

of the body should avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.). Physicians may wish to limit or avoid use of phototherapy in patients that use Dovonex®.

“Calcipotriene did not elicit any mutagenic effects in an Ames mutagenicity assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration assay, or in a micronucleus assay conducted in mice.”

7.1.12 Special Safety Studies

The applicant conducted four special safety studies: a study to assess the systemic effects on the HPA axis and calcium metabolism and three dermal safety studies:

- MBL 0404 FR (HPA axis and calcium metabolism)
- photo-allergy test (MBL 0301 UK; 5.3.5.4.3)
- repeat insult patch test/21-day cumulative irritation test (MBL 0302 FR; 5.3.5.4.2)
- photo-toxicity test (MBL 0303 FR; 5.3.5.4.1)

MBL 0404 FR: “Effect of DAIVOBET/DOVOBET Gel on the HPA Axis and Calcium Metabolism in Patients with Extensive Scalp Psoriasis”

Study objectives: To evaluate the effect of once daily use of DAIVOBET/DOVOBET suspension and ointment on the hypothalamic-pituitary-adrenal (HPA) axis and on calcium metabolism in subjects with extensive scalp and body psoriasis

Study methodology: This study was a prospective, uncontrolled study conducted in Europe (one site each in Denmark, France, and Germany) in which subjects with extensive scalp and body psoriasis were treated daily for up to 8 weeks with the new combination product (scalp) and calcipotriol/betamethasone ointment, i.e. Taclonex to the body. Study visits were at Day-14, between Day -10 and Day-5, Days -2 to 1, Days 8, 15 and 22, Days 27 to 29, Days 36, 43 and 50, and Days 55 to 57.

Visits 3, 7 and 11 were in-patient visits during which subjects received an individualized calcium diet (based on their average calcium intake). A 24-hour urine collection for assessment of calcium was taken on Days -1, 28 and 56. An adrenocorticotrophic hormone (ACTH) testing was performed at 8 a.m. between Days -10 to -5, on Days 29 and 57. If HPA axis suppression was noted at Visits 7 or 11 ACTH testing was repeated 28 days later. Study products were applied once daily. Subjects whose scalp lesions had cleared after 4 weeks left the study; subjects who had scalp lesions after 4 weeks continued daily treatment for another 4 weeks (body lesions were treated as needed). A complete physical examination (including vital signs), an ECG and routine blood and urine laboratory tests were conducted at Day -14 and at the end of the study (Day 29 or 57). Serum cortisol was measured on Days -14, 5, 29 and 57. Serum

calcium was measured Days -14, 1, and all subsequent visits. Blood samples for pharmacokinetic assessment of calcipotriol, betamethasone and their metabolites (MC1080 and betamethasone 17-propionate, respectively) were taken on Days 1, 27 and 55 before application of study medication and after 1, 2, 3, 5, and 7 hours. Adverse events were recorded at all visits except Day -14. Psoriasis on the scalp and body was assessed by the investigator's global assessment of disease severity.

Number of subjects enrolled: 58 subjects were enrolled and screened and 35 received treatment ("full analysis set/safety analysis set"); 32 subjects had baseline cortisol levels ≤ 18 mcg/dL ("per protocol analysis set")

Duration of treatment: 4 or 8 weeks

Criteria for safety evaluation: *

Primary endpoint: The adrenal response to ACTH stimulation test defined as serum cortisol concentration obtained after 30 minutes at baseline, week 4 and week 8.

Secondary endpoints:

- Adrenal response to ACTH stimulation test defined as the serum cortisol concentration obtained after 60 minutes at baseline, week 4 and week 8
- Adrenal response to ACTH stimulation test defined as rise in serum cortisol from time zero to 30 and 60 minutes after injection at baseline, week 4 and week 8
- Change in 24 hour urinary calcium excretion from baseline to week 4 and week 8
- Change in serum calcium from baseline to week 4 and week 8
- Any reported adverse events or adverse drug reactions.
- Reasons for withdrawal from the study.

Main Inclusion Criteria:

- Patients either sex, aged from 18 to 60 years
- Patients with psoriasis on scalp and trunk/limbs with an extension of in total 15-30% of BSA, where involvement on scalp should be more than or equal to 30% of the scalp
- Psoriasis vulgaris (scalp, trunk and limbs) amenable to topical treatment with a maximum of 110 g of study medication (total amount of gel and ointment) per week
- Disease severity on the scalp as well as on trunk/limbs graded as Moderate, Severe or Very severe according to the investigator's global assessment of disease severity
- Patients with a normal HPA axis function defined by:
 - baseline serum cortisol concentration above 5 mcg/dL
 - serum cortisol above 18 mcg/dL 30 minutes after ACTH (

stimulation

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- Serum calcium levels at baseline should be within reference range

Exclusion Criteria (partial list):

- Known or suspected severe renal insufficiency
- Known or suspected severe hepatic disorders

Investigator Global Assessment Scale

Clear	Plaque thickening = none (no elevation or thickening over normal skin) Scaling = none (no evidence of scaling) Erythema = none or slight (hyperpigmentation or residual red coloration)
Minimal there is a	Plaque thickening = none or slight (possible but difficult to ascertain whether slight elevation above normal skin level) Scaling = none or slight (residual surface dryness and scaling) Erythema = up to mild (up to light red or pink coloration)
Mild	Plaque thickening = slight (slight but definite elevation) Scaling = fine (fine scales partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
Moderate edges)	Plaque thickening = moderate (moderate elevation with rounded or sloped Scaling = coarser (most lesions at least partially covered) Erythema = moderate (definite red coloration)
Severe edges)	Plaque thickening = marked (marked elevation typically with hard sharp Scaling = coarse (non-tenacious scale predominates, covering most or all of the lesions) Erythema = very severe (very bright red coloration)
Very severe or sharp edges)	Plaque thickening = very marked (very marked elevation typically with hard Scaling = very coarse (thick tenacious scale covers most or all of the lesions) Erythema = very severe (extreme red coloration; deep red coloration)

Comment: The scale does not address the extent of body surface area involvement.

Data Sets Analyzed:

1. Full Analysis Set/Safety Analysis Set

This population was defined as “all included patients who have received at least one application of study drug and for whom safety data is available.” This data set included 35 subjects.

2. Per Protocol Analysis Set

This population was defined as “all included patients who received study treatment, who satisfied the entry criteria and completed the entire study without serious protocol violations.” This data set included 32 subjects.

The following were identified as serious protocol violations and resulted in the exclusion of subjects from the safety analysis set to form the per protocol analysis set:

- the subject did not provide any data related to the HPA axis tests following the start of treatment
- the subject did not have a baseline serum cortisol concentration >18 mcg/dL 30 minutes after ACTH stimulation (3 subjects)

All subjects provided data related to HPA axis function testing following start of treatment. Three subjects (CRF=0023, 0024 and 0029) had serum cortisol concentrations ≤18 mcg/dL 30 minutes after pre-treatment ACTH stimulation at Visit 2 and were excluded from the per protocol analysis set. Therefore, the per protocol analysis set consists of 32 subjects.

Baseline disease severity is presented in the following tables:

Table 6: Investigator’s global assessment of disease severity on the scalp: safety and per protocol analysis sets¹

Investigator’s global assessment	All enrolled patients (n=58)		Safety (n=35)		Per Protocol (n=32)	
	Number of patients	%	Number of patients	%	Number of patients	%
Clear	1	1.7	0	0.0	0	0.0
Minimal	4	6.9	0	0.0	0	0.0
Mild	5	8.6	0	0.0	0	0.0
Moderate	19	32.8	15	42.9	13	40.6
Severe	25	43.1	17	48.6	17	53.1
Very Severe	4	6.9	3	8.6	2	6.3
Total	58	100.0	35	100.0	32	100.0

1) Visit 1 assessment was used for the 23 patients who failed screening, otherwise the visit 3 assessment was used for patients assigned treatment.

Table 7: Investigator's global assessment of disease severity on the body (trunk/limbs): safety and per protocol analysis sets¹

Investigator's global assessment	All enrolled patients (n=58)		Safety (n=35)		Per Protocol (n=32)	
	Number of patients	%	Number of patients	%	Number of patients	%
Clear	0	0.0	0	0.0	0	0.0
Minimal	3	5.2	0	0.0	0	0.0
Mild	10	17.2	0	0.0	0	0.0
Moderate	20	34.5	14	40.0	12	37.5
Severe	24	41.4	21	60.0	20	62.5
Very Severe	1	1.7	0	0.0	0	0.0
Total	58	100.0	35	100.0	32	100.0

1) Visit 1 assessment was used for the 23 patients who failed screening, otherwise the visit 3 assessment was used for patients assigned treatment.

