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APPLICATION NUMBER:

21-852

MEDICAL REVIEW(S)

CLINICAL REVIEW NDA 21-852

Application Type	505(b)(1)
Submission Number	000
Submission Code	N
Letter Date	March 9, 2005
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Reviewer Name	Brenda Carr, M.D.
Review Completion Date	January 4, 2006
Established Name	calcipotriene hydrate and betamethasone dipropionate
(Proposed) Trade Name	Dovobet® Ointment
Therapeutic Class	vitamin D analog and corticosteroid
Applicant	LEO Pharmaceutical Products Ltd. A/S
Priority Designation	S
Formulation	ointment
Dosing Regimen	once daily for four weeks
Indication	topical treatment of psoriasis vulgaris in adults aged 18 years and above
Intended Population	adults aged 18 years and above

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The applicant submitted a marketing application for a new fixed combination product containing the two active ingredients calcipotriene hydrate (a vitamin D analog) and betamethasone dipropionate (a corticosteroid) for the proposed indication of treatment of psoriasis vulgaris in adults aged 18 years and above. Both active ingredients have been approved individually for marketing in the United States, and the applicant's combination product is currently marketed in Europe, Canada, Asia, and South America. The applicant conducted one adequate and well-controlled pivotal trial, and the study was of appropriate design to demonstrate the contribution of each component to efficacy so as to comply with the combination policy, as put forth in 21 CFR 300.50. Specifically, the combination product was compared to each monad in the product vehicle (the product was also compared to vehicle itself). Additional efficacy data was submitted from trials which supported overseas marketing. The reviewer considers the applicant to have submitted adequate evidence of effectiveness of the combination product for treatment of psoriasis vulgaris.

From a clinical perspective, it is recommended that the application is approvable for the once daily topical treatment of psoriasis vulgaris in adults aged 18 years and above. The approvable recommendation is based on the applicant's proposal to market of the product in [redacted] tube sizes when 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 recommended, as it would make product available to patients in amounts that, if used, would put them at increased risk for side effects. Therefore, it is recommended that tube sizes not exceed 100 gm.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

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.

The submission detailed the applicant's proposed approach to the classification and reporting of adverse drug reactions and medication errors. The applicant also committed to weekly searches of the world literature using relevant terms derived from MEDLINE and Excerpta Medica.

1.2.2 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).

1.2.3 Other Phase 4 Requests

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

1. 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.
2. 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
3. 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
4. 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

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The applicant conducted one adequate and well-controlled pivotal trial, MCB 0003 INT, in which their fixed combination product was evaluated in the once daily treatment of psoriasis vulgaris. The treatment arms were: the combination product, calcipotriene hydrate, betamethasone dipropionate, and vehicle. Treatment duration was four weeks. The trial was conducted at multiple centers in Europe and Canada, and a total of 1605 subjects were enrolled in the study. Primary efficacy was assessed on a static Investigator's Global Severity scale (the endpoint recommended by the Division) and by the percent change on the Psoriasis Area Severity Index (PASI; the endpoint chosen by the applicant). Primary efficacy on the global

severity scale was assessed by the proportion of subjects classified as having "Controlled Disease" at the end of treatment. "Controlled disease was defined as "Absence of Disease" or "Very Mild Disease." The combination was superior to each monad and to vehicle as assessed by the Investigator's Global Severity scale and by the percent change in PASI.

Also, in support of efficacy, the applicant submitted data from four additional studies that included treatment arms in which 1,058 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 percent change in PASI. The PASI results from these additional studies were consistent with those from the pivotal study. One of the trials also included an assessment by a static investigator's global assessment.

The primary safety database that supports the once daily dosing of the product for four weeks included 2,448 subjects. Of the 2,448 subjects, 1,539 received once daily treatment, and 909 received twice daily treatment.

1.3.2 Efficacy

A total of 1605 subjects were enrolled in the pivotal study, MCB 0003 INT. Of the 1605 enrolled, 1603 subjects were randomized to treatment. All 1603 of those subjects received study medication, and they constitute the intent-to-treat population. Efficacy of the combination product was adequately demonstrated in study MCB 0003 INT. The combination product was superior to each monad and to vehicle in both primary analyses:

Statistical Reviewer's Table 1. Efficacy Results for Percent with Controlled Disease (ITT)

	Combination	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	276 (56.3%)	176 (37.0%)	107 (22.3%)	16 (10.2%)
p-value		$p < .0001$	$p < .0001$	$p < .0001$
p-value		$p < .0001$	$p < .0001$	$p < .0001$

Statistical Reviewer's Table 2. Efficacy Results for Percent Reduction in PASI: Study MCB-0003-INT.

	Combination QD	Betamethasone QD	Calcipotriol QD	Vehicle QD
N	490	476	480	157
Mean (SD)	71.3% (25.7%)	57.2% (29.8%)	46.1% (30.9%)	22.7% (33.5%)
p-value		$p < .0001$	$p < .0001$	$p < .0001$

Supportive evidence of efficacy was provided from four additional trials, in which 1,058 subjects with psoriasis vulgaris received once daily dosing of the combination product for four weeks. Efficacy was generally assessed by the PASI in the supportive studies. The PASI results in the supportive studies were generally consistent with each other and with those from the pivotal trial. Additionally, in one study, efficacy was also assessed on a global severity scale and

the combination product was superior to the comparators. The reviewer considers these additional data to be adequately supportive of efficacy.

1.3.3 Safety

Twenty-one studies were conducted with the combination ointment and were included in the safety database. The applicant considered 17 of the 21 studies to be Core Studies, as the populations in those studies were representative of the applicant's proposed target population. Core Studies were further divided into "Short-Term" and "Long-Term" core studies. A total of 2,448 subjects with psoriasis vulgaris received treatment with the combination ointment in the Short-Term Core Studies. Of the 2,448 subjects, 1,539 received once daily treatment, and 909 received twice daily treatment. No new safety concerns were raised on review of the data in the application.

In the Short-Term Core Studies, for the combination product treatment group, adverse events in the Skin and subcutaneous tissue disorders category that were reported for ≥ 1% of subjects were pruritus, psoriasis, and rash scaly:

- Pruritus was reported for 3.1% of subjects in the combination group, 9.1% in the vehicle group, 5.7% in the calcipotriol group and 3.3% in the betamethasone group.
- Psoriasis was reported for 1.2% of subjects in the combination group, 1.1% in the vehicle group, 1.5% in the calcipotriol group and 1.2% in the betamethasone group.
- Rash scaly was reported for 1.2% of subjects in the combination group, 0.2% in the vehicle group, 1.3% in the calcipotriol group and 3.3% in the betamethasone group.

Adverse Events Reported by ≥ 1% of Subjects by Preferred Term: Short-Term Core Studies

	Number (%) of subjects with Adverse Event			
	Combination N=2448	**Vehicle N=470**	**Calcipotriol N=3197**	**Betamethasone N=1164**
Any Adverse Event	663 (27.1)	157 (33.4)	1055 (33.0)	329 (28.3)
Preferred Term	**#of subjects (%)**			
Pruritus	75 (3.1)	43 (9.1)	183 (5.7)	38 (3.3)
Headache	69 (2.8)	12 (2.6)	75 (2.3)	44 (3.8)
Nasopharyngitis	56 (2.3)	9 (1.9)	77 (2.4)	34 (2.9)
Psoriasis	30 (1.2)	5 (1.1)	47 (1.5)	14 (1.2)
Rash scaly	30 (1.2)	1 (0.2)	40 (1.3)	0 (0.0)
Influenza	23 (0.9)	6 (1.3)	34 (1.1)	14 (1.2)
Upper respiratory tract infection	20 (0.8)	3 (0.6)	19 (0.6)	12 (1.0)
Arthralgia[+]	16 (0.7)	3 (0.6)	20 (0.6)	9 (0.8)
Erythema	15 (0.6)	5 (1.1)	54 (1.7)	3 (0.3)
Application site pruritus	13 (0.5)	6 (1.3)	24 (0.8)	10 (0.9)
Skin irritation	11 (0.4)	5 (1.1)	60 (1.9)	8 (0.7)
Pain	7 (0.3)	5 (1.1)	12 (0.4)	3 (0.3)
Burning sensation	6 (0.2)	6 (1.3)	30 (0.9)	3 (0.3)

[+]Occurred in ≥ 1% of subjects in an unlisted comparator group only

The applicant conducted a study to compare the effect of once daily use of the combination product with that of a marketed betamethasone dipropionate ointment on the hypothalamic-pituitary-adrenal (HPA) axis in subjects with psoriasis vulgaris. The study enrolled 24 subjects, 12 per treatment group. HPA axis testing was done at baseline and at Week 4 (end of treatment).

No subjects in the combination group showed evidence of suppression after four weeks of treatment. One subject in the betamethasone dipropionate group, who had normal HPA axis testing at baseline, showed evidence of suppression after four weeks of treatment.

One study evaluated the impact of once daily treatment with the combination product on calcium metabolism. Nine of 141 subjects (6.4%) who received once daily treatment showed evidence of hypercalcemia after four weeks of treatment with the combination product. Calcium levels generally normalized at follow-up testing, for subjects who had such testing.

HPA axis suppression and hypercalcemia have been reported with the individually marketed products betamethasone dipropionate and calcipotriene, respectively.

The applicant also conducted a long-term safety study, in which subjects with psoriasis vulgaris used study products once daily, on an as needed basis, for up to 52 weeks. Subjects were assessed every four weeks. In this study, 212 subjects were randomized to combination treatment, seven of whom underwent HPA axis testing at baseline, 4 weeks and 52 weeks. One subject showed evidence of HPA axis suppression at 52 weeks. No other laboratory monitoring was done in this study, including the assessment on calcium metabolism.

1.3.4 Dosing Regimen and Administration

The recommended dosing regimen is once daily for up to four weeks, and maximum usage should not exceed 100 gm per week. The applicant does not propose that a limitation to duration of treatment be applied. However, data in the marketing application were considered inadequate to support treatment beyond four weeks. Specifically, safety assessments in trials of longer duration (i.e. longer than four weeks) were inadequate to assess systemic tolerance in regard to effects on calcium metabolism and the HPA axis.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were not done.

1.3.6 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.

The product has not been studied in the pediatric population. A deferral was issued for study of the product in the age group of 12 to 17 years, and a Pediatric Written Request will be issued to the applicant. Recommendations regarding the design of the pediatric study will reflect input from the Pediatric Implementation Team. A partial waiver was issued for study of the product in the age group of 0 through 11 years.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

PAREXEL International (Parexel) has submitted a marketing application for a new fixed combination product containing the two active ingredients calcipotriene hydrate (a vitamin D analog) and betamethasone dipropionate (a corticosteroid). The combination product is proposed for the once daily topical treatment of psoriasis vulgaris in adults aged 18 years and above, and, per Section 2.5.4.7 of the Clinical Overview, is intended for up to four weeks of continuous use. The combination product is an ointment formulation, and both active ingredients have been approved individually for marketing in the United States. In this review, "calcipotriol" and "calcipotriene" refer to the same substance.

Parexel is acting as the U.S. agent for LEO Pharmaceutical Products Ltd. A/S (Leo) of Ballerup, Denmark. Leo is the manufacturer of calcipotriene hydrate. In this review, the term "applicant" refers to Leo.

2.2 Currently Available Treatment for Indications

Description of available treatment options for psoriasis vulgaris will be limited to those available for disease of an extent that is amenable to topical treatment, as this is the patient population the applicant is targeting.

Marketed topical therapies include: corticosteroids, calcipotriene and tarzarotene.[1,2,3] Corticosteroids and calcipotriene will be addressed later in the review, as they are both contained in the applicant's combination product. Tarzarotene is a topical retinoid, available in gel formulations at two concentrations.[4]

2.3 Availability of Proposed Active Ingredient in the United States

The applicant proposes marketing of a new combination product containing the two active ingredients calcipotriene hydrate and betamethasone dipropionate. Both active ingredients have been approved individually for marketing in the United States.

