriasis. Part 1. Topical therapy. J Am Acad Dermatol 2001;45:487-98.
[3] Arndt KA, Bowers KE. Manual of Dermatologic Therapeutics With Essentials of Diagnosis (Philadelphia: Lippincott Williams & Wilkins,2002)
[4] Package insert for Tazorac
[5] Carroll MF, Schade DS. A Practical Approach to Hypercalcemia. Am Fam Physician 2003;67:1959-66.
[6] Hemphill RR. Hypercalcemia. eMediceine. Last Updated January 5, 2005 hypercalcemia
[7] Package insert for Diprosone ointment
[8] Wolverton SE. *Comprehensive Dermatologic Drug Therapy.* (Philadelphia: WB Saunders, 2001)
[9] Meeting minutes (End of Phase 2)
[10] Meeting minutes (Guidance)
[11] Meeting minutes (preNDA)
[12] Lebwohl (clinician's paradigm)
[13] Carroll
[14] Carroll
[15] Hemphill
[16] Carroll
[17] Carroll
[18] Hemphill

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

/s/

Brenda Carr
1/9/2006 01:15:36 PM
MEDICAL OFFICER

Jill Lindstrom
1/9/2006 02:42:35 PM
MEDICAL OFFICER