The mean weekly amount of scalp product used was 23.7 gm; the mean amount of Taclonex ointment used was 40.2 gm.

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Table 11: Use of study medication: safety analysis set

Visit Medication used once daily	DAIVOBET gel plus DAIVOBET ointment (n=35)	Number of patients	%
VISIT 4 (week 1)			
Yes		32	94.1
No: ≤10% days missed		0	0.0
No: >10% to ≤20% days missed		2	5.9
Total number of patients with compliance data		34	100.0
VISIT 5 (week 2)			
Yes		33	94.3
No: ≤10% days missed		1	2.9
No: >10% to ≤20% days missed		1	2.9
Total number of patients with compliance data		35	100.0
VISIT 6 (week 3)			
Yes		33	97.1
No: ≤10% days missed		0	0.0
No: >10% to ≤20% days missed		1	2.9
Total number of patients with compliance data		34	100.0
VISIT 7 (week 4)			
Yes		31	91.2
No: ≤10% days missed		0	0.0
No: >10% to ≤20% days missed		3	8.8
Total number of patients with compliance data		34	100.0
VISIT 8 (week 5)			
Yes		11	100.0
No: ≤10% days missed		0	0.0
No: >10% to ≤20% days missed		0	0.0
Total number of patients with compliance data		11	100.0
VISIT 9 (week 6)			
Yes		11	91.7
No: ≤10% days missed		0	0.0
No: >10% to ≤20% days missed		1	8.3
Total number of patients with compliance data		12	100.0

[table is continued on next page]

VISIT 10 (week 7)		
Yes	10	90.9
No: $\leq 10\%$ days missed	0	0.0
No: $>10\%$ to $\leq 20\%$ days missed	1	9.1
Total number of patients with compliance data	11	100.0
VISIT 11 (week 8)		
Yes	12	100.0
No: $\leq 10\%$ days missed	0	0.0
No: $>10\%$ to $\leq 20\%$ days missed	0	0.0
Total number of patients with compliance data	12	100.0
TOTAL TREATMENT PERIOD		
Yes ¹	29	82.9
No ² : $\leq 10\%$ days missed	5	14.3
$>10\%$ to $\leq 20\%$ days missed	1	2.9
Total number of patients with compliance data	35	100.0
1) 'Yes' recorded at all attended post treatment visits.		
2) At least one 'No' recorded.		

For the per protocol analysis set, 5 of 32 (15.6%) subjects had serum cortisol ≤ 8 mcg/dL 30 minutes post-stimulation at week 4. Four of these subjects stopped treatment at week 4 because their scalp psoriasis had cleared. On post-treatment repeat testing, three had serum cortisol >18 mcg/dL at 30 minutes, and one had a serum cortisol of 16.30 mcg/dL. One subject continued in the study (i.e. through Week 8) and had serum cortisol at 30 minutes of 17.71 mcg/dL and 16.77 mcg/dL at weeks 4 and 8 respectively. Of the 11 subjects who continued to week 8, 2 (18.2%) had serum cortisol ≤ 8 mcg/dL 30 minutes post-stimulation, one of whom also had a value of ≤ 8 mcg/dL at 30 minutes at week 4.

The numbers of subject with serum cortisol ≤ 18 mcg/dL 30 minutes post-stimulation at Weeks 4 and 8 are presented for the per protocol analysis set in the following table:

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Table 70: Patients with serum cortisol ≤ 18 mcg/dL 30 minutes after the ACTH challenge test at Weeks 4 and 8 in the HPA axis study: per protocol analysis set

Visit Serum cortisol after 30 mins	Daivobet® gel plus Daivobet® ointment (n=32)	
	Number of Patients	%
Visit 7 (week 4)		
>18 mcg/dL	27	84.4
≤ 18 mcg/dL	5	15.6
Total	32	100.0
Visit 11 (week 8)		
>18 mcg/dL	9	81.8
≤ 18 mcg/dL	2	18.2
Total	11	100.0

Source: MBL 0404 FR Clinical Study Report, Table 12

Individual data for subjects with cortisol ≤ 18 mcg/dL 30 minutes post-stimulation (from Applicant Table 71 and Amendment 8)

Subject	Disease Severity at Baseline scalp/body	Total Amount Gel/Ointment Used in grams (mean weekly)	Visit	Pre- stimulation Cortisol	30 minutes Post- stimulation Cortisol
0001- FR187	severe/severe	87.8/436.0 (14.9/56.5)	Baseline	15.32	22.09
			Week 4	11.41	17.71
			Week 8	10.54	16.77
0003- FR187	severe/severe	193.3/318.5 (28.8/43.5)	Baseline	10.68	18.91
			Week 4	11.34	18.65
			Week 8	11.55	17.57
0025- DK177*	severe/moderate	30.8/157.1 mean?	Baseline	9.53	18.83
			Week 4	14.31	17.71
			Week 8	3.19	16.30 ⁺
0035- DE117*	moderate/severe	161.1/235.2 (41.8/61.0)	Baseline	8.55	19.20
			Week 4	13.76	17.31

			Week 8	10.65	24.37
0056- DE117*	moderate/severe	49.8/178.6 mean?	Baseline	10.32	24.01
			Week 4	8.40	17.09
			Week 8	10.97	18.07
0058- DE117*	severe/moderate	83.8/144.9 mean?	Baseline	9.45	18.83
			Week 4	8.69	17.20
			Week 8	13.58	20.50

*discontinued at Week 4

*Testing done at Day 83

No further testing was done on subjects 0001 FR187 or 0003 FR187 (although the protocol called for retesting of subjects who showed evidence of suppression at Week 8). Thus, there is no information regarding recovery of HPA axis function. However, recovery is generally prompt on withdrawal of the corticosteroid-containing product. Subject 0025-DK177 had follow-up testing done 83 days following the Week 4 testing (the protocol called for testing 28 days after the first test). The subject had not taken any medications to which the continued suppression might be attributed.

MBL 0301 UK: Assessment of the photosensitisation potential of DAIVOBET/DOVOBET gel containing Calcipotriol 50 mcg/g plus Betamethasone 0.5 mg/g (as dipropionate)

Objective: to determine the photoallergic potential of combination product and the vehicle after repeated applications and irradiation to the skin of healthy subjects.

Study design: Single center, randomized, double-blinded, vehicle-controlled assessor- and investigator-blinded study with intra-individual comparison of treatments in healthy subjects.

Number of healthy volunteers enrolled: 50 subjects planned; 49 enrolled; 45 subjects completed the challenge phase

Study methodology: At screening, each subject's minimal erythral dose (MED) was assessed by recording the responses of untreated skin to 8 ultraviolet (UV) light exposures of increasing duration. The spectral output of the radiation source was filtered to match the solar spectrum and produce wavelengths in the UVA + B (290 – 400 nm and < 1% of the output less than or equal to 290 nm). The skin was assessed immediately after and 23 h ± 1 h after irradiation (for determination of MED). DAIVOBET/DOVOBET gel and gel vehicle were applied under patch occlusion on each subject's back on a total of 7 occasions as described below.

Induction phase (Weeks 1, 2 and 3)

Test products were applied on Days 1 and 4 of Weeks 1, 2 and 3. Test sites assigned to receive irradiation were irradiated on Days 2 and 5, i.e. approximately 24 hours after each patch application. Skin assessments were performed prior to irradiation. The erythema grading scale was: 0 = No reaction; 1 = Mild erythema; 2 = Moderate erythema; 3 = Severe erythema.

Other reactions were also recorded: spreading of reactions beyond the patch sites (S) papules (Pa), vesicles (V), blisters (B), dryness (D), cracking (C), peeling (Pe) and others were to be recorded, as well as pigmentation (P) induced by UV radiation.

Rest phase (Weeks 4 and 5)

No test products were applied.