Calcipotriene hydrate (calcipotriene) is currently marketed in the United States by Bristol-Meyers Squibb in three formulations under the trade name Dovonex®:

- Dovonex® ointment was approved under NDA 20-723 on December 29, 1993 and is indicated for once or twice daily treatment of plaque psoriasis in adults.
- Dovonex® cream was approved under NDA 20-554 on July 22, 1996 and is indicated for treatment of plaque psoriasis.
- Dovonex® Scalp Solution was approved under NDA 20-611 on March 3, 1997 and is indicated for treatment of chronic, moderately severe scalp psoriasis.

The cover letter to the submission indicates that Leo has the right of reference to all of the studies conducted with calcipotriene, and some of those studies are included in the marketing application under current review.

Bethamethasone dipropionate (bethamethasone) is currently marketed in the United States in a number of formulations including creams, ointments, and lotions. The initial approval of a product containing this active ingredient appears to have been February 1, 1977, and several products containing the substance have been approved under abbreviated new drug applications. With the antifungal clotrimazole, betamethasone is also currently marketed in combination products (cream and lotion formulations) in patients 17 years and older for the topical treatment of certain symptomatic, inflammatory fungal infections of the skin.

2.4 Important Issues With Pharmacologically Related Products

The adverse event profiles for each of the active ingredients are well-established. As a vitamin D analog, safety concerns pertaining to calcipotriene would relate to those seen with vitamin D toxicity, namely the manifestations of hypercalcemia. Signs and symptoms of hypercalcemia are a function of the extent of the calcium elevation may include anorexia, nausea, vomiting, constipation, altered mental status, bone pain, arrhythmias, etc.[5,6]

As a topical corticosteroid, safety concerns pertaining to betamethsone relate to the local effects seen with this class of drugs, which include atrophy, telangiectasias, hypopigmentation, striae, etc. Additionally, should there be sufficient systemic absorption of the topical corticosteroid, manifestations of toxicity would be those seen with systemic administration of corticosteroids, such as hypothalamic-pituitary-adrenal (HPA) axis suppression, cushingoid changes, hypertension, etc.[7,8]

2.5 Presubmission Regulatory Activity

In the United States, the development program was conducted under IND 62,993. The applicant met with the Division on three occasions in the pre-submission period:

End-of-Phase 2 meeting, June 26, 2000

Note: The product was already being marketed in other countries at the time of this meeting. Clinical trials to support marketing outside of the United States were conducted in Europe and Canada (also see Section 2.6).

Advice from the biopharmaceutics/clinical pharmacology reviewer included that:

> HPA-axis suppression data would be needed for 25 to 30% of body surface area with psoriasis. Maximum duration, frequency, and body surface area allowed for in product labeling should be tested with the to-be-marketed formula. Regarding a bioavailability study conducted in normal volunteers (study MCB 9901 NL), "...use of normal volunteers was a question of relevance since the product was being applied to diseased skin."[9]

Advice from the clinical reviewer included:

- For a 505(b)(1) application, generally two adequate and well-controlled studies are required.
- The suggested primary endpoint was the Investigator's Global Assessment of Disease Severity. "Clinical Signs Scoring" was suggested to be a useful secondary endpoint and would be reflective of the global assessment. Details were provided for each of the assessment types.

Guidance Meeting June 9, 2003

The applicant indicated that they planned to submit their marketing application under section 505(b)(1) of the code.

The applicant [redacted] and HPA-axis data would become available prior to NDA submission. The applicant was advised to submit the information to the IND, but that "ultimately it is...our determination that the standards for bioavailability testing/determination have been met."[10]

Citing the guidance entitled, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," the applicant inquired whether the single pivotal trial MCB 0003 INT would be sufficient to support an NDA (along with their supportive data). The Agency responded that, "The Sponsor's supportive data are noted, and, as the Sponsor has indicated, there are circumstances under which a single pivotal trial might be sufficient to support an NDA. Ultimately, however, whether or not data are sufficient to support approval of an NDA is a review issue. Generally, two adequate and well-controlled studies are required in support of a 505(b)(1) application."

The applicant was advised that they would need to either provide data to support that the patient populations studied outside of the United States are reflective of the U.S. population, or conduct a trial in the United States. The Sponsor was referred to the ICH E1A Guideline for Industry.

Pre-NDA Meeting: May 10, 2004

Regarding their HPA axis study, the applicant was advised that, "It is recommended that the data from the HPA axis suppression study (MCB 0201 FR) be analyzed to apply the 30 minute Cortrosyn criteria. The agency finds a 30-minute post-stimulation cortisol level > than 18 ug/dl to be the most relevant. It is noted that this study intended for 24 subjects to complete the study, only approximately 12 of whom would have received treatment with the sponsor's product, since randomization was to two treatment groups (Dovobet and Diprosone). Additional HPA axis data may be needed, including study of subjects down to 12 years of age, and a minimum of 30 evaluable subjects studied following treatment with the sponsor's product under maximum use conditions would be recommended. It is noted that a long-term study (52 weeks) is underway and that HPA axis suppression is being investigated in a subgroup of 19 subjects in this study. However, since study drug usage in the long-term study is on an 'as needed' basis, it would appear possible that HPA axis testing in this study might not reflect maximal use conditions."[11]

Additional Information

The applicant opened the IND on July 27, 2001 with a protocol for a Phase 1 dermal safety study. The pivotal trial MCB 0003 INT was underway when the applicant opened the IND. The HPA axis study was underway when the applicant submitted the protocol for review (also see Section 7.1.12). The long-term safety trial was underway at the time of the pre-NDA meeting.

2.6 Other Relevant Background Information

Leo is the manufacturer of calcipotriene hydrate, and their drug substance is contained in a product globally marketed under the trade names Dovonex®, Daivonex® and Psorcutan®. This product contains the single active ingredient calcipotriol at the same concentration as is contained in the combination product, i.e. 50 mcg/g.

According to the cover letter, the combination product has been approved in 61 countries and is currently marketed in 48 of those countries. Marketing for the topical treatment of psoriasis vulgaris was launched in Denmark in October 2001. Through the Mutual Recognition Procedure, marketing was granted in all European Union countries, Norway, and Iceland on September 8, 2002. The combination product is marketed in Europe, Canada, Asia, and South America. Trade names for the marketed product include Dovobet®, Daivobet® and Psorcutan Beta®.

For marketing of the product in the United States, the applicant proposed the trade name Dovobet®; however, the Division of Medical Errors and Technical Support (DMETS) does not recommend use of this name (see Section 8.8).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Dovobet® ointment is a fixed combination of calcipotriene [redacted]g (as hydrate) and betemethasone 0.5 mg/g (as dipropionate). The vehicle consists of [redacted] polyoxypropylene-(15)-stearyl ether, α-tocopherol and [redacted]

At the pre-NDA meeting, the applicant indicated that, "The proposed draft PI is written in US English using the USAN name for the active substance calcipotriene whereas the remaining eCTD will be written in UK English using the INN Name calcipotriol." Also, on p. 8 of the Summary of Clinical Safety, the applicant indicates that calcipotriol is the International Non-Proprietary Name (INN), and calcipotriene is the US Adopted Name (USAN). The applicant states that calcipotriol and calcipotriene are identical.

In a submission dated August 11, 2005, the applicant indicated that, "all the batches used in the clinical development program...have been identical to those intended to be marketed, except for the...batches where the active substances were ^{3}H radio-labeled."

For marketing in the United States, the applicant proposes to package the product in 3g, 15g, 30g, 60g and [redacted]ibes.

Comment: The proposed packaging of — cannot be reconciled with the proposed maximum use of 100 gram per week, and is not recommended.

The chemistry reviewer recommends approval from a chemistry standpoint.

Please see the chemistry review of Mr. Ernest G. Pappas.

3.2 Animal Pharmacology/Toxicology

In Section 2.5.5.2 of the Clinical Overview, the applicant indicates that a dermal photo(co)carcinogenicity study conducted in the hairless mouse with calcipotriene in the marketed scalp solution vehicle, at a dose of 30 mcg/kg (7.5 mcg/mL) produced a "very slight increase in UV-induced tumor onset" in the male mouse. The significance of these findings for humans is unclear. The concentration of calcipotriene in the combination ointment is the same as in the marketed scalp solution; therefore, the data from the studies conducted with the solution may apply to the combination ointment.

In the discussion of carcinogenicity in the draft pharmacology/toxicology review (p.22), the following information was presented,

[ ]

Comment: The "Carcinogenesis, Mutagenesis, Impairment of Fertility" sections of the package inserts for all three formulations of Dovonex now include the following wording,

[ ]

Labeling for the product under current review will also reflect these findings.

Per the draft pharmacology/toxicology review (p. 65), "The sponsor has committed to conduct the following nonclinical studies post-approval of the NDA:

1. 'Evaluation of the carcinogenicity of calcipotriene (this matter is currently being evaluated by the sponsor as a post-approval commitment to NDA 20-273).

2. '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.

3. '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.

4. 'Evaluation of betamethasone dipropionate for effects upon female fertility, including prenatal and postnatal function.

"The sponsor should be asked to conduct the following studies post-approval (but has not currently agreed to do so):

1. [ ]

"Note: Although data from published literature were deemed adequate to support approval of the product, partially in view of the available clinical experience with topical betamethasone dipropionate products, these data were considered to have been less than fully desirable. The available data which describe the teratology of betamethasone dipropionate should be supplemented through submission within a reasonable time frame of data from new teratology studies which are fully compliant with ICH guidelines and GLP regulations."

In the draft pharmacology/toxicology review, the reviewer recommends that the application is approvable with respect to nonclinical concerns.

Please see the pharmacology/toxicology review of Dr. Norman See.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of data used in the review were the clinical trials conducted by the applicant and post-marketing safety data. None of clinical trials were conducted in the United States.

4.2 Tables of Clinical Studies

All studies were conducted in Europe and Canada.

Study/Type/ # and type of subjects	Design, Control Type/ Treatment Duration	Objective	Test products/Dosage/ Route of administration
MCB 9810 NL/ PK/4 healthy	Open,non-comparative/ single dose	Percutaneous absorption of calcipotriol (absorption study)	Combination (radiolabelled calcipotriol)/ Single dose/topical
MCB 9901 NL/ PK/24 healthy	Open,active/Single dose or 4 wks	Absorption and excretion balance of calcipotriol and betamethasone	-Combination (radiolabelled calcipotriol) days 1&36;unlabeled days 8-35/BID -Calcipotriol (m.v.*),radiolabelled days 1&36; unlabeled days 8-35/BID -Calcipotriol (n.v.) raidolabelled, single dose -Combination (radiolabelled betamethasone),single dose -Betamethasone (n.v.*),radiolabelled,single dose Topical
MCB 9902 FR/ PD/102 healthy	Double-blind,active-contolled,intra-individual comparison/ Single dose	Bioavailability and bioequivalence (vasoconstrictor assay)	Combination +Betamethsone (m.v.)/ Single dose/Topical
MCB 9903 DE/ PD/45 healthy	Double-blind,active-& vehicle-contolled,intra-individual comparison/ 4 weeks	Atrophogenic potential (skin atrophy study)	- Combination +Betamethasone (m.v.)/ - Combination +New vehicle Twice daily/Topical
MCB 0003 INT/ 1605 psoriais vulgaris	Double-blind,active-& vehicle-contolled	Safety,efficacy	-Combination -Calicpotiol (n.v.) -Betamethasone (n.v.) -New vehicle Once daily/topical
MCB 0002 INT/ 974 psoriasis vulgaris	Partly double-blind,active-controlled 12weeks	Safety,efficacy	-Combination 8 weeks+Calcipotriol (m.v.)x4wks QD -Calcipotriol (m.v.) x 4wks, once daily -Combinationx4wks =calcipotriol (m.v.) weekdays &combination weekends qd Calcipotriol (m.v.)x 12wks BID
MCB 0001 INT/ 501 with psoriasis vulgaris	Double-blind,active-controlled 8 weeks	Safety,efficacy	-Combination x4wks + calcipotriol (m.v.) x 4 wks -Tacalcitol x 8wks Once daily
MCB 9905 INT 831 with psoriasis vulgaris	Double-blind,active- and vehicle-controlled 4 weeks	Safety,efficacy	-Combination QD + new vehicle QD -Combination BID -Calcipotriol (m.v.) BID -New vehicle BID
MCB 0201 FR 24 wit psoriasis	Double-blind,active-controlled	HPA axis suppression	Combination QD Betamethasone (m.v.) QD