Challenge phase (Day 36, Week 6)

Test products were applied on Day 36. The skin was assessed on Day 37, and test sites assigned to receive irradiation were irradiated. Assessments for photosensitization reactions were performed 72 h after UV exposure. Photosensitization reactions were evaluated as follows: 0 = Negative; 1 = Equivocal; 2 = Positive (definitions for the reactions were not found in the protocol). Any positive or equivocal reaction as well as any unexpected and/or severe skin reaction was to have been photographed, and a consultant dermatologist was asked for an opinion on these findings. Additionally, a global clinical score (GCS) assessment was performed before application and irradiation and approximately 24, 48 and 72 h after irradiation. GCS was scored using the following scale:

0 = Normal skin aspect

1 = Slight erythema with small papules and/or slight edema

2 = Moderate erythema with papules and/or vesicles and/or slight edema

3 = Intense erythema, edema, confluent vesicles forming blisters

Other reactions were recorded (see reactions described above for Induction phase).

RESULTS

Four subjects were excluded from the Challenge phase analysis set: headache (1), sunburn (1), unable to attend challenge phase of the study (2). The Challenge phase results for photosensitization reactions for the remaining 45 subjects are presented in the following table:

Applicant Table 14.4.1.1

UV Exposure	Investigational Product	Photosensitisation*		
		Negative n (%)	Equivocal n (%)	Positive n (%)
UVB+A	DAIVOBET/DOVOBET	45 (100.0)	0	0
	Vehicle Gel	45 (100.0)	0	0
	Untreated	45 (100.0)	0	0
UVA	DAIVOBET/DOVOBET	45 (100.0)	0	0
	Vehicle Gel	45 (100.0)	0	0
	Untreated	45 (100.0)	0	0
Unexposed	DAIVOBET/DOVOBET	45 (100.0)	0	0
	Vehicle Gel	45 (100.0)	0	0

The Challenge phase results for the GCS for the remaining 45 subjects are presented in the following table:

Applicant Table from Section 14.4.2.2.1 of Study Report

Study Day	N	GCS Score	Exposed UVB+A n (%)			Exposed UVA n (%)		
			DAIVOBET/ DOVOBET	Vehicle Gel	Untreated	DAIVOBET/ DOVOBET	Vehicle Gel	Untreated
Day 36	45	0	45 (100.0)	45 (100.0)	44 (97.8)	45 (100.0)	45 (100.0)	45 (100.0)
		1	0	0	1 (2.2)	0	0	0
		2	0	0	0	0	0	0
Day 37	45	0	45 (100.0)	45 (100.0)	45 (100.0)	45 (100.0)	45 (100.0)	45 (100.0)
		1	0	0	0	0	0	0
		2	0	0	0	0	0	0
Day 38	45	0	45 (100.0)	45 (100.0)	45 (100.0)	42 (93.3)	42 (93.3)	43 (95.6)
		1	0	0	0	1 (2.2)	1 (2.2)	0
		2	0	0	0	2 (4.4)	2 (4.4)	2 (4.4)
Day 39	45	0	45 (100.0)	45 (100.0)	45 (100.0)	44 (97.8)	43 (95.6)	43 (95.6)
		1	0	0	0	1 (2.2)	1 (2.2)	1 (2.2)
		2	0	0	0	0	1 (2.2)	1 (2.2)
Day 40	45	0	45 (100.0)	45 (100.0)	45 (100.0)	44 (97.8)	44 (97.8)	44 (97.8)
		1	0	0	0	0	0	0
		2	0	0	0	1 (2.2)	1 (2.2)	1 (2.2)

Conclusions: Under the conditions of the study, no photosensitization reaction was seen for the combination product or its vehicle.

MBL 0302 FR: Repeat insult patch test with DAIVOBET/DOVOBET gel including 21-days cumulative irritation study and sensitisation potential in 200 healthy subjects.

Objective: to determine the skin irritation potential and sensitization potential of DAIVOBET/DOVOBET gel and the gel vehicle after repeated application on the skin of healthy subjects.

Study design: Single center, randomized, double-blinded, vehicle-controlled study with intra-individual comparison of DAIVOBET/DOVOBET gel versus the gel vehicle

Number of healthy volunteers enrolled: 220 subjects enrolled; 211 completed

Study methodology: The study consisted of a 2-week run in period (if required), followed by a 3-week induction phase, 2-week rest phase and a one week challenge phase. A follow-up visit was performed 2 weeks after the subject's last on-treatment visit in the event of an ongoing adverse event.

Fifty mcl of each test product was applied to the skin of the back under occlusive conditions

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Induction phase (Days 1-21)

A total of 15 applications of each test product were performed over 21 days (24 hour applications during the week; 48 hours over the weekends) to two sites on the left side of the back (i.e. one product to each site). Each test site was assessed for irritation potential after 24 hours prior to subsequent application of test product (approximately 30 minutes after patch removal). Assessment for irritation potential was based on the Cumulative Irritancy Index (CII) calculated for each of the two products, based on visual scoring of any skin reaction according to the scale below. For each subject and treatment, the maximum visual scoring during the induction phase and the maximum visual scoring during the challenge phase was recorded.

- 0: No erythema;
- 1: slight erythema with or without edema;
- 2: Moderate erythema with or without edema;
- 3: Severe erythema, edema with or without papules;
- 4: Severe erythema, edema, vesicles or blisters

CII = Sum of clinical scores across readings (Day 2-22) / Number of readings.

A Mean Cumulative Irritancy Index (MCII) was be calculated for each product by averaging individual CII's across subjects. MCII's were used for classifying each product into an irritancy category according to the following scale:

MCII	Product classification
≤0.25	Non-irritant
>0.25 and ≤1	Slightly irritant
>1 and ≤2	Moderately irritant
>2 and ≤3	Very irritant
>3 and ≤4	Extremely severely irritant

Rest phase (Days 22-35)

This was a 2 week period during which no test product was applied.

Challenge phase (Days 36-40)

Test products were applied to two naïve sites on the back and left in place for 48 hours. Test sites were evaluated 24 and 48 hours following removal of the patches. At 48 hours, skin reactions were assessed as negative (0), equivocal (1) or positive (2) for evidence of sensitization. The protocol did not define these reactions, but states: "At the end of the challenge phase (Day 40) the investigator will give his opinion concerning a possible sensitisation reaction of each site taking into account all visual scorings and other reasons on that site (challenge phase vs. induction phase)...The investigator will provide a narrative description of each possible sensitization reaction." (Section 13.3)

For each subject and treatment, the maximum visual scoring during the induction phase and the maximum visual scoring during the challenge phase was listed.

Rechallenge phase (Day 47)

Subjects whose reaction were judged as equivocal for sensitization at the 48 hour time point during the Challenge phase on Day 40 were re-challenged after an approximately one-week rest period under the same conditions as for the challenge.

RESULTS

Of the 220 subjects randomized, 212 subjects completed the study: six subjects withdrew consent for personal reasons, one subject No. 220 was withdrawn because of an adverse event (gastroenteritis), one subject did not meet an inclusion criterion (aged between 18 and 65 years).

During the induction phase, one subject had a score of 4 (severe erythema, oedema, vesicles or blisters) on Day 15 after combination product application and was discontinued. No other subjects had score above 1 (i.e. no erythema or a slight erythema with or without oedema) was reported after application of any study product.

There was no significant difference between the combination product vehicle in the Cumulative Irritancy Index (CII). The mean CII for the combination product was 0.05 whereas it was 0.02 for gel vehicle. Thus, the applicant classified the combination

product and the vehicle as non-irritants. No subject experienced a sensitization reaction for either test product.

Conclusion: Under the conditions of study, the combination product showed no potential for sensitization and repeated applications revealed low potential for irritancy. The product can be classified as a slight irritant. Although the applicant concluded from the study that their product was a “non-irritant”, the mean score would appear to allow a conclusion that the product is a slight irritant, but also that the potential for irritancy is limited. This may be due to what is known about calcipotriene, i.e. that it is a potential irritant. There was no evidence of sensitization for irritation.

MBL 0303 FR: Assessment of the Phototoxicity Potential of Daivobet/Dovobet (Calcipotriol 50mcg/g plus Betamethasone 0.5 mg/g (as Dipropionate)) Gel

Objective: to evaluate the phototoxic potential of DAIVOBET/DOVOBET gel

Study design: Single center, randomized, investigator blinded study with intra-individual comparison of treatments

Number of healthy volunteers enrolled: 34 healthy volunteers were enrolled and 32 were randomized.