vulgaris	4 weeks		
MCB 9904 INT 1113 with psoriasis vulgaris	Double-blind,active-controlled with open-label extension 4 wk +wks open-label calcipotriol (m.v.) BID	Safety and efficacy	-Combination x 4 wks + calcipotriol (m.v.) x 4 wks -Calcipotriol 4 + 4 wks -Betamethasone (m.v.) x 4 wks + calcipotriol x 4 wks BID
MCB 9802 INT 1043 with psoriasis vulgaris	Double-blind,active-and vehicle controlled	Safety and efficacy	-Combination -Calcipotriol (n.v.) -Betamethasone (n.v.) New vehicle BID
MCB 0102 INT 636 with psoriasis vulgaris	Double-blind,active controlled	Safety + HPA axis suppression	-Combination X 52 wks -Combination and calcipotriol (m.v.) in alternating 4-wk periods -Combination x 4 wks + calcipotirol (m.v.) x 48 wks QD as required
MCB 0101 FR 32 healthy	Investigator-blinded, vehicle-controlled,intra-individual comparison	Phototoxicity	Combination + new vehicle Single dose
MCB 0202 FR 220 healthy	Double-blind, vehicle-controlled,intra-individual comparison	Sensitization	Combination + new vehicle Once daily 3 applications/week +single challenge application after 2 wks
MCB 0203 FR 32 healthy	Investigator-blinded, vehicle-controlled,intra-individual comparison	Skin irritation potential (21-day cumulative irritancy)	Combination + new vehicle Once daily; 5 applications/week for 3 wks
MCB 0204 FR 32 healthy	Investigator-blinded, vehicle-controlled,intra-individual comparison	Photosensitization potential	Combination + new vehicle Once daily; 2 applications/week then UVA/UVB radiation 3 wks + single challenge after 2 wks rest
MCB 0306 UK 25 healthy	Double-blind, active & vehicle-controlled,intra-individual comparison	UV light penetration potential	Combination ointment + new vehicle + calcipotriol solution + calcipotriol vehicle + standard sunscreen + standard emollient Single dose followed by UVA/UVB irradiation
MHO0201 FR 23 with psoriasis vulgaris	Investigator-blinded, vehicle-controlled,intra-individual comparison	Anti-psoriatic effect of calcipotriol/hydrocortisone Ointment; dose-finding	Combination + calciptriol & hydrocortisone ointment (6 concentrations) + ointment vehicle 3 weeks
MBL 0201 FR 22 with psoriasis vulgaris	Investigator-blinded, active & vehicle-controlled,intra-individual comparison	Anti-psoriatic effect of calcipotriol/betamethasone gel; dose-finding	Combination +calcipotriol and betamethasone (gel vehicle) + gel vehicle 6 days per week 3 weeks

MCB 0207 DK	Double-blind, active & vehicle-controlled,intra-individual comparison	Efficacy in contact dermatitis	Combination + calcipotriol (n.v.) + betamethasone (n.v.) + untreated control 10 days
MCB 0303 INT 428 with pustulosis palmoplantaris	Double-blind,active-control	Safety and efficacy	Combination Betamethsone (m.v.) BID for 8 wks

*m.v.= marketed vehicle; n.v.= new vehicle

4.3 Review Strategy

The applicant conducted one pivotal trial, MCB 0003 INT, in support of the marketing application. In the review of efficacy results, emphasis was placed on MCB 0003 INT as it was the only trial that was both designed to demonstrate the contribution of each component to efficacy so as to be in compliance with 21 CFR 300.50 and designed to evaluate the recommended primary endpoint of global severity. To provide supportive evidence of efficacy, the applicant submitted data from the clinical trials that were conducted to support marketing overseas. All trials were considered in the safety assessment.

4.4 Data Quality and Integrity

Division of Scientific Investigations inspections were not requested. The applicant's analyses were reviewed and independently analyzed.

4.5 Compliance with Good Clinical Practices

The applicant provided a statement that all studies in the development program were conducted in accordance with Good Clinical Practice (Module 2, Volume 2, Section 2.5.1.7). For the pivotal trial, a signed and dated informed consent form was obtained prior to any study-related procedures being carried out.

No subjects were excluded from the intention-to-treat or safety analysis sets of the pivotal trial (MCB 0003 INT) for protocol deviations.

4.6 Financial Disclosures

The applicant submitted a completed FDA Form 3454. The applicant stated that they acted with "due diligence" to obtain the required information from clinical investigators. Pertaining to the pivotal trial, there were no financial disclosures for any of the investigators who completed the disclosure forms. Reasons for not obtaining the disclosure forms were: investigator no longer worked at the study site and new address was unknown; death; illness; retirement; maternity leave.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

According to the applicant, the metabolism of the two active ingredients and the drug combination have been studied in human liver homogenates. The qualitative and quantitative profiles of metabolites for each active ingredient were similar, whether measured singly or in combination with the other active. The applicant therefore concluded that neither active ingredient showed signs of drug interaction from a metabolic standpoint.

According to the applicant, the conduct of traditional pharmacokinetic studies was challenging because of:

- the low concentration of drug in the topical formulation
- the low transdermal absorption of each active ingredient
- the rapid metabolism of any absorbed drug.

Because of analytical limitations, traditional pharmacokinetic parameters (AUC's and C_{max}) have not been determined for either active ingredient.

When the combination product was applied to healthy skin, less than 1% of either active ingredient was systemically absorbed. Further, the applicant indicateed that both drugs are rapidly metabolized. The applicant concluded that these factors make systemic interactions with other drugs unlikely and conducted no additional drug interaction studies.

Comment: The applicability of data from the above study conducted on subjects with normal skin to subjects with psoriasis is unclear, since absorption through skin affected by psoriasis may be different.

Please see the review of Dr. Abimbola Adebowole.

5.2 Pharmacodynamics

From the Dovonex ointment package insert (CLINICAL PHARMACOLOGY Section):

"In humans, the natural supply of vitamin D depends mainly on exposure to the ultraviolet rays of the sun for conversion of 7-dehydrocholesterol to vitamin D_3 (cholecalciferol) in the skin. Calcipotriene is a synthetic analog of vitamin D_3...

"Vitamin D and its metabolites are transported in the blood, bound to specific plasma proteins. The active form of the vitamin, 1,25-dihydroxy vitamin D3 (calcitriol), is known to be recycled via the liver and excreted in the bile. Calcipotriene metabolism following systemic uptake is rapid, and occurs via a similar pathway to the natural hormone. The primary metabolites are much less potent than the parent compound."

Calcipotriene binds with certain vitamin D receptors and may disrupt the pathogenic pathway of psoriasis by inhibiting "hyperproliferation and abnormal differentiation of keratinocytes."[12]

Manifestations of toxicity would be those of hypercalcemia (see Section 2.4).

From the Diprosone ointment package insert (CLINICAL PHARMACOLOGY Section):

"The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses, corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects.

"Topical corticosteroids, such as betamethasone dipropionate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known,the exact mechanisms of their actions in each disease are uncertain. Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs." Such effects could include reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients."

The applicant conducted a bioequivalence study:

MCB 9902 FR: "In Vivo Bioequivalence Study of Betamethasone Dipropionate in Dovobet® Ointment and Diprosone® Ointment

This was a double-blind, randomized, single-center, bioequivalence study with intra-individual comparisons conducted in 102 healthy subjects in France. The objective of the study was to investigate the local bioequivalence of betamethasone in the combination ointment and betamethasone in the marketed product, Diprosone® ointment.

Fixed concentrations of the active substances were used and the same amount was applied to each application site. Different "doses" of the drug delivered to the skin were achieved by varying the duration of exposure of the dose on the skin, i.e. dose duration. The study was conducted in two phases: pilot and pivotal. The pilot phase determined the conditions for the pivotal phase which investigated whether the vasoconstrictive effect of betamethasone in Dovobet® ointment was bioequivalent to that in Diprosone® ointment.

Comment: This review will focus on the pivotal phase of the study.

In both phases of the study, investigational products were applied under non-occlusive conditions to test sites on the ventral forearms. Untreated test sites served as controls. The number of test sites was 16 (eight per arm). As a measure of vasoconstriction, skin blanching was assessed using chromametry and visual scoring. Test sites were studied over a 24-hour period.

Results from the pivotal phase revealed that the vasoconstriction exerted by betamethasone in the combination product, as assessed by chromametry, was locally bioequivalent to that in Diprosone®. These results indicate that the combination product can be considered to contain a potent topical corticosteroid.

5.3 Exposure-Response Relationships

In study MCB 9905 INT, the applicant compared once daily and twice daily dosing of the combination product for a duration of up to 4 weeks. The primary response criterion was the percentage change in Psoriasis Area Severity Index score, and the results (from the clinical study report) were: a -68.6% percent change for the once daily group and a -73.8% for the twice daily group. This difference was statistically significant, but not clinically so. Skin and subcutaneous disorders were the most frequently reported adverse events, and were reported in 11.9% of subjects in the once daily group and 11.1% in the twice daily group. Post-treatment high albumin-corrected calcium levels were seen in 6.4% of the once daily group and 2.3% of subjects in the twice daily group (and 2.6% of subjects in the vehicle group). Based on the results from this study, the applicant pursued development of the product for once daily dosing.

Comment: It is noted that the rate of hypercalcemia was higher for subjects who were dosed once daily compared to twice daily. However, the significance of this is unclear, since it is also noted that the vehicle group had a slightly higher rate of hypercalcemia than the twice daily group.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant's proposed indication is the topical treatment of psoriasis vulgaris in adults aged 18 years or older.

6.1.1 Methods

The applicant conducted one pivotal trial in support of their application, MCB 0003 INT. Additionally, they submitted six studies as being supportive of efficacy: MCB 0002 INT, MCB 0001 INT, MCB 9905 INT, MCB 0201 FR , MCB 9904 INT, and MCB 9802 INT. However, the applicant is principally relying on the following four studies as supportive, as these studies included treatment arms in which subjects received once daily dosing for four weeks (as was evaluated in the pivotal trial):

- MCB 0002 INT
- MCB 0001 INT
- MCB 9905 INT
- MCB 0201 FR

Note: Subjects received twice daily dosing in studies MCB 9904 INT and MCB 9802 INT, and these studies will only be considered in the safety review.

6.1.2 General Discussion of Endpoints

In all of the applicant's efficacy studies, enrollment and efficacy were based on the Psoriasis Area and Severity Index (PASI), either solely or along with an investigator's global assessment (two studies had static global assessments). The applicant was advised at the End-of-Phase 2/ Pre-IND meeting that the Division does not rely on the PASI score for determination of efficacy. Instead, it was recommended that efficacy be assessed on a static investigator's global scale. The applicant incorporated this advice into the design of the pivotal trial, but also chose the PASI as a co-primary endpoint.

Comment: According to Section 9.3 of the protocol for the pivotal study MCB 0003 INT, PASI is "the primary measure of efficacy for European regulatory authorities. It is a widely used, validated scale. Change in PASI measures the whole body clinical response of the patient. Comparison of the percentage change in PASI between treatment groups will therefore reflect the comparative efficacy of the treatments." While it may be true that the PASI is widely applied in clinical trials, it is unclear how widely it is employed in the clinical arena in the United States. Also, it could be argued that presentation of results by a global scale (e.g. "clear" or "almost clear") might more readily bring forth a clinical image than a result presented in terms of a percent reduction of a PASI score.

6.1.3 Study Design

The pivotal study, MCB 0003 INT, is discussed below.

MCB 0003 INT: "Calcipotriol/Betamethasone Dipropionate Once Daily in Psoriasis Vulgaris

Study Period: First subject enrolled: February 13, 2001
Date of last subject's visit: June 19, 2001

The pivotal study MCB 0003 INT (0003 INT) was an international, multi-center, prospective, randomized, double-blind, four-armed, parallel group study of four weeks duration. The study was of appropriate design for the applicant's fixed combination product, in that it was designed to evaluate the contribution to efficacy of each of the two active ingredients.

The stated primary objective of the study was to compare the clinical efficacy of the combination product with each of its constituent active ingredients and vehicle for treatment of psoriasis vulgaris. Subjects were randomized to one of four treatment groups (3:3:3:1):

- combination ointment
- calcipotriene in the applicant's ointment vehicle
- betamethasone in the applicant's ointment vehicle, and
- the applicant's ointment vehicle.

All study products were applied once daily for up to four weeks. Subjects were assessed after 1, 2, and 4 weeks. The study did not include any post-treatments assessments.

Inclusion Criteria

1. Clinical diagnosis of psoriasis vulgaris amenable to treatment with a maximum of 100g of topical medication per week, involving arms and/or trunk and/or legs
2. A minimum PASI score for **extent** of 2 in at least one body region (i.e. psoriasis affecting at least 10% of arms, and/or 10% of trunk, and/or 10% of legs).
3. An investigator's global assessment of disease severity of mild, moderate, severe, or very severe disease.
4. Attending hospital outpatient clinic or general practice for psoriasis treatment.
5. Aged 18 years or above.
6. Either sex.
7. Any ethnic origin.
8. Following receipt of verbal and written information about the study, the patient must provide signed and dated informed consent before any study related activity is carried out.
9. Females of child-bearing potential must have a negative urine pregnancy test before randomization and must agree to use an adequate method of contraception during the study.

Comment: 1) The Division would have recommended against enrollment of subjects with mild disease at baseline (Inclusion Criterion #3), as primary efficacy could have been achieved by only one-grade improvement on the global scale (scale is presented below). One-grade improvement could reflect the absence of sharp clinical distinctions from one grade to the next or could reflect vehicle effect. However, as previously noted, this trial was already underway when the applicant opened their IND; therefore, the Division had no opportunity to comment on the protocol. The statistical reviewer performed an analysis which considered two-grade improvement (i.e. from "mild" to "absence of disease") as success for subjects who had mild disease at baseline, and the results from that analysis are presented in the discussion of results below. 2) In a General Correspondence submitted August 21, 2001 to IND 62,993, the applicant explained that the reason for requiring contraception in females of child-bearing potential in the Phase 3 studies (Inclusion Criterion # 9) was that it was a requirement for conducting clinical studies in Europe.

Exclusion Criteria

1. Current diagnosis of unstable forms of psoriasis in the area to be treated with study medication, including guttate, erythrodermic, exfoliative or pustular psoriasis.
2. Other inflammatory skin diseases in the area that can be treated with study medication that may confound the evaluation of the psoriasis.
3. Systemic antipsoriatic treatment or PUVA therapy within the 4 week period prior to visit 1 or during the study.
4. UVB therapy within the 2 week period prior to visit 1 or during the study.
5. Topical antipsoriatic treatment of psoriasis of trunk or limbs during the study including the use of emollient.
6. Initiation of or changes to non antipsoriatic concomitant medication that could affect psoriasis (e.g. beta blockers, lithium) during the study.
7. Known or suspected hypersensitivity to any of the constituents of the study medications.
8. Patients with history/signs/symptoms suggestive of a clinically significant abnormality in calcium homeostasis associated with hypercalcemia.
9. Concomitant treatment of facial psoriasis with retinoids, calcipotriol, tacalcitol, or very potent WHO group IV topical corticosteroids.
10. Concomitant treatment of facial psoriasis with retinoids, calcipotriol, tacalcitol, or very potent WHO group IV topical corticosteroids.
11. Treatment of lesions with study medication where topical corticosteroid is not indicated.

12. Females who are pregnant, breast feeding or who wish to become pregnant during the study period.
13. Planned exposure to sun, UVA, or UVB that may affect the psoriasis during the study period.
14. Patients who have received treatment with an investigational drug within the previous month (for Ireland only, patients who have received treatment with an investigational drug within the previous 16 weeks), or are currently participating in another clinical trial.
15. Previous randomization in this study.
16. Patient known or suspected of being unable to comply with the study protocol, e.g. due to alcoholism, drug dependence or psychotic state.

Comment: 1) It is noted that there was no specified washout period for topical therapies (Exclusion Criterion #5). This would have been recommended to try to avoid subjects having partially treated disease at the start of study treatment. However, this issue would likely be "corrected" by randomization. 2) The WHO classification for topical corticosteroids (Exclusion Criteria #'s 9 and 10) was presented in Appendix V of the protocol. It ranks topical corticosteroids from "weak' (Group I) to "very potent" (Group IV). In the United States, corticosteroids are ranked in the reverse order on scales that have approximately 7 levels, with the highest potency products being in Class 1 and the lowest potency products in Class 7. Betamethaosone dipropionate is in Class III ("potent") on the WHO scale and in Class 1 on the scale used in the United States (i.e. since the betamethasone dipropionate in the applicant's product is bioequivalent to Diprosone®)

Concomitant treatment of facial and scalp psoriasis with retinoids and potent steroid was excluded due to the possibility of systemic absorption of these treatments which could affect the psoriasis on the body, and confound the effect of the study treatment. Inhalation steroids, bath oils and moisturizing soaps were allowed during the study.

Study drug was packaged in 50 g tubes, and subjects received two tubes of study product per week. Subjects were advised to use a maximum of two tubes (100 g) of study product per week. Study product was to be applied to affected skin on the trunk, arms and legs once daily. At each visit, study product dispensed at the previous visit was to have been returned. Ultimately, all study products were to have been returned to the applicant, and all tubes were weighed by Leo to determine the amount of use.

Per Section 11.6.3 of the protocol, subjects were advised to not apply study drug in the two-hour period before a clinic visit to avoid "hiding" any scaling.

Comment: A two-hour period may not have been sufficiently long to avoid impacting (i.e. minimizing) the appearance of scale at assessment.

Investigator's Global Assessment of Disease Severity

An assessment of the global disease severity was made at all visits according to the scale below. The assessment was made considering the condition of psoriasis at all treated sites at the time of the evaluation, not in relation to the condition at a previous visit.

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

Comment: The definition for "very mild disease" does not address scaling or erythema. Also, the term "discoloration" is vague, and it is unclear if it was intended to encompass the assessment for the presence of erythema. In the context of the scale, "discoloration" more suggests post-inflammatory pigmentary changes to the reviewer.

Subjects classified as having "Absence of Disease" or "Very Mild Disease" were considered to have "Controlled Disease."

Psoriasis Area Severity Index

The extent and severity was assessed by the PASI scoring system at each visit.

The **extent** of psoriatic involvement was recorded for each of the three areas: arms, trunk and legs using the following scale:
0 = no involvement
1 = < 10%
2 = 10 – 29%
3 = 30 – 49%
4 = 50 – 69%
5 = 70 – 89%
6 = 90 – 100%

Note: the neck and buttocks belong to the trunk, the axillae to the arms and the genito-femoral folds to the legs.

The **severity** of the psoriatic lesions in each of the three areas was recorded for each of the symptoms of redness, thickness and scaliness using the scale below:
0 = absent
1 = slight
2 = moderate
3 = severe
4 = severest possible

The following formula was used to calculate the PASI:

Arms: $0.2 (R + T + S)E = X$
Trunk: $0.3 (R + T + S)E = Y$
Legs: $0.4 (R + T + S)E = Z$

Where R = score for redness, T = score for thickness, S = score for scaliness, and E= score for extent

The sum of $X + Y + Z$ gives the total PASI, which can, according to the protocol, range from 0 to 64.8.

Primary Response Criteria

- The proportion of patients classified as "controlled disease ("absence of disease" or "very mild disease") by the investigator's global assessment of disease severity at the end of treatment
- The percentage reduction in PASI from baseline to end of treatment

Secondary Response Criteria

- The percentage reduction in PASI from baseline to visit 2 (to assess speed of response)
- The proportion of patients classified as "treatment success" ("marked improvement" or "cleared") at the end of treatment according to the patients' global assessment of treatment response.
- The change in PASI (actual and percentage) from baseline to each subsequent visit and end of treatment
- The distribution of the investigators' global assessment of disease severity at each visit and end of treatment
- The distribution of the patients' global assessment of treatment response at each on-treatment visit and end of treatment
- Reasons for withdrawal
- Adverse events

6.1.4 Efficacy Findings

This portion of the efficacy review focuses on the clinical data from the one pivotal trial, MCB 0003 INT. The supportive studies will be discussed individually.

Dispostion of Subjects

A total of 1605 subjects were enrolled in the pivotal study. Of the 1605 enrolled, 1603 subjects were randomized to treatment. All 1603 of those subjects received study medication, and they constitute the intent-to-treat population. [The reasons for not randomizing the other two subjects were: withdrawal of consent and violation of exclusion criteria (subject was considered unable to comply with the study protocol)].

Enrolled Subjects (Applicant Table 1)

Country	Total (n=1603)	Combination (n=490)	Calcipotriol (n=480)	Betamethasone (n=476)	Vehicle (n=157)
Belgium	166	51	50	50	15
Canada	502	151	154	146	51
France	235	71	69	71	24
Germany	162	51	47	47	17
Ireland	29	8	10	8	3
Spain	64	19	20	19	6
Sweden	52	17	17	14	4
United Kingdom	393	122	113	121	37

Summary of Discontinuation Reasons-All Subjects (Sources: Applicant Tables 3a and 3b)

	Combination (n=490) # (%)	Calcipotriol (n=480) # (%)	Betamethasone (n=476) # (%)	Vehicle (n=157) # (%)
Primary Reason for Withdrawal[1]				
Unacceptable adverse event(s)	3 (0.6)	15 (3.1)	5 (1.1)	12 (7.6)
Death	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Exclusion criteria emerging during study	0 (0.0)	3 (0.6)	1 (0.2)	1 (0.6)
Lost to follow-up	2 (0.4)	7 (1.5)	7 (1.5)	2(1.3)
Medical deterioration	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.6)
Required no further treatment before visit 4	7 (1.4)	1 (0.2)	4 (0.8)	0 (0.0)
Other reasons[2]	2 (0.4)	3 (0.6)	4 (0.8)	4 (2.5)
Unacceptable treatment efficacy	4 (0.8)	18 (3.8)	8 (1.7)	13 (8.3)
Voluntary	3 (0.6)	5 (1.0)	4 (0.8)	2 (1.3)
Total withdrawn	20 (4.1)	40 (8.3)	26 (5.5)	25 (15.9)
Total attending visit 4	473 (96.5)	445 (92.7)	454 (95.4)	136 (86.6)

[1]Subjects may have had more than one reason for withdrawal

[2] #5985 (combination): ointment too greasy; stained pajamas/bedding
#7239 (combination): withdrew consent
#5061 (calcipotriol): nearly cleared according to subject
#5482 (calcipotriol): unable to attend visits due to work
#5881 (calcipotriol): withdrew consent
#5457 (vehicle): withdrew consent
#6109 (vehicle): wife suspected subject was non-compliant
#5499 (betamethasone): unable to keep visits
#6148 (betamethasone): needed no further treatment; didn't want visit 4
#6754 (betamethasone): family problems
#7116 (betamethasone): possible pregnancy
#5283 (vehicle): unable to continue visits due to work
#6037 (vehicle): hospitalization

Data Sets Analyzed

All randomized subjects were included in the intention-to-treat (ITT) analysis set. Thus, 1603 subjects were included in the ITT data set: 490 subjects randomized to combination, 480 to calcipotriol, 476 to betamethasone, and 157 to vehicle. Subjects who provided efficacy data only from visit 1, had those data treated as end-of-treatment data.