Study methodology:

Day 1: MED was determined on Days 1 and 2. Test products (the combination product and its vehicle) were applied under occlusion for 24 hours (50 mcl to each treated test site). The test products were applied on the back.

Day 2: Test chambers were removed after 24 hours, and test areas on the left side of the back were irradiated with (20 J/cm² UVA + 0.75 x MED UVA+UVB). The set of three test areas of the right side served as non-irradiated control. There six test sites on each subject (the back):

- two irradiated sites to which the combination product and its vehicle had been applied
- two non-irradiated sites to which the combination product and its vehicle had been applied
- two untreated sites one of which was irradiated and the other not

Test areas were evaluated 60 min after irradiation, and then 24, 48 and 72 hours after irradiation (Days 3, 4 and 5, respectively). At the end of the study, the investigator assessed the test sites for a possible phototoxic reaction by comparing treated, irradiated sites to the corresponding untreated irradiated, non-irradiated site. Test sites were evaluated using a 5

point scale:

- 0: No erythema;
- 1: Mild but definite erythema with clearly defined border (MED);
- 2: Moderate, clearly defined erythema with or without edema or papules;
- 3: Severe erythema, edema with or without papules;
- 4: Severe erythema, edema with vesicles or bullous reaction at 1, 24, 48 and 72 hours after irradiation.

RESULTS

There was one subject who had a score of grade 3 at an untreated, irradiated test site, and this occurred on the day of irradiation. All other scores for all subjects at all test sites were ≤ 2 and there was no pattern in the distribution of the scores, i.e. no scores correlated with a particular test site. However, most of the grade 2 reactions occurred on the day of irradiation and phototoxicity was not assessed for this timepoint.

Reviewer's conclusions: Under conditions of the study, combination product showed no phototoxicity potential. No phototoxic reactions were observed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The objective of study MBL 0503 INT was to assess the potential for relapse and rebound. Subjects were treated for eight weeks with either the combination product or a marketed scalp solution containing calcipotriene. Subjects were followed for eight weeks post-treatment.

A total of 135 of 145 subjects treated with the combination product and 29 of 32 subjects treated with the scalp solution achieved controlled disease at Week 8 and entered the follow-up period. Two subjects treated with the applicant's product experienced worsening in disease severity relative to baseline in the post-treatment follow-up period, i.e. "rebound." Both had moderate disease at baseline and developed severe disease during the follow-up period (at Week 4 post-treatment for both subjects). There were no other reports of rebound in this study. It is unclear whether these events were related to treatment or a function of the natural history of the disease.

7.1.14 Human Reproduction and Pregnancy Data

Three confirmed pregnancies and one possible pregnancy were reported in the development program in women who were treated with or exposed to the combination product:

MBL0406 4882 IE050 (pivotal)

This 35-year-old subject started study medication on 02-FEB-2005. She had a positive pregnancy test or _____ and the last application of study product and withdrawal

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from the study occurred on that same day (due to the pregnancy). She experienced a spontaneous abortion (considered unrelated to study medication) on _____

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MBL0407 7652 FR133 (long-term safety)

This 29-year-old subject started study medication on 11-MAR-2005. She had a positive pregnancy test on _____ The pregnancy was "estimated" to have occurred on _____, and the last application of study medication was on 11-JUL-2005. The patient experienced a miscarriage (date not provided), which the investigator rated as possibly related to study medication.

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MBL0302 129 FR187 (contact sensitization/cumulative irritancy)

This 30-year-old subject had study medication applied from 13-JUN-2005 to 20-JUL-2005. She had a positive pregnancy test on _____, 2 days after the first day of her last menstrual period). Per the Integrated Summary of Safety, her beta-hCG was 9.868 IU/L on 27-JUL-2005, but it had "decreased" to 605 IU/L by 03-AUG-2005. "It" (? the investigator?) was concluded that there had been no pregnancy. The subject reported previous occurrences of positive pregnancy tests spontaneously resolving.

b(6)

Comment: It that the values for the beta-hCG may have been transposed in the summary.

MBL0302 195 FR187 (contact sensitization/cumulative irritancy)

This was 28-year-old subject had a positive urine pregnancy test at the last visit. Study medication was applied from 13-Jun-2005 to 20-Jul-2005. At the last study visit _____, the urine pregnancy test was positive and her beta-HCG was 60.640 IU/LBeta-hCG. She gave birth to a healthy boy on 25-Feb-2006. No information was provided about the pregnancy itself.

b(6)

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

There have been no reports of overdose.

7.1.17 Postmarketing Experience

The product is not marketed in any country.

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

The number of subjects exposed to the combination product and evaluable for safety in the in the “controlled scalp studies” group it was 1953. The long-term controlled study: MBL 0407 INT included 419 subjects treated with the combination product and evaluable for safety.

The mean duration of exposure was 7.3 weeks for the combination group, 7.1 weeks for the betamethasone group, 7.2 weeks for the calcipotriol group, and 7.2 weeks for the gel vehicle group. A total of 1525 subjects were exposed to the combination product for at least 8 weeks (53 days).

Mean total exposure was 134 g for the combination group, 163 g for the betamethasone group, 149 g for the calcipotriol group, and 176 g for the vehicle group. The mean amount used per week was 18.6 g for the combination group, 22.8 g for betamethasone, 20.7 g for calcipotriol, and 25.7 g for vehicle. Mean total exposure in the long-term study was 471 g for the combination group and 440 g for the calcipotriol group. The mean amounts of combination product and calcipotriol were lower than for the ‘controlled scalp studies’ at 10.6 g per week and 12.8 g per week, respectively.

7.2.1.1 Study type and design/patient enumeration

Table 2: Number of patients exposed in study groupings and individual studies presented in the summary of clinical safety: safety analysis set

Study code	Daivobet® gel (n=2658)		Betamethasone gel (n=1297)		Calcipotriol gel (n=1058)		Gel vehicle (n=213)		Daivonex® scalp solution (n=104)	
	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%
Controlled scalp studies	1953	73.5	1214	93.5	979	92.5	173	81.2	104	100.0
Multiple dose studies	2556	96.2	1297	100.0	1058	100.0	213	100.0	104	100.0
All clinical studies	2658	100.0	1297	100.0	1058	100.0	213	100.0	104	100.0
MBL 0407 INT	419	15.8			431	40.7				
MBL 0404 PR	35	1.3								

Study code	Daivobet® gel (n=2658)		Betamethasone gel (n=1297)		Calcipotriol gel (n=1058)		Gel vehicle (n=213)		Daivonex® scalp solution (n=104)	
	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%
Controlled scalp studies	1953	71.5	1214	93.6	979	92.5	173	81.2	104	100.0
Multiple dose studies	2556	96.2	1297	100.0	1858	100.0	213	100.0	104	100.0
All clinical studies	2658	100.0	1297	100.0	1858	100.0	213	100.0	104	100.0
MBL 9407 INT	419	15.8			431	40.7				
MBL 9404 PR	35	1.3								

7.2.1.2 Demographics

Applicant Table 13: Demographic characteristics for the controlled studies for the 'controlled scalp studies'

Demographic	Daivobet® gel (n=1953)	Betamethasone gel (n=1214)	Calcipotriol gel (n=979)	Gel vehicle (n=173)	Daivonex® scalp solution (n=104)
Age (years)					
Median	49.0	50.0	49.0	56.0	49.0
Mean	48.4	49.8	49.2	49.0	51.1
SD	15.6	16.0	15.7	15.3	15.5
Minimum	17	18	17	18	24
Maximum	92	91	91	97	85
Number	1953	1214	979	173	104
Age group (Number %)					
<= 35 years	449 23.0	289 23.8	212 21.7	40 23.1	19 18.3
36 to 50 years	681 30.8	335 27.6	299 30.5	49 28.3	35 34.6
51 to 64 years	569 29.1	363 29.9	280 28.6	60 34.7	28 26.9
>= 65 years	334 17.1	227 18.7	188 19.2	24 13.9	21 20.2
Total	1953 100.0	1214 100.0	979 100.0	173 100.0	104 100.0
>= 75 years	24 4.3	51 4.2	50 5.1	9 5.2	7 6.7
Sex (Number %)					
Male	894 45.8	537 44.2	444 45.4	97 50.3	44 42.3
Female	1059 54.2	677 55.8	535 54.6	86 49.7	60 57.7
Total	1953 100.0	1214 100.0	979 100.0	173 100.0	104 100.0
Race (Number %)					
Caucasian/White	1823 93.3	1176 96.9	948 96.6	143 82.7	103 99.0
African-American/Black	67 3.4	5 0.4	5 0.5	19 11.0	0 0.0
Oriental/Asian	31 1.6	19 1.6	21 2.1	3 1.7	0 0.0
Other	32 1.6	14 1.2	5 0.5	8 4.6	1 1.0
Total	1953 100.0	1214 100.0	979 100.0	173 100.0	104 100.0

Mean duration of psoriasis was 16.0 years for the combination group, 16.8 years for the betamethasone group, 16.8 years for the calcipotriol group, and 15.3 years for the vehicle group. Baseline investigator's global assessment of disease severity at baseline showed a similar distribution across the treatment groups. 'Mild' disease was reported for 0.0% to 6.8% of subjects across the treatment groups, 'Moderate' disease was reported for 54.5% to 61.5%, 'Severe' disease for 31.1% to 35.0% and 'Very severe' disease for 4.6% to 6.7% patients. d.