Demographics and Other Baseline Characteristics

The mean age of subjects was similar across treatment groups. There were more males than females in all treatment groups. Most subjects were Caucasian.

Demographic Characteristics ITT (Sources: Applicant Tables 6, 7 and 8)

	Combination (n=490) #(%)	Calcipotriol (n=480) #(%)	Betamethasone (n=476) #(%)	Vehicle (n=157) #(%)
Age				
Mean	47.6	48.9	48.2	49.8
SD	14.4	14.7	15.0	14.4
Minimum	19	17	18	18
Maximum	83	90	83	87
Gender				
Male	308 (62.9)	283 (59.0)	291 (61.1)	88 (56.1)
Female	182 (37.1)	197 (41.0)	185 (38.9)	69 (43.9)
Race				
Caucasian	473 (96.5)	461 (96.0)	465 (97.7)	153 (97.5)
Black	3 (0.6)	5 (1.0)	1 (0.2)	0 (0.0)
Asian	11 (2.2)	13 (2.7)	8 (1.7)	2 (1.3)
Other	3 (0.6)	1 (0.2)	2 (0.4)	2 (1.3)

Baseline Disease Characteristics

Duration of psoriasis was similar across treatment groups: 18.3 years in the combination group, 20.3 years in the calcipotriol group, 19.4 years in the betamethasone group, and 18.3 years in the vehicle group.

Baseline Investigator's Global Assessment (Source: Applicant Table 10)

Baseline Global*	Combination (n=490) #(%)	Calcipotriol (n=480) #(%)	Betamethasone (n=476) #(%)	Vehicle (n=157) #(%)
Mild Disease	81 (16.5)	79 (16.5)	90 (18.9)	29 (18.5)
Moderate Disease	311 (63.5)	300 (62.5)	297 (62.4)	99 (63.1)
Severe Disease	89 (18.2)	92 (19.2)	85 (17.9)	28 (17.8)
Very Severe Disease	9 (1.8)	9 (1.9)	4 (0.8)	1 (0.6)

*no subjects were "very mild" or "absence" at baseline

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

Baseline PASI (Source: Applicant Table 9)

PASI	Combination (n=490)	Calcipotriol (n=480)	Betamethasone (n=476)	Vehicle (n=157)
Mean	9.9	10.4	9.8	9.5
SD	6.0	6.4	6.1	6.3
Minimum	1.2	1.2	1.2	2.3
Maximum	42.8	44.5	49.5	36.9

Mean PASI scores were similar for all treatment groups.

Extent of Exposure

The mean amount of study medication used over the four-week treatment period was similar across treatment groups.

Extent of Exposure (Source: Applicant Table 15)

Amount Used over treatment period (g)*	Combination (n=445)	Calcipotriol (n=432)	Betamethasone (n=441)	Vehicle (n=148)
Mean	133.7	142.3	139.9	133.4
SD	97.6	99.2	97.4	103.8
Min	0.0	0.0	5.0	0.0
Max	371.3	386.1	382.9	377.5

*Only subjects who returned all dispensed tubes provided data

EFFICACY RESULTS: Study MCB 0003 INT

Note: Please also see the statistical review by Dr. Mat Soukup and Mr. Steve Thomson.

The applicant's chosen co-primary response criteria were:

- The proportion of patients classified as "Controlled Disease" ("absence of disease" or "very mild disease") by the investigator's global assessment of disease severity at the end of treatment
- The percentage reduction in PASI from baseline to end of treatment

All results presented are for the intention-to-treat analysis set.

Controlled Disease

Controlled Disease at End of Treatment (Source: Applicant Table 24)

	Combination (n=490) #(%)	Calcipotriol (n=480) #(%)	Betamethasone (n=476) #(%)	Vehicle (n=157) #(%)
All Subjects	276 (56.3)	107 (22.3)	176 (37.0)	16 (10.2)

Statistical Reviewer's Table 3. Efficacy Results for Percent with Controlled Disease (ITT)

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	276 (56.3%)	176 (37.0%)	107 (22.3%)	16 (10.2%)
p-value[1]		$p < .0001$	$p < .0001$	$p < .0001$
p-value[2]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.
[2] p-value is based upon sponsor's logistic regression using sponsor defined pooled center.
Source: Reviewer's analysis and Page 105 of MCB-0003 Study Report (5.3.5.1.1 MCB-0003-INT Appendix II).

Statistical Reviewer's Table 4. Efficacy Results for Percent with Controlled Disease (2 Grade Improvement)

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	235 (47.8%)	125 (26.3%)	79 (16.5%)	12 (7.6%)
p-value[2]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.
Source: Reviewer's analysis.

Comment: In all of the above analyses, the applicant's combination product demonstrates superiority to each monad and vehicle on the Investigator's Global Assessment scale. In the "2-Grade Improvement" analysis, subjects with mild disease at baseline were required to achieve a status of "absence of disease" in order to be considered a success.

Percent Change in PASI

Percent Change in PASI from Baseline to End of Treatment (Source: Applicant Table 21)

	Combination (n=490)	Calcipotriol (n=480)	Betamethasone (n=476)	Vehicle (n=157)
Mean	-71.3	-46.1	-57.2	-22.7
SD	25.7	30.9	29.8	33.5
Minimum	-100	-100	-100	-100
Maximum	38	81	83	72
Lower 95% CL	-73.6	-48.8	-59.9	-28.0
Upper 95% CL	-69.1	-43.3	-54.5	-17.4

Statistical Reviewer's Table 5. Efficacy Results for Percent Reduction in PASI: Study MCB-0003-INT.

	Dovobet® QD	Betamethasone QD	Calcipotriol QD	Vehicle QD
N	490	476	480	157
Mean (SD)	71.3% (25.7%)	57.2% (29.8%)	46.1% (30.9%)	22.7% (33.5%)
p-value[1]		$p < .0001$	$p < .0001$	$p < .0001$

[1] p-value is based upon reviewer's analysis using ANOVA with design variables for treatment and reviewer's definition of pooled center.

Comment: In the above analyses, the applicant's combination product demonstrates superiority to each monad and vehicle in the percent change in PASI from baseline to end of treatment (i.e. shows a greater percent change).

Results by Baseline Global Severity

Controlled Disease at End of Treatment by Baseline Global Severity (Source: Applicant Table 29)

Baseline Global	Combination (n=490) #(%)	Calcipotriol (n=480) #(%)	Betamethasone (n=476) #(%)	Vehicle (n=157) #(%)
Mild Disease	54 (66.7)	29 (36.7)	57 (63.3)	5 (17.2)
Moderate Disease	171 (55.0)	62 (20.7)	101 (34.0)	8 (8.1)
Severe Disease	48 (53.9)	15 (16.3)	17 (20.0)	3 (10.7)
Very Severe Disease	3 (33.3)	1 (11.1)	1 (25.0)	0 (0.0)

Statistical Reviewer's Table 6. Percent of Subjects with Controlled Disease by Baseline IGA Disease Severity

Success/Total (Percent Success)	Dovobet®	Betamethasone	Calcipotriol	Vehicle
Base = Mild	54/81 (66.7%)	57/90 (63.3%)	29/79 (36.7%)	5/29 (17.2%)
Base = Moderate	171/311 (55%)	101/297 (34.0%)	62/300 (20.7%)	8/99 (8.1%)
Base = Severe	48/89 (53.9%)	17/85 (20.0%)	15/92 (16.3%)	3/28 (10.7%)
Base = Very Severe	3/9 (33.3%)	1/4 (25%)	1/9 (11.1%)	0/1 (0%)
Total	276/490 (56.3%)	176/476 (37.0%)	107/480 (22.3%)	16/157 (10.2%)

Source: Page 108 of MCB-0003 Study Report (5.3.5.1.1 MCB-0003-INT Appendix II).

Comment: The rates of Controlled Disease (success) for subjects who had baseline disease of severity of "moderate" and "severe" were similar. The rate of success was lowest for subjects who had very severe disease at baseline (although even in this group, one third of subjects had a successful outcome). The rate of success was highest for subjects with mild disease at baseline; however, in the applicant's analysis it was easier for these subjects to attain success, as only one grade of improvement was required.

Percent Change in PASI from Baseline to End of Treatment Investigator's Global Assessment at Baseline (Source: Applicant Table 21)

Baseline Global	Combination (n=490) #(%)	Calcipotriol (n=480) #(%)	Betamethasone (n=476) #(%)	Vehicle (n=157) #(%)
Mild Disease				
Mean	-68.5	-36.0	-59.8	-19.3
SD	25.4	37.2	30.5	31.7
Minimum	-100	-100	-100	-100
Maximum	2	81	13	30
Number	81	79	90	29
Moderate Disease				
Mean	-70.5	-47.1	-56.5	-21.4
SD	27.2	29.4	30.7	32.6
Minimum	-100	-100	-100	-94
Maximum	38	31	83	67
Number	311	300	297	99
Severe Disease				
Mean	-76.3	-48.6	-56.1	-30.3
SD	20.7	28.0	25.9	38.7
Minimum	-100	-100	-99	-91
Maximum	0	50	17	72
Number	89	92	85	28
Very Severe Disease				
Mean	-75.6	-73.5	-79.2	-39.5
SD	15.0	22.2	14.8	-
Minimum	-90	-98	-100	-40
Maximum	-39	-25	-68	-40
Nimber	9	9	4	1

Comment: The percent change in PASI trended towards progressive increase with increasing baseline severity of disease. The percentage change in PASI was similar for subjects who had mild and moderate disease at baseline and for subjects who had severe and very severe disease at baseline in the combination group.

Subgroup Analyses

Controlled Disease at End of Treatment by Gender (Source: Applicant Table 26)

	Combination (n=490) #(%)	Calcipotriol (n=480) #(%)	Betamethasone (n=476) #(%)	Vehicle (n=157) #(%)
Female	98 (53.8)	38 (19.3)	72 (38.9)	7 (10.1)
Male	178 (57.8)	69 (24.4)	104 (35.7)	9 (10.2)

Rates for Controlled Disease were generally similar for each treatment group for both genders.

Controlled Disease at End of Treatment by Ethnic Origin (Source: Applicant Table 27)

	Combination (n=490) #(%)	Calcipotriol (n=480) #(%)	Betamethasone (n=476) #(%)	Vehicle (n=157) #(%)
Caucasian	269 (56.9)	103 (22.3)	171 (36.8)	16 (10.5)
Black	1 (33.3)	2 (40.0)	1 (100.0)	-
Asian	5 (45.5)	2 (15.4)	3 (37.5)	0 (0.0)
Other	1 (33.3)	0 (0.0)	1 (50.0)	0 (0.0)

Comment: The results in Asians showed consistency with the other analyses, i.e. the combination was superior to each monad and vehicle, and rates were highest in the combination and betamethasone groups. When ethnic groups are compared, for the combination group, only Caucasians had a higher rate of subjects who had Controlled Disease versus Non-controlled Disease; however, the numbers of non-Caucasians are far too few to attach any significance to this observation.

Controlled Disease at End of Treatment by Age Group (Source: Applicant Table 28)

	Combination (n=490) #(%)	Calcipotriol (n=480) #(%)	Betamethasone (n=476) #(%)	Vehicle (n=157) #(%)
≤35 years old	59 (51.3)	15 (16.5)	38 (36.2)	3 (10.0)
36 to 50 years old	92 (55.1)	38 (21.1)	56 (36.1)	4 (8.3)
51 to 60 years old	62 (57.9)	24 (24.5)	39 (36.4)	4 (10.3)
Over 60 years old	63 (62.4)	30 (27.0)	43 (39.4)	5 (12.5)

Comment: For subjects who received treatment with the combination product, rates for Controlled Disease progressively increase with increase in age group.

SUPPORTIVE STUDIES

The applicant is principally relying on four studies as providing supportive evidence of efficacy. These studies included treatment arms in which subjects received once daily dosing for four weeks (as was evaluated in the pivotal trial, MCB 0003 INT):

- MCB 0002 INT
- MCB 0001 INT
- MCB 9905 INT
- MCB 0201 FR

NOTE: Only the statistical reviewers' efficacy results will be presented for the supportive studies.

MCB 0002 INT: Different Treatment Regimes with Calcipotriol/Betamethasone Ointment and Calcipotriol Ointment in Psoriasis Vulgaris (February 6, 2001-August 29, 2001)

Objective: The stated primary objective was to compare the clinical efficacy of calcipotriol (as the marketed product Dovonex®) twice daily for 12 weeks in patients with psoriasis vulgaris with each of the following two treatment regimens:

- the combination product once daily for 8 weeks, followed by calcipotriol once daily for 4 weeks.
- the combination product once daily for 4 weeks, followed by 8 weeks of treatment with calcipotriol once daily on weekdays (5 days) and the combination product once daily on the weekends (2 days).

However, while total treatment durations were 12 weeks (irrespective of the treatment arm), the primary objective was to compare the efficacy after 8 weeks of treatment.

Study Design: This was an international, multi-center, randomized, partly double-blind, active-controlled, three arm parallel group study.

Subjects were assessed on inclusion and after 1, 2, 4, 5, 8, and 12 weeks. The primary response criteria were

- The percentage change in PASI from baseline to end of 8 weeks of treatment
- The proportion of patients with Controlled Disease (defined as absence of disease or very mild disease) according to the Investigator's Global Assessment of Disease Severity at end of 8 weeks of treatment.

Inclusion Criteria included:

- Clinical diagnosis of psoriasis vulgaris amenable to treatment with a maximum of 100g of topical medication per week, involving arms and/or trunk and/or legs.
- A minimum PASI score for extent of 2 in at least one body region (i.e. psoriasis affecting at least 10% of arms, and/or 10% of trunk, and/or 10% of legs).
- An investigator's global assessment of disease severity of mild, moderate, severe, or very severe disease.

Exclusion Criteria included:

- Current diagnosis of unstable forms of psoriasis in the area to be treated with study medication, including guttate, erythrodermic, exfoliative or pustular psoriasis.

Comment: The above inclusion and exclusion criteria were the same as for the pivotal study, MCB 0003 INT.

Investigators' Global Assessment of Disease Severity

Level	Definition
Absence of Disease	The disease is controlled. No evidence of redness, no evidence of infiltration, and no evidence of scaling
Very Mild Disease	The disease is controlled, but not entirely cleared. The overall clinical picture is consisting of lesions with some discoloration with absolutely discrete infiltration.
Mild Disease	The overall clinical picture is consisting of lesions with light red coloration, slight infiltration and a fine, thin scale layer
Moderate Disease	The overall clinical picture is consisting of lesions with red coloration, a moderate infiltration and a moderate, somewhat coarse scale layer
Severe Disease	The overall clinical picture consisting of lesions with very red coloration, thick infiltration and a severe, coarse thick scale layer
Very Severe Disease	The overall clinical picture is consisting of lesions with extreme deep red coloration, very thick infiltration and a very severe, coarse thick scale layer

Comment: This was the only supportive study to employ a static global severity scale. The scale is very similar to that used in study MCB 0003 INT. The principle difference is that the term "infiltration" in the above scale is substituted by "thickness" in the scale used in MCB 0003 INT. However, these terms may connote different things.

RESULTS

The study enrolled 972 subjects, and randomization was 1:1:1 (322:323:327). Subjects received up to 12 weeks of treatment as needed with two week follow-up at the end of study if there were ongoing adverse drug reactions. Mean PASI scores at baseline were similar between treatment groups: 10.3 for the combination/calcipotriol (8 weeks/4weeks) group, 10.4 for the combination/calcipotiol (intermittent use) and 10.9 for the calcipotriol group. Most subjects in all treatment groups had disease of moderate severity at baseline (on the global scale).

Source: Statistical Reviewer's Table A.4.2.3*
Investigator Global Assessments Proportion with Controlled Disease

Invest. Assess. # resp/N (%)	Week 2[1]	Week 4	Week 4 ITT-LOCF
Calc BID 12wks	47/323 (14.8 %)	87/305 (28.5 %)	89/326 (27.3 %)
Comb QD 4wks	104/319 (32.6 %)	165/314 (52.5 %)	166/322 (51.6 %)
Comb QD 8wks	100/318 (31.4 %)	163/314 (51.9 %)	165/320 (51.6 %)
Calc – Comb 4wks p-value			<0.0001
Calc – Comb 8wks p-value			<0.0001

*In the statistical review, this table also includes results at Weeks 8 and 12

Source: Statistical Reviewer's Table A.4.2.1*
Percent Change from Baseline and Change from Baseline

Mean (SD)	Treatment	Week 0[1]	Week 2	Week 4	Week 4* ITT-LOCF
% Change	Calc BID 12 wks		-45.7 (23.2)	-57.2 (24.0)	-55.0 (25.7)
	Comb QD 4 wks		-58.1 (23.4)	-68.7 (23.6)	-67.6 (24.7)
	Comb QD 8 wks		-58.2 (21.8)	-70.3 (21.2)	-69.8 (21.8)
	Calc – Comb 4wks p-value		12.1 (1.7) < 0.0001	11.3 (1.7) < 0.0001	12.4 (1.7) < 0.0001
	Calc – Comb 8wks p-value		12.3 (1.7) < 0.0001	13.0 (1.7) < 0.0001	14.6 (1.7) < 0.0001
Change	Calc BID 12wks	10.3 (5.8)	-5.0 (3.8)	-6.3 (4.6)	-6.2 (4.7)
	Comb QD 4wks	10.4 (5.9)	-6.1 (4.1)	-7.2 (4.5)	-7.1 (4.8)
	Comb QD 8wks	10.3 (5.6)	-5.9 (3.6)	-7.2 (4.7)	-7.2 (4.5)
	Calc – Comb 4wks p-value	0.53 (0.42) 0.2060	1.01 (0.28) 0.0003	0.77 (0.34) 0.0237	0.94 (0.34) 0.0053
	Calc – Comb 8wks p-value	0.61 (0.42) 0.1536	0.88 (0.28) 0.0014	0.83 (0.34) 0.0145	1.10 (0.33) 0.0011

*In the statistical review, this table also includes results at Weeks 8 and 12

Comment: 1) Both combination arms were superior to calcipotriol at Week 4 on the Investigator's Global Assessment scale (Controlled Disease), and the difference between each combination group and calcipotriol was statistically significant. 2)Both combination arms were superior to calcipotriol in the percentage change in PASI at Week 4, and the difference between each combination group and calcipotriol was statistically significant. The results for the percentage change in PASI at Week 4 for both combination groups were similar to each other (-67.6 and -69.8) and generally similar to the results in the pivotal study (-71.3).

MCB 0001 INT: "Calcipotriol/Betamethasone Once Daily versus Tacalcitol Once Daily in Psoriasis Vulgaris" (September 19, 2001 to January 28, 2002)

Objective(s): The primary objective was to compare the clinical efficacy of the combination product used once daily with tacalcitol ointment used once daily in subjects with psoriasis vulgaris after up to four weeks of treatment. Per Section 6.2 of the protocol, "Tacalcitol

ointment has been shown to be safe and effective for treatment of psoriasis and is currently available on prescription in many European countries." Tacalcitol ointment is described as a vitamin D_3 analogue (Section 9.2 of the protocol).

Study Design: The study was multi-centered, prospective, randomized, double-blind, and active-controlled. Subjects were randomized to one of two treatment groups:

- four weeks treatment with the combination product applied once daily followed by four weeks treatment with Dovonex® or
- eight weeks treatment with Tacalcitol ointment applied once daily (marketed as [redacted]

Comment: Per Section 9.3 of the protocol, the treatment regimen of four weeks of treatment with the combination product followed by four weeks of Dovonex® was chosen because the combination product was registered in Denmark for 4 weeks BID treatment, while the recommended treatment duration for tacalcitol is 8 weeks. According to Section 9.3 of the protocol, "tacalcitol treatment is recommended for an 8 weeks (sic) period." Therefore, results from comparative efficacy assessment at four weeks are difficult to interpret, as it is not clear that efficacy has been established for tacalcitol at four weeks.

Subjects were assessed on inclusion, and after 2, 3, 4, and 8 weeks.

Main Inclusion Criteria:

1. clinical diagnosis of psoriasis vulgaris amenable to treatment with a maximum of 50g of topical medication per week, involving arms and/or trunk and/or legs
2. A minimum PASI score for **extent** of 2 in at least one body region (i.e. psoriasis affecting at least 10% of arms, and/or 10% of trunk, and/or 10% of legs).

Comment: These Inclusion Criteria are similar to those in the pivotal trial, with the difference being that for this study, the extent of psoriasis was to be amenable to treatment with a maximum of 50g of medication (it was 100g in the pivotal trial).

Exclusion Criteria included:

- Current diagnosis of unstable forms of psoriasis in the area to be treated with study medication, including guttate, erythrodermic, exfoliative or pustular psoriasis.

Primary Efficacy Criterion: the percentage change in PASI from baseline to up to four weeks with the combination product and with talcalcitol

RESULTS

The study enrolled 501 subjects: 249 in the combination + calcipotriol group and 252 in the tacalcitol group. Mean baseline PASI scores were comparable in both treatment groups: 9.7 in the combination group and 9.9 in the tacalcitol group. Mean duration of disease was 20.2 years in the combination group and 18.6 years in the tacalcitol group.

Comment: The previously-discussed Studies MCB 0003 INT (pivotal) and MCB 0002 INT: stipulated that subjects have disease of an extent that was treatable with up to a maximum of 100g of study medication. Mean PASI scores for the four treatment groups in MCB 0003 INT were: 9.9, 10.4, 9.8 and 9.5. Mean PASI scores in MCB 0002 INT were 10.3, 10.4, and 10.9. Thus, mean PASI scores at baseline were similar in the three studies, despite the fact that in study MCB 0001 INT, maximum amount of study medication to be used was half as much as in the other two studies (50g versus 100g). This could suggest a population amenable to topical therapy is selected based more on the clinical assessment alone, rather than the clinical assessment and the maximum amount of medication to be used in a given period. If the latter were the case, it would seem that mean PASI scores might have been higher where 100g of medication per week was allowed.