The investigator's assessment of extent of scalp psoriasis showed a similar distribution across the treatment groups. p. 49 iss:

Applicant Table 14: Baseline characteristics for the "controlled scalp studies"

Characteristic	Daivobet® gel (n=1953)	Betamethasone gel (n=1214)	Calcipotriol gel (n=979)	Gel vehicle (n=173)	Daivonex® scalp solution (n=104)					
Duration of Psoriasis¹ (years)										
Median	12.0	13.0	14.0	11.0	14.0					
Mean	15.0	15.0	15.0	15.3	19.0					
SD	13.3	13.6	13.5	12.6	15.7					
Minimum	0	0	0	1	1					
Maximum	66	71	72	60	70					
Number	1945	1104	979	173	104					
Investigator's global assessment of disease severity (Number %)										
Mild	117	6.0	83	6.8	50	5.1	10	5.9	0	0.0
Moderate	1117	57.2	666	54.9	534	54.5	97	55.1	64	61.5
Severe	607	31.1	406	33.4	343	35.0	50	33.5	33	31.7
Very severe	112	5.7	59	4.9	52	5.3	8	4.6	7	6.7
Total	1953	100.0	1214	100.0	979	100.0	173	100.0	104	100.0
Investigator's assessment of extent of scalp psoriasis (Number %)										
No involvement	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<10%	0	0.0	3	0.2	0	0.0	0	0.0	0	0.0
10-29%	757	38.8	400	32.9	352	36.0	67	38.7	45	43.3
30-49%	474	24.3	314	25.9	265	27.1	45	26.6	19	18.3
50-69%	291	14.8	190	15.7	145	14.9	24	13.9	14	13.5
70-89%	243	12.4	172	14.2	115	11.7	19	11.0	12	11.5
90-100%	189	9.6	135	11.1	101	10.3	17	9.8	14	13.5
Total	1953	100.0	1214	100.0	979	100.0	173	100.0	104	100.0

1) Excludes MEL 0401 INT where duration of psoriasis was not recorded.

Baseline demographic characteristics are summarized for the long-term study below:

Applicant Table 15 Demographic characteristics for the long-term controlled study

	All patients (safety) (n=850)		Daivobet® gel (n=419)		Calcipotriol gel (n=431)	
Age (years)						
Mean	48.7		48.5		49.0	
SD	15.0		15.3		14.7	
Median	48.0		48.0		48.0	
Minimum	18		18		19	
Maximum	86		86		84	
Number	850		419		431	
Sex (Number %)						
Male	374	44.0	185	44.2	189	43.9
Female	476	56.0	234	55.8	242	56.1
Total	850	100.0	419	100.0	431	100.0
Race (Number %)						
Caucasian/White	822	96.7	404	96.4	418	97.0
African- American /Black	4	0.5	3	0.7	1	0.2
Oriental/Asian	20	2.4	10	2.4	10	2.3
Other	4	0.5	2	0.5	2	0.5
Total	850	100.0	419	100.0	431	100.0

Source: MEL 0407 IMP Clinical Study Report, Table 4, Table 5, Table 6

In the long-term study, mean duration of psoriasis was 17.7 years for the combination group and 17.4 years for the calcipotriol group. The investigator's global assessment of disease severity at baseline showed a similar distribution across the treatment groups. 'Moderate' disease was reported for 55.6% and 55.5% of patients in the combination and calcipotriol groups,

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respectively, 'Severe' disease was reported for 37.7% and 37.8%, and 'Very severe' disease for 6.7% in both groups. The investigator's assessment of extent of scalp psoriasis showed a similar distribution across the two treatment groups.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

See section 7.1.12 for discussion of special safety studies.

7.2.2.2 Postmarketing experience

The product is not marketed.

7.2.2.3 Literature

The applicant included reference articles in the submission. The applicant indicated in the Safety Update that they perform weekly literature searches for Taclonex ointment in the Medline and Embase databases.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the new product under the proposed dosing regimen to permit characterization of its safety for the intended use of once daily for up to eight weeks. The designs of the Phase 3 studies were generally adequate to assess the safety of the product for its intended use, although the assessment of calcium metabolism was conducted only through Week 4. Topical safety was adequately evaluated in the development program and included assessment for local adverse events and formal dermal safety studies. The numbers of subjects in each dermal safety study were in line with those recommended. Systemic safety was adequately evaluated in the development program and included the collection of systemic adverse event data, monitoring of albumin-corrected calcium and urinary calcium, and assessment of HPA axis function. Sufficient numbers of subjects were exposed to the product for the requisite time periods as recommended in the ICH E1A guideline.

There is also a body of information available for the marketed combination ointment that contains the same active ingredients at the same concentrations as the new product. Additionally, there is a body of information available for the active ingredients marketed individually. The development program did not raise any new safety concerns.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Per the Nonclinical Overview, the approach to testing strategy for the new combination product was essentially based on that employed to support the marketing application for the applicant's approved product, Taclonex® ointment. This was because both products contain the same active ingredients at the same concentrations, the same treatment frequency (although different durations) and dose and the same indication though different treatment areas. The applicant performed the following studies with the new combination product to bridge to the existing safety database for Taclonex® ointment and individual drug substances:

- Mass balance and excretion studies following dermal administration to rats and minipigs to investigate potential absorption differences from the new formulation compared with Taclonex® ointment.
- A 4-week local dermal tolerance study in rabbits in order to assess any irritant potential of the gel vehicle
- An acute eye irritation study in rabbits.

Comment: The applicant states in Section 9.2 of the protocol for the pivotal study MBL 0405 INT, "It can be concluded that a single application of (the new formulation) to the rabbit eye

caused only a transient and fully reversible ocular irritation in the form of ptosis and slight pink discoloration of the orbital ring. No other changes of the conjunctiva, cornea or iris were seen in any of the rabbits. Consequently, an unintentional exposure of the human eye to (the new formulation) would not be expected to produce any serious adverse effects." Regarding nonclinical studies, the pharmacology/ toxicology reviewer concluded that, "Taclonex scalp gel was essentially non-irritating to the skin or eyes."

The pharmacology/ toxicology reviewer concluded that, "The clinical formulation of the drug product and the individual components of the product have been adequately evaluated for safety and the database supports the safety of the proposed use of the product."

Adequacy of Routine Clinical Testing

See Section 7.2.3.

7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

The following information regarding the active ingredients is from the Taclonex ointment package insert.

b(4)

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

“(O)nce 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.”

7.2.6 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 adverse events that are associated the drug classes of each active ingredient were adequate in the development program, as pertains to local tolerance, collection of adverse event data, and the potential for systemic effects (calcium metabolism and/or the HPA axis).

7.2.7 Assessment of Quality and Completeness of Data

See Sections 7.2.3 and 7.2.7.

7.2.8 Additional Submissions, Including Safety Update

The 120-day Safety Update was submitted on October 22, 2007. The submission included the 52-week safety data from study MBL 0502 US. The first eight weeks were double-blind, and subjects applied either the combination product or its vehicle to the scalp. All subjects applied the approved combination ointment) Taclonex to the body. Data from this portion of the study were submitted in the original NDA (and combined in the “controlled scalp studies”). Weeks 9 through 52 were open-label, and data from this phase of the study was provided in the Safety Update. Follow-up visits were every four weeks during the open-label phase. Safety monitoring included evaluation of serum calcium, albumin and glucose at Weeks 12, 24, 40 and end of study. Fasting glucose levels were obtained at baseline, Week 24 and end of study.