Efficacy

Statistical Reviewer's Table A.4.1.1 Percent Change from Baseline and Change from Baseline

	Week 0[1]	Week 2	Week 2 ITT-LOCF	Week 4	Week 4* ITT-LOCF
%Chng Comb (SD)[2]		-50.5 (26.1)	-48.6 (27.3)	-66.7 (27.8)	-65.0 (29.1)
Tacal (SD)[2]		-24.5 (27.3)	-23.9 (27.2)	-35.0 (40.1)	-33.3 (39.4)
Diff (SE)[3]		-25.7 (2.3)	-24.3 (2.3)	-30.7 (3.1)	-31.5 (3.0)
Test of diff[4]				< 0.0001	< 0.0001
Change Comb (SD)	9.7 (6.1)	-4.8 (3.9)	-4.7 (3.9)	-6.4 (4.7)	-6.2 (4.7)
Tacal (SD)	9.9 (6.0)	-2.4 (2.9)	-2.3 (2.9)	-3.4 (4.4)	-3.2 (4.3)
Diff (SE)	-0.2 (0.5)	-2.4 (0.3)	-2.3 (0.3)	-2.8 (0.4)	-2.9 (0.4)
Test of diff				< 0.0001	< 0.0001

*- Percent change at Week 4 in ITT-LOCF population is primary endpoint.
[1]- Week 0 nominal change values correspond to baseline PASI score.
[2]- SD denotes simple standard deviation of treatment PASI score
[3]- SE denotes standard error of difference adjusted for sites.
[4]– Test of treatment differences adjusted for sites

Comment: The percentage change in PASI at Week 4 for the combination group was similar to the results from the studies MCB 0003 INT and MCB 0002 INT. The combination treatment was superior to tacalcitol at Week 4, and the difference was statistically significant. However, assessment of tacalcitol effect at four weeks does not reflect recommended conditions of use for this product (per the applicant, recommended treatment is eight weeks). Therefore, a demonstration of superiority of the combination product at four weeks may have limited utility, as efficacy of tacalcitol at four weeks may not be established.

MCB 9905 INT: Calcipotriol/Betamethasone Once and Twice Daily in Psoriasis Vulgaris (January 18, 2000-August 2, 2000)

Objective(s): The primary objectives were to compare the clinical efficacy, as assessed by the percentage reduction in PASI after four weeks of treatment in:

- combination product used once daily vs vehicle
- combination product used once daily versus Dovonex® twice daily

- combination product used once daily versus combination product (evening) and vehicle (morning)

Study Design: This was an international, multicenter, randomized, double-blind vehicle-controlled study with four treatment arms.

- the applicant's combination product dosed once daily (evening) and vehicle used once daily (morning)
- the combination product used twice daily
- Dovonex® ointment used twice daily
- vehicle used twice daily

Main Inclusion Criteria:

1. A clinical diagnosis of psoriasis vulgaris amenable to treatment with topical medication, involving arms and/or trunk and/or legs
2. A minimum PASI score for **extent** of 2 in at least one body region (i.e. psoriasis affecting at least 10% of arms, and/or 10% of trunk, and/or 10% of legs).

Exclusion Criteria included:

- Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis, atopic dermatitis, seborrhoeic dermatitis or other inflammatory skin disease.

Comment: These inclusion and exclusion criteria are generally the same as for the previously-discussed studies; however, the amount of study medication to be used was not specified.

RESULTS

A total of 828 subjects were randomized: 152 to combination once daily, 237 to combination twice daily, 231 to calcipotriol, and 208 to vehicle. Mean PASI scores were similar across treatment groups: 9.9 for the once daily group, 10.6 for the twice daily group and 10.4 for the vehicle group.

Efficacy Results

Statistical Reviewer's Table A.3.1.1 Efficacy Results for Percent Reduction in PASI

	Dovobet® QD	Dovobet® BID	Calcipotriol BID	Vehicle BID
N	152	237	231	208
Mean (SD)	67.7% (24.7%)	72.9% (22.4%)	57.7% (29.4%)	26.4% (31.2%)
p-value[1]		$p = .0208$[2]	$p = .0005$	$p < .0001$

[1] p-value is based upon reviewer's analysis using ANOVA with design variables for treatment and reviewer's definition of pooled center (this is defined as in Study MCB-0003-INT).
[2] Dovobet® BID is significantly better than Dovobet® QD.

Comment: A question of the contribution to efficacy by vehicle might be raised in the once daily treatment arm. However, the percentage change in PASI for this arm (67.7%) is similar to the results reported in the other trials for once daily dosing (and there is no issue of a vehicle effect in those studies).

MCB 0201 FR: "Effect of Calcipotriol/Betamethasone Dipropionate Ointment Compared to Betamethasone Dipropionate Ointment on the HPA Axis in Patients with Psoriasis Vulgaris (April 15, 2003-January 13, 2004)

Objective: The stated objective of the study was to compare the effect of once daily use of the combination product with that of Diprosone® ointment, a marketed betamethasone dipropionate ointment, on the hypothalamic-pituary-adrenal axis (HPA axis) in subjects with psoriasis vulgaris.

Comment: This was a safety study, and is discussed in more detail in Section 7.1.12, "Special Safety Studies." Assessment of efficacy was not stated to be an objective of the study (Section 7 of the protocol).

Study design: single-center, prospective, randomized, active-controlled, double-blind, two-arm, parallel group

Subjects presented for four visits: two during screening (Visits 1 and 2) and two during the treatment phase on Day 0 (Visit 3) and Day 28 (Visit 4; end-of-treatment). The PASI score was determined at baseline and at the end of treatment.

Main Inclusion Criterion

Patients with psoriasis vulgaris on trunk and/or limbs amenable to topical treatment, with lesions involving between 15 to 30% of the body surface area on trunk and/or limbs

Main Exclusion Criterion:

Erythrodermic, exfoliative or pustular psoriasis

Comment: This study did not exclude guttate psoriasis.

RESULTS

The study enrolled 24 subjects. The mean PASI at baseline was 11.9 for the combination group and 14.3 for the Diprosone® arm.

Statistical Reviewer's Table A.4.5.1 Results on PASI Score

	Baseline		Week 4		
	N	PASI	PASI	Change in PASI	% Change
Combination	12	11.9	3.7	8.2	69.8
Diprosone	12	14.3	5.0	9.3	63.6

Comment: These results are similar to those reported the pivotal study and the other supportive studies.

6.1.5 Clinical Microbiology

This section is not applicable.

6.1.6 Efficacy Conclusions

The combination product was adequately demonstrated to be effective in the treatment of psoriasis vulgaris.

Efficacy in the Pivotal Trial: MCB 0003 INT

Efficacy of the combination product was adequately demonstrated in study MCB 0003 INT. The combination product was superior to each monad and to vehicle in both primary analyses. Specifically, the combination product was superior to all comparators in the proportion of subjects with "Controlled Disease" as assessed on a static global severity scale, the Division's recommended approach to primary efficacy assessment. ("Controlled Disease" was defined as subjects with "absence of disease" or "very mild disease" at efficacy assessment). The results were highly statistically significant ($p < .0001$). The level of significance did not change when an analysis was performed in which subjects with mild disease at baseline were required to improve to "absence of disease" to have been considered a success, i.e. two-grade improvement on the global severity scale. Two-grade improvement on the global scale is a more convincing demonstration of efficacy because of the linearity of the global scale. The rates of Controlled Disease for subjects who had baseline disease of "moderate" and "severe" were similar. The rate of success was lowest for subjects who had "very severe" disease at baseline (although even in this group, approximately one third of subjects had a successful outcome).

The combination product was also superior to all comparators in the percent change in PASI at efficacy assessment, and the results were again highly statistically significant. PASI was the applicant's chosen primary endpoint.

In both primary analyses, rates were consistently higher in the combination and betamethasone arms. This could suggest that efficacy of the combination product is driven by the betamethsone component (although the contribution of calcipotriol to efficacy was adequately demonstrated).

The trial was appropriately designed for the fixed combination product, and was in compliance with 21 CFR 300.50.

Efficacy in the Supportive Studies

Supportive evidence of efficacy was provided from four additional trials: MCB 0002 INT, MCB 0001 INT, MCB 9905 INT, and MCB 0201 FR. The patient populations and the inclusion and exclusion criteria were generally similar across studies. Efficacy was assessed on a static global severity scale and by the PASI in study MCB 0002 INT. In the remaining studies, efficacy was assessed using the PASI. Per the statistical review, "should efficacy based upon

PASI scores show strong statistical significance it is likely that efficacy would also have been established using IGA as an endpoint."

In study MCB 0002 INT, both treatment arms in which the combination product was dosed once daily were superior to the comparator, calcipotriol, in the percent change in PASI at Week 4, and the difference between each combination group and the comparator was statistically significant. Also, the results for the percent change in PASI at Week 4 for both combination groups were similar to each other and generally similar to the results in the pivotal study. Both combination arms were superior to calcipotriol at Week 4 on the Investigator's Global Assessment scale (Controlled Disease), and the difference between each combination group and calcipotriol was statistically significant.

In study MCB 0001 INT, the combination treatment was superior to the comparator, tacalcitol, at Week 4, and the difference was statistically significant. The utility of the demonstration of superiority of the combination product at four weeks is brought into question because the efficacy of tacalcitol at four weeks may not be established (the recommended treatment is eight weeks). However, the percent change in PASI at Week 4 for the combination group was similar to the results from the studies MCB 0003 INT and MCB 0002 INT.

In study MCB 9905 INT, the combination product dosed once daily was superior to calcipotriol and vehicle. A question might be raised arm regarding a possible contribution to efficacy by use of vehicle once daily. However, once again, the percent change in PASI for the combination arm (once daily) is similar to the results reported in the other trials for once daily dosing.

Study MCB 0201 FR was primarily a safety study; however, the percent change in PASI at Week 4 following once daily treatment with the combination product was similar to the results from the pivotal study and the other supportive studies.

Thus, PASI results in the supportive studies were generally consistent with each other and with those from the pivotal trial.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Twenty-one studies were conducted with the combination ointment and are included in the safety database. All of the clinical studies conducted with the combination ointment were included in the integrated analysis of safety. The studies in subjects with psoriasis were divided into "Core Studies and "Non-Core" studies.

The applicant considered 17 of the 21 studies to be Core Studies, as the populations in those studies were representative of the applicant's proposed target population. Core Studies were further divided into "Short-Term" and "Long-Term" core studies. A total of 2,448 subjects with psoriasis vulgaris received treatment with the combination ointment in the Short-Term Core Studies (treatment duration up to 12 weeks). Of the 2,448 subjects, 1,539 received once daily treatment, and 909 received twice daily treatment. One study is considered to be a Long-Term Core Study, and subjects in this study received once daily treatment for up to 52 weeks.

The applicant classified four studies as "Non-Core," and 68 subjects are in this category (23 with contact dermatitis; 45 with psoriasis). Two of these studies included other topical

medications in which the combination ointment served as an active control for intra-individual comparison in subjects with psoriasis (studies MBL 0201 FR and MHO 0201 FR). Two other intra-individual comparison studies were conducted in conditions other than psoriasis vulgaris: MCB 0207 DK (nickel-induced contact dermatitis) and MCB 0303 INT (pustulosis palmoplantaris). MCB 0303 INT was ongoing as the Summary of Clinical Safety was being finalized; however, all serious adverse events that had been reported to the applicant were included in the marketing application.

A total of 490 healthy volunteers were exposed to the combination ointment, 155 of whom received one application and 335 of whom received 3-to 4-week exposures.

A total of 207 subjects received once daily treatment (as needed) with the combination ointment in the long-term study (52 weeks). The other two treatment arms in the long-term study were alternating 4-week courses of the combination ointment and calcipotriol ointment and combination ointment for 4 weeks followed by 48 weeks of calcipotriol ointment.

Inclusion/exclusion criteria were similar across studies conducted in subjects with psoriasis. Main inclusion criteria were: psoriasis vulgaris involving trunk and/or limbs amenable to topical treatment with extent of at least 10% in at least one of the body regions (trunk, arms or legs). In the long-term study, up to 30% of the body surface area was to have been treated, and in a subset selected for adrenal function testing, a minimum of 10% of the body surface area was to have been treated. In a hypothalamic-pituitary-adrenal (HPA) axis study, extent of disease was to have been between 15 and 30% of the body surface area. Investigator's Global Assessment of Disease Severity was recorded in three studies and was required to be at least mild in two (MCB 0002 INT and MCB 0003 INT) or moderate (MCB 0102 INT). Females who had a negative pregnancy test and were using adequate contraception were included.