A total of 128 subjects were exposed to the combination scalp product for up to 52 weeks. An additional 38 subjects were exposed for up to 44 weeks. All of these subjects were also using Taclonex ointment. The mean weekly amount of the combination scalp product used was 12.7g with a range of 0.3 to 36.2g for the full 52-week period. The mean weekly amount of Taclonex ointment used was 25.4g with a range of 0.3 to 84.3g over the full 52-week period

No additional deaths occurred in Weeks 9 through 52. One additional serious adverse event was reported: hysterectomy in a 40 y/o (MBL0502 4613 US039). There were 3 subjects discontinued for adverse events:

- osteoarthritis (58 y/o male; MBL0502 4512 US038)
- psoriasis (i.e. flare of ; 28y/o male; MBL0502 5300 US046)
- hypertension, headache (54-y/o female; MBL0502 6001 US053). This subject had a history of hypertension and was on 3 anti-hypertensives prior to the study.

There were no clinically significant changes in albumin-corrected serum calcium. There was no clinically relevant change in mean diastolic or systolic blood pressure during the study. There are no other ongoing clinical studies with the product. The Safety Update did not raise any new safety concerns.

Table 28: Change in albumin-corrected serum calcium from baseline with respect to reference range: safety analysis set.

Visit	Baseline category ¹	Daivobet [®] gel (n=128)			Gel vehicle (n=38)		
		Low	Normal	High	Low	Normal	High
Visit 2	Baseline low	0	3	0	0	0	0
	Baseline normal	3	107	0	0	33	0
Visit 3	Baseline low	0	2	0	0	0	0
	Baseline normal	1	107	1	1	33	0
End of double-blind phase	Baseline low	0	3	0	0	0	0
	Baseline normal	1	119	1	0	36	0
Visit 6	Baseline low	1	1	0	0	0	0
	Baseline normal	2	103	0	0	27	0
Visit 9	Baseline low	0	2	0	0	0	0
	Baseline normal	1	93	0	0	25	0
Visit 13	Baseline low	0	2	0	0	0	0
	Baseline normal	2	78	1	0	23	0
End of trial	Baseline low	0	3	0	0	0	0
	Baseline normal	1	120	0	0	36	0

1) Number of patients with albumin-corrected serum calcium below, within or above the reference range.
 2) Albumin-corrected calcium at visit 2, visit 3, end of double-blind phase, visit 6, visit 9, visit 13, or end of trial as appropriate.

There were no changes in albumin-corrected serum calcium of clinical significance. There was no clinically relevant change in mean diastolic or systolic blood pressure during the study.

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Table 34: Adverse drug reactions to the gel during the complete study period by MedDRA primary System Organ Class and preferred term by ethnicity: Daivobet® gel safety analysis set

System Organ Class ¹ Preferred Term	Daivobet® gel ³ (n=161)	
	HISPANIC OR LATINO (n=89)	NOT HISPANIC OR LATINO (n=72)
Gastrointestinal disorders		
Constipation	0	1
General disorders and administration site conditions		
Tenderness	1	0
Immune system disorders		
Seasonal allergy	1	0
Infections and infestations		
Body tinea	0	1
Folliculitis	1	0
Tinea capitis	0	1
Nervous system disorders		
Dizziness	0	1
Dysgeusia	0	1
Headache	1	2
Hyperaesthesia	1	0
Hypoaesthesia	1	0
Paraesthesia	1	2

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Respiratory, thoracic and mediastinal disorders		
Cough	0	1
Skin and subcutaneous tissue disorders		
Acne	0	1
Alopecia	1	1
Dry skin	0	1
Exanthem	0	1
Hyperhidrosis	0	1
Pruritus	2	1
Psoriasis	1	0
Rash	0	1
Skin irritation	2	0
Skin striae	1	0
Vascular disorders		
Hot flush	0	1
Hypertension	0	1
Total number of adverse events²	14	19
1) Classification according to MedDRA 6.1. 2) Different adverse events within the same preferred term and involving the same patient have been counted as one. A single patient could appear in multiple classes. 3) Adverse events in vehicle group not ongoing at the end of double-blind phase and patients of the vehicle group without safety data after double-blind phase were excluded		

There were no pregnancies or reports of overdose in this study. The safety profile was similar to that of other studies.

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Table 35: Adverse drug reactions to the gel during the complete study period by MedDRA primary System Organ Class and preferred term by race: Daivobet® gel safety analysis set

System Organ Class ¹ Preferred Term	Daivobet® gel ¹ n= (161)		
	BLACK OR AFRICAN AMERICAN (n=72)	OTHER (n=24)	WHITE (n=65)
Gastrointestinal disorders			
Constipation	1	0	0
General disorders and administration site conditions			
Tenderness	0	0	1
Immune system disorders			
Seasonal allergy	0	1	0
Infections and infestations			
Body tinea	1	0	0
Folliculitis	0	1	0
Tinea capitis	1	0	0
Nervous system disorders			
Dizziness	1	0	0
Dysgeusia	1	0	0
Headache	2	0	1
Hyperaesthesia	0	1	0
Hypoaesthesia	0	0	1
Paraesthesia	2	0	1
Respiratory, thoracic and mediastinal disorders			
Cough	1	0	0
Skin and subcutaneous tissue disorders			
Acne	1	0	0
Alopecia	1	0	1
Dry skin	1	0	0
Exanthem	1	0	0
Hyperhidrosis	1	0	0
Pruritus	1	1	1
Psoriasis	0	0	1
Rash	1	0	0
Skin irritation	0	2	0
Skin striae	0	0	1

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Vascular disorders			
Hot flush	1	0	0
Hypertension	1	0	0
<hr/>			
Total number of adverse events ¹	19	6	8
<hr/>			
1) Classification according to MedDRA 6.1. 2) Different adverse events within the same preferred term and involving the same patient have been counted as one. A single patient could appear in multiple classes. 3) Adverse events in vehicle group not ongoing at the end of double-blind phase and patients of the vehicle group without safety data after double-blind phase were excluded			

The last Periodic Safety Update Report for Taclonex covers the one-year period from 1 April 2006 to 31 March 2007. The Safety Update covered 1 April 2007 to 31 August 2007. A total of 49 non-serious case reports of 76 adverse drug reactions were received in this period (26 were from consumers without medical confirmation). The majority of non-serious reactions (55) were classified as Skin and subcutaneous tissue disorders (primarily psoriasis) and General disorders and administration site conditions (primarily drug ineffective). The rest of the reactions were very heterogeneous in nature ranging over more than 10 system/organ classifications.

Events which reflected possible systemic effects of calcipotriol or corticosteroids, all of which were reported as non-serious were (one report each):

- hypercalcemia
- increased blood glucose
- inadequate control of diabetes mellitus
- constipation in association with abdominal distension, flatulence and pruritus

In the period since the lock date of the NDA and the cut-off date of 1 September 2007, the applicant states that there have been no relevant case reports in the literature (Medline and Embase databases). One study has been published.

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

The adverse event profile of each active ingredient is well-established. An important issue is whether the actives in combination impact the occurrence of known adverse events of each of the actives. 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.

“Adverse drug reactions” were those adverse events for which the investigator had not excluded a causal relationship to study product. The most frequently reported adverse

drug reaction in the controlled studies in subjects treated with the combination product was pruritus. Treatment-related pruritus was reported for 1.8% of subjects in the combination group, 1.7% in the betamethasone group, 7.4% in the calcipotriol group, and 4.0% in the vehicle group. All other adverse drug reactions in the combination group occurred in $\leq 0.5\%$ of subjects.

In the reviewer's opinion, 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. Irritation has been reported in clinical trials conducted with marketed calcipotriene-containing products (as described in the package inserts).

For unclear reasons, the applicant assessed calcium metabolism at Week 4 in the pivotal studies, and such would not support the safety of the proposed eight-week treatment course. However, the applicant also assessed parameters of calcium metabolism in the 52-week study conducted to address ICH E5.

Assessment of HPA axis revealed evidence of adrenal suppression in several subjects at the end of treatment. However, it should be noted that the test results reflect use of both the new product to scalp lesions and the approved combination product to body lesions (the approved product which contains the same active ingredients in the same concentrations). Thus, subjects in this study were exposed to two corticosteroid-containing products in this study, rather than only the new product. For subjects who had follow-up testing, recovery of adrenal function was observed, consistent with what is known about recovery following withdrawal of the topical corticosteroid.

The findings are consistent with what is known about the active ingredients. No new safety concerns were raised in the development program. The applicant had adequately demonstrated that under the proposed conditions of use, their combination product is safe in the treatment of moderate to severe psoriasis of the scalp.

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

Data were pooled from studies (or phases from certain studies) when dosing was the same, i.e. once daily for up to eight weeks. Some of the pooled data also included subjects who were also being treated with Taclonex ointment.

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

The average weekly dose of combination product in the controlled scalp studies was 18.6 gm. The incidence of adverse events in subjects receiving ≥ 40 g of combination product per week was compared to that of subjects receiving < 40 g per week and was found to be similar: 35.4% and 31.6%, respectively. The greatest difference was seen for influenza, reported for 1.0% of subjects who received < 40 g per week of the combination product compared with 3.1% subjects who received ≥ 40 g per week. Acne was also reported at a lower incidence in subjects who received < 40 g per week (0.1%) compared with 1.6% of subjects who received gel ≥ 40 g per week.

7.4.2.2 Explorations for time dependency for adverse findings

Clinical evaluations were generally timed to permit interval clinical assessments and comparison of end-of-treatment results to baseline results. Laboratory testing for systemic effects was not always timed to reflect exposure to that proposed for the marketplace, i.e. once daily for up to 8 weeks.

7.4.2.3 Explorations for drug-demographic interactions

The incidence of subjects with at least one adverse event and at least one lesional/perilesional adverse event on the scalp was evaluated by the following intrinsic factors for the controlled scalp studies and the long-term controlled study:

- Age: up to 35, 36-50, 51-64, and 65 years or older
- Sex: male and female
- Race/ethnicity: Caucasian/White, African-American/Black, Oriental/Asian, and other
- Baseline disease severity: mild, moderate, severe, and very severe according to the investigator's global assessment of disease severity.

Age

The incidence of subjects experiencing at least one adverse event in the combination group was similar for all age groups, ranging between 33.2% for subjects 51-64 years and 36.3% for patients aged ≤ 35 years. The profiles of adverse events in the combination group were similar across the age subgroups. The incidence of subjects experiencing at least one lesional/perilesional adverse event on the scalp in the combination group, was similar for all age groups: 4.9% for those aged ≤ 35 years, 4.8% for those aged 36-50 years, 5.4% for those aged 51-64 years and 5.7% for those aged ≥ 65 years. The profiles of lesional/perilesional adverse events on the scalp in the combination group were generally similar across the age subgroups.

In the long-term controlled study, there was no pattern to suggest a different response across the age subgroups compared. The profiles of common adverse events were similar across the subgroups. The incidences of patients with at least one lesional/perilesional adverse event on the scalp in the combination group ranged from 9.1% for patients aged ≤ 5 years to 17.1% for those aged 51-64 years. In the calcipotriol group, the incidence ranged from 20.0% for subjects aged 36-50 years to 26.7% for those aged ≥ 65 years.

Sex

In the combination group, 29.1% of males experienced at least one adverse event compared to 39.1% of females. The incidence of adverse events was higher in females than males in all treatment groups (from 4.6 to 10.7% higher), except in the Daivonex® scalp solution group where the incidence of adverse events was 11.9% higher for males than females. The profiles of adverse events were similar across the subgroups.

In the combination group 4.0% of males experienced at least one lesional/perilesional adverse event on the scalp compared with 6.1% of females. The profiles of lesional/perilesional adverse events on the scalp were similar across the subgroups.

In the long-term controlled study, the following incidences of subjects with at least one lesional/perilesional adverse event on the scalp were reported in the combination group: 9.2% for males and 14.1% for females compared with 18.0% for males and 24.4% for females in the calcipotriol group. Pruritus appeared to be reported at a higher incidence in females than males for both treatments; 5.6% and 12.4% for females in the combination group and calcipotriol vehicle groups, respectively, compared with 2.7% and 6.9%, respectively, for males.

Race/ethnicity

The majority of subjects in the “controlled scalp studies” were Caucasian/White. There was no indication of an increased incidence of subjects experiencing at least one adverse event in any of the racial subgroups. In the combination group, the incidence of subjects experiencing at least one adverse event ranged between 32.3% for Oriental/Asian patients and 43.8% for the ‘other race’ subgroup (ie, not Caucasian/White, African-American/Black or Oriental/Asian). The profiles of adverse events were similar across the subgroups.

There was no indication of an increased incidence of subjects experiencing at least one lesional/perilesional adverse event on the scalp in any of the racial subgroups. In the combination group, the incidence of subjects experiencing at least one lesional/perilesional adverse event on the scalp ranged between 0% for Oriental/Asian subjects and 7.5% for the African-American/Black subgroup. The profiles of adverse events were similar across the subgroups. It was noted that two African-American/Black subjects had folliculitis (3.0%) in the combination group, the corresponding numbers for Caucasian/White subjects was 6 (0.3%). This difference is considered to be due to the differences in sample size. In the long-term study, Due to the small sample size only two groups were considered, i.e. Caucasian/White and non-Caucasian. Examination of the incidence of subjects reporting at least one adverse event indicated no pattern to suggest a

different response across the subgroups compared. The profiles of common adverse events were similar across the subgroups. The majority of subjects were Caucasian/White in both groups. The following incidences of subjects with at least one adverse event were reported in the combination group: 67.8% for Caucasians/Whites and 40.0% for non-Caucasians compared with 71.3% for Caucasians/Whites and 92.3% non-Caucasians in the calcipotriol group, however, there were few non-Caucasian subjects. The following incidences of subjects with at least one lesional/perilesional adverse event on the scalp were reported in the combination group: 12.4% for Caucasians/Whites and 0% (0/15) for non-Caucasians compared with 21.3% for Caucasians/Whites and 30.8% (4/13) for non-Caucasians in the calcipotriol group, however, there were few non-Caucasian subjects.

7.4.2.4 Explorations for drug-disease interactions

The applicant assessed drug-disease interactions by baseline disease severity. There was no apparent effect of baseline disease severity on the incidence of subjects experiencing at least one adverse event. The incidence of lesional/perilesional events by baseline disease severity was 12.8% for patients with mild disease at baseline, 4.7% for moderate, 5.3% for severe and 1.8% for those with very severe, and the profiles of adverse events were similar across the subgroups.

7.4.2.5 Explorations for drug-drug interactions

Formal drug-drug interaction studies were not done.

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

See Section 5.3.

8.2 Drug-Drug Interactions

Formal drug-drug interaction studies were not done.

8.3 Special Populations

The product has not been adequately studied in subjects with renal or hepatic insufficiency. Pregnant and nursing women were excluded from study. There were no particular concerns identified pertaining to the geriatric age group.

8.4 Pediatrics

The applicant's plans for pediatric development were discussed at the End-of-Phase 2 meeting (December 1, 2004). The applicant proposed conducting a Phase 4 study evaluating the safety and efficacy of their product in adolescents (12 to 17 years) with scalp psoriasis. The study would include HPA axis testing. The applicant also indicated that they planned to submit a partial pediatric waiver for children up to 12 years of age. The Agency stated, "This appears to be a reasonable approach."

In the marketing application, the applicant requested a deferral for the above study of adolescents. The rationale for the request for deferral is: Adult studies are completed and ready for approval). They plan to submit a protocol _____

Additionally, the applicant requests a partial waiver in newborn infants, infants and toddlers, and children (children below the age of 12 years). The applicant believes it would be inappropriate to use their product in patients younger than 12 years because of the potent corticosteroid contained in the product. Thus, the request for a partial waiver is based

on the rationale that the product is not considered a safe treatment in this age group.

8.5 Advisory Committee Meeting

There was no Advisory Committee Meeting.

8.6 Literature Review

See Section 7.2.2.3

8.7 Postmarketing Risk Management Plan

The applicant will monitor for clinical signs, symptoms or complications of HPA axis suppression and clinical signs, symptoms or complications of hypercalcemia. The results of the regular monitoring will be submitted in each new Periodic Safety Update Report.

Whenever a signal is detected and confirmed this will be communicated to the Competent Authorities.

8.8 Other Relevant Materials

None

9 Overall Assessment

9.1 Conclusions

The applicant conducted two adequate and well-controlled pivotal trials. Efficacy of the combination product was adequately demonstrated in both pivotal trials. The combination product was superior to all comparators in each study for the proportion of subjects with "Controlled Disease" at Week 8, as assessed on a static global severity scale. ("Controlled Disease" was defined as subjects with "absence of disease" or "very mild disease" at efficacy assessment.) The degree of superiority was statistically significant for all comparisons in both pivotal trials.

Both pivotal trials were appropriately designed to allow for demonstration of the contribution to efficacy for each of the active ingredients in the fixed combination product. Each active ingredient was adequately shown to contribute to efficacy, and thus 21 CFR 300.50 was adequately addressed. The combination product was superior to each monad and to vehicle in MBL 0405 INT, and the combination product was superior to each active comparator in MBL 0406 INT.

Supportive evidence of efficacy was provided from four additional trials which included once daily treatment for 8 weeks under controlled conditions (i.e. the 8-week period included a control of some sort, active or vehicle): MBL 0502 US, MBL 0503 INT, MBL 0401 INT, and MBL 0407 INT. The combination product was superior to comparator in each of the supportive studies.

When baseline disease was considered, superiority over all comparators in the proportion of subjects who achieved "absence" or "very mild disease", (i.e. "Controlled disease") was demonstrated in both studies only for "moderate" to "severe" baseline. The combination product was not superior to betamethasone in study 0405 for subjects with "mild" or "very severe" baseline disease, and thus the contribution of calcipotriene to efficacy was not demonstrated for subjects in these two categories.

In both pivotal studies, the percentage of subjects with controlled disease by Week 2 was highest in subjects treated with the combination product.

An adequate number of subjects were exposed to the new product under the proposed dosing regimen to permit characterization of its safety for the intended use of once daily for up to eight week. The designs of the Phase 3 studies were generally adequate to assess the safety of the product for its intended use. Topical safety was adequately evaluated in the development program and included assessment for local adverse events and formal dermal safety studies. The numbers of subjects in each dermal safety study were in line with those recommended. Systemic safety was adequately evaluated in the development program and included the collection of systemic adverse event data, monitoring of albumin-corrected calcium and assessment of HPA axis function.

Sufficient numbers of subjects were exposed to the product for the requisite time periods as recommended in the ICH E1A guideline.

The adverse event profile of each active ingredient is well-established. An important issue is whether the actives in combination impact the occurrence of known adverse events of each of the actives. 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.

“Adverse drug reactions” were those adverse events for which the investigator had not excluded a causal relationship to study product. The most frequently reported adverse drug reaction in the controlled studies in subjects treated with the combination product was pruritus. Treatment-related pruritus was reported for 1.8% of subjects in the combination group, 1.7% in the betamethasone group, 7.4% in the calcipotriol group, and 4.0% in the vehicle group. All other adverse drug reactions in the combination group occurred in $\leq 0.5\%$ of subjects.

In the reviewer’s opinion, 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. Irritation has been reported in clinical trials conducted with marketed calcipotriene-containing products (as described in the package inserts).

For unclear reasons, the applicant assessed calcium metabolism at Week 4 in the pivotal studies, and such would not support the safety of the proposed eight-week treatment course. However, the applicant also assessed parameters of calcium metabolism in the 52-week study conducted to address ICH E5.

Assessment of HPA axis revealed evidence of adrenal suppression in several subjects at the end of treatment. However, it should be noted that the test results reflect use of both the new product to scalp lesions and the approved combination product to body lesions (the approved product which contains the same active ingredients in the same concentrations). Thus, subjects in this study were exposed to two corticosteroid-containing products in this study, rather than only the new product. For subjects who had follow-up testing, recovery of adrenal function was observed, consistent with what is known about recovery following withdrawal of the topical corticosteroid.

The findings are consistent with what is known about the active ingredients. No new safety concerns were raised in the development program. The applicant has adequately demonstrated that under the proposed conditions of use, their combination product is safe in the treatment of moderate to severe psoriasis of the scalp. There is also a body of information available for the marketed combination ointment that contains the same active ingredients at the same concentrations as the new product. Additionally, there is a body of information available for the active ingredients marketed individually. The development program did not raise any new safety concerns.

The applicant has adequately demonstrated that their product is safe and effective for the treatment of moderate to severe psoriasis of the scalp in subjects 18 years and older under the proposed conditions of use of once daily for up to eight weeks.

9.2 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that the application be approved.

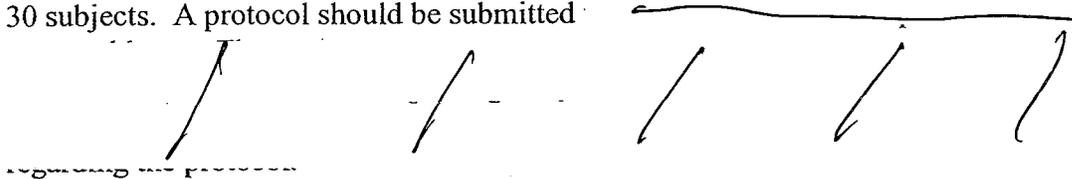
9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no recommendations for a specific post-marketing risk management plan.

9.3.2 Required Phase 4 Commitments

The applicant should conduct a study in pediatric patients with scalp psoriasis, ages 12 to 17 years. Enrollment should be sufficient to allow for 100 evaluable subjects. The sponsor should evaluate the effect of their product on calcium metabolism in all subjects and the effects of their product on the hypothalamic-pituitary-adrenal axis in a subset of 30 subjects. A protocol should be submitted



b(4)

The applicant should evaluate the carcinogenicity of calcipotriene in a two-year oral study in rats. The applicant 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 22-185.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

See Appendix 10.2.

9.5 Comments to Applicant

There were no clinical comments for the applicant.

23 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

REFERENCES

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/s/

Brenda Carr
4/17/2008 11:21:33 AM
MEDICAL OFFICER

Jill Lindstrom
4/23/2008 12:47:31 PM
MEDICAL OFFICER

Stanka Kukich
4/23/2008 01:37:52 PM
MEDICAL OFFICER

DDDP CLINICAL FILING CHECKLIST FOR NDA 22-185

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	x			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5. Are all documents submitted in English, or are English translations provided when necessary?	x			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	x			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56 ¹ and 201.57, current divisional and Center policies, and the design of the development package?	x			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9. Has the applicant submitted the integrated summary of safety (ISS)?	x			
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11. Has the applicant submitted a benefit-risk analysis for the product?	x			
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(1)			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: MBL 0201FR Study Title: "A DOSE FINDING PLAQUE TEST OF CALCIPOTRIOL/BETAMETHASONE DIPROPIONATE GEL IN PSORIASIS VULGARIS" Sample Size: 22 Arms: 1. Calcipotriol / betamethasone dipropionate gel (6 concentrations) 2. Gel vehicle 3. Daivobet® ointment	x			not done with the to-be-marketed formulation
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1: MBL 04505 INT	x			

¹ http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

Pivotal Study #2: MBL 04506 INT	Indication: scalp psoriasis				
	Indication: scalp psoriasis				
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x				
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x				"Controlled disease"= absence of or very mild disease
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x				most clinical data is from EU and Canada
SAFETY					
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x				
19. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	x				
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	x				from development program; product not marketed
OTHER STUDIES					
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	x				
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (e.g., labeling comprehension)?					NA
PEDIATRIC USE					
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x				deferral for 12-17 yrs; waiver for < 12 yrs
ABUSE LIABILITY					
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?					NA
FOREIGN STUDIES					
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x				
DATASETS					
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?					
27. Has the applicant submitted datasets in the the format agreed to previously by the Division?					
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?					
29. Are all datasets to support the critical safety analyses available and complete?					
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?					
CASE REPORT FORMS					

31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	x			
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	x			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Brenda Carr, M.D.

Reviewing Medical Officer

Clinical Team Leader

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this page is the manifestation of the electronic signature.**

/s/

Brenda Carr
8/15/2007 01:36:18 PM
MEDICAL OFFICER

Jill Lindstrom
8/15/2007 05:49:51 PM
MEDICAL OFFICER