Main exclusion criteria were guttate (except MCB 0102 INT and MCB 0201 INT), erythrodermic, exfoliative or pustular psoriasis, systemic treatment or phototherapy within a specified time period (varied but was up to six weeks before start of study), topical treatment of trunk or limbs up to two weeks before study start, use of very potent topical corticosteroids, use of other medication that could affect response to study treatment or changes in concomitant medications that could influence the disease. Subjects with known or suspected abnormalities in calcium homeostasis were excluded from all studies. Pregnant or breast feeding women were excluded.

In most studies, cutaneous adverse events were recorded as lesional/perilesional (generally ≤ 2 cm from the lesional border) or distant (> 2 cm from the lesional border).

In the integrated analyses, common adverse events were defined as those occurring in at least 1% of subjects in at least one treatment group. For presentation of data from the long-term study and from the individual studies in Appendix Table 9 (2.7.4.7), the applicant defined common adverse events as those occurring in at least 2% of subjects in at least one treatment group.

Adverse events selected for further review by the applicant were skin atrophy, teleangiectasia, ecchymosis, purpura, skin hypo- or depigmentation, hyperpigmentation, rash pustular, skin papilloma, folliculitis, furuncle, skin striae, hypertrichosis, cellulitis, cushingoid, hypothalamic-pituitary disorders, blood calcium increased, blood calcium abnormal and hypercalcemia. These events were thought to relate directly to the pharmacologic effects of the active ingredients in the study product.

In the Long-Term Core Study, a panel of three independent dermatologists was responsible for identification of events that might reflect the effects of long-term use of topical corticosteroids. Their assessment was based on review of blinded data.

7.1.1 Deaths

Two deaths occurred in the applicant's development program. Neither subject received treatment with the combination product, and neither death was considered by the investigator to have been related to study treatment:

- A 65-year-old male in the calcipotriol group died due to a myocardial infarction on [redacted] The subject had a history of hypertension, hypercholesterolemia, psoriatic arthritis, glaucoma and gastro-esophageal reflux. He received study treatment from March 30, 2001 until April 21, 2001.
- A 49-year-old female in the tacalcitol (a vitamin D analogue not marketed in the United States) group died due to cardiac arrest. She received study treatment from October 10, 2001 until November 26, 2001. On [redacted], she experienced headache and aggression and was hospitalized with an apparent evolving right hemiparesis. A CT-scan revealed areas of decreased attenuation. She became more unresponsive. A magnetic resonance imaging scan showed extensive infarction in the brain stem. She developed aspiration pneumonia and died on [redacted]

7.1.2 Other Serious Adverse Events

In the Short-Term Core Studies, a total of 16 serious adverse events were reported by 15 combination-treated subjects (0.6%), 4 subjects in the vehicle group (0.9%), 29 subjects in the calcipotriol group (0.9%) and 6 subjects in the betamethasone group (0.5%).

Three cases were of possible or probable relationship to study treatments:

- two cases in the combination group (one case of "cushingoid" in a subject receiving twice daily treatment and one case of subcutaneous abscess)
- one case of HPA axis deficiency in the betamethasone group

Serious Adverse Events by SOC[+] and Preferred Term: Short-Term Core Studies* by Treatment Group

System Organ Class Preferred Term	Number (%) of subjects with Serious Adverse Event			
	Combination N=2448	Vehicle N=470	Calcipotriol N=3197	Betamethasone N=1164
Any Serious Adverse Event	15 (0.6)	4 (0.9)	29 (0.9)	6 (0.5)
Cardiac Disorders				
Angina pectoris	2 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	3 (0.1)	1 (0.1)
Tachycardia	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders				
Deafness unilateral	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Endocrine disorders				
Cushingoid	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothalmo-pituitary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Eye disorders				
Lens dislocation	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Gastrointestinal disorders				
Constipation	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Intestinal obstruction	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mouth ulceration	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain lower	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Ascites	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Colitis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Ileitis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Subileus	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
General disorders and administration site conditions				
Chest pain	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Hepatobiliary disorders				
Cholelithiasis	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations				
Pilonidal abscess	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subcutaneous abscess	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Viral infection	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Infection	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Postoperative infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Injury, poisoning and procedural complications				
Upper limb fracture	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Accident	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Contusion	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Facial bone fractures	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Haemothorax	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Injury	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Joint sprain	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Meniscus lesion	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Muscle injury	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Rib fracture	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Spinal fracture	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthritis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Pharyngeal cancer stage unspecified	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Nervous system disorders				
Cerebrovascular accident	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphasia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Brain stem infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular disorder	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Grand mal convulsion	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions				
Pregnancy	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Psychiatric disorders				
Confusional state	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bipolar disorder	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Depression	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Renal and urinary disorders				
Renal insufficiency	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				

Chronic obstructive airways disease exacerbated	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Surgical and medical procedures				
Cholecystectomy	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders				
Lymphoedema	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)

+System Organ Class
*Applicant's Appendix Table 3 (in Summary of Clinical Safety Section 2.7.4)

Serious Adverse Events by SOC+ and Preferred Term: Short-Term Core Studies for Combination Treated Subjects by Treatment Frequency*

System Organ Class Preferred Term	Number (%) of subjects with Serious Adverse Event	
	Combination once daily N=1539	Combination twice daily N=909
Any Serious Adverse Event	11 (0.7)	4 (0.4)
Cardiac Disorders		
Angina pectoris	2 (0.1)	0 (0.0)
Endocrine disorders		
Cushingoid	0 (0.0)	1 (0.1)
Gastrointestinal disorders		
Constipation	1 (0.1)	0 (0.0)
Mouth ulceration	1 (0.1)	0 (0.0)
Intestinal obstruction	0 (0.0)	1 (0.1)
Hepatobiliary disorders		
Cholelithiasis	1 (0.1)	0 (0.0)
Infections and infestations		
Pilonidal abscess	1 (0.1)	0 (0.0)
Subcutaneous abscess	1 (0.1)	0 (0.0)
Viral infection	1 (0.1)	0 (0.0)
Injury, poisoning and procedural complications		
Upper limb fracture	1 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	0 (0.0)	1 (0.1)
Nervous system disorders		
Cerebrovascular accident	1 (0.1)	0 (0.0)
Dysphasia	1 (0.1)	0 (0.0)
Psychiatric disorders		
Confusional state	1 (0.1)	0 (0.0)
Surgical and medical procedures		
Cholecystectomy	0 (0.0)	1 (0.1)

+System Organ Class
*Applicant's Table T35 (in Summary of Clinical Safety Section 2.7.4)

Of the 16 serious adverse events that were reported by combination-treated subjects in the Short-Term Core Studies, 12 were reported by 11 subjects who received once daily treatment, and 4 were reported by 4 subjects who received twice daily treatment. Narratives for these 16 combination-treated subjects follow:

MCB 0001 INT CRF 1075: Angina Pectoris. A 51-year-old-male received study medication from November 5 until November 30, 2001. On December 2, he experienced new onset angina. A myocardial infarction screen was negative, but an exercise test was positive. He was treated

with atenolol, aspirin and glyceryl trinitrate. He was discharged on [redacted] with outpatient follow-up. He withdrew from the study. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 0001 INT CRF 1323: Abdominal pain. An 80-year-old female (history of hypertension, angina pectoris and depression) received study medication from October 11 until November 6, 2001. She was hospitalized on [redacted] due to abdominal pain; she also presented with constipation. She was treated with an enema; the constipation resolved. She was discharged on [redacted] and resumed study drug on the same day (it was not used during the hospitalization as she had not taken it with her). Investigator assessment: "not related" to study medication. *The reviewer agrees however, constipation can be a manifestation of hypercalcemia.*

MCB 0001 INT CRF 1365: Cholelithiasis. A 53-year-old female (history of chronic abdominal pain) used study medication from November 8, 2001 until January 3, 2002. She was referred for hepatic echography which showed biliary stones. She was hospitalized from [redacted] 2001 for cholecystectomy. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 0002 INT CRF 6130: Confusional state. A 97-year-old male received study medication from May 3 until May 27, 2001. He was hospitalized with confusion on [redacted] and was withdrawn form the study. Investigator assessment: "not related" to study medication. *The reviewer agrees; however, altered mental status can be seen with hypercalcemia and corticosteroids.*

MCB 0002 INT CRF 6196: Viral infection. A 25-year-old male received study medication from April 3 until July 8, 2001. He was hospitalized on [redacted] because of severe headaches and suspected viral meningitis. He "recovered" on May 10, 2001. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 0002 INT CRF 6556: Upper limb fracture. A 56-year-old female received study medication form March 30 until May 6, 2001. She fell and fractured her arm on May 6. She withdrew form the study on June 1 as she was unable to apply study medication. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 0002 INT CRF 6682: Angina pectoris. A 59-year-old male (history of angina) received study medication from March 29 until June 20, 2001. He underwent planned stent placement on April 24 and on April 28, experienced worsening of his angina. He was hospitalized or [redacted] and on May 7 was found to have a "plugged" posterior artery. He was discharged on [redacted] Study product was discontinued during the hospitalizations. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 0003 INT CRF 5732: Pilonidal abscess. A 30-year-old female received study medication form April 6 through May 8, 2001. On May 7, she was diagnosed with a pilonidal abscess. She was admitted for drainage on [redacted] nd had the procedure on May 9. Study medication was stopped on May 8. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 0201 FR CRF 016: Subcutaneous abscess. A 41-year-old male with a history of pneumopathy received study medication from October 14 until November 10, 2003. He was hospitalized on [redacted] or pain due to an abscess on buttock. Surgery was performed, and he was discharged on [redacted] Investigator assessment: initially "not related" to study medication, but changed to "possible related" after becoming aware of the HPA axis suppression in two betamethasone-treated subjects.

MCB 9904 INT CRF 6555: Cushingoid. A 45-year-old male with a 22-year history of widespread psoriasis began study medication on March 7, 2000. At inclusion, his psoriasis was "widespread," "oozing/crusting," "severely itching (*sic*)." Pruritus was treated with Zyrtec. He used 92.4 g of study medication in the first week. On March 13, slight improvement was noted in the efficacy assessment; however, pruritus had resolved, and Zyrtec was discontinued. In the second week, he used 88.5 g of ointment. Marked improvement was noted on March 21, and the investigator noted "mild" facial edema at this visit, which the subject said had gradually developed from March 14. On March 23, his blood pressure was 180/114, and his white cell count was elevated at 9.5 x 10^9/L (upper limit of reference range was 9.0 x 10^9/L). Hematology values were otherwise within the reference range as were potassium, sodium, glucose, ACTH and serum cortisol. The investigator considered the subject to be at high risk for "rebound phenomenon/Addison-like symptoms" if study medication were stopped abruptly. The subject continued study medication until March 28. In this third week, he had applied up to 100g of study medication. "Marked improvement" in psoriasis was noted on March 29, and "moon face-like" appearance persisted; he was withdrawn from the study that same day. He was begun on Locoid cream BID. At follow-up on April 4, psoriasis was beginning to flare; Locoid was continued. On April 13, "moon face" was no longer observed. Investigator assessment: "probably related" to study medication.

Comment: The subject's adrenal status at the beginning of treatment was not known; however, given his long history of psoriasis, it is possible (even likely) that he had received corticosteroids at some point over the course of his disease. Also, from the history provided, factors which would have increased his risk for systemic exposure from the topical product include the widespread extent of disease and a compromised epidermal barrier. It is noted that the subject used amounts of medication within the range of what was proposed by the applicant, i.e. maximum of 100g per week. No other signs or symptoms were described, e.g. weight gain; his glucose was normal. An elevation in blood pressure was reported, but only this single isolated report. Formal testing of adrenal function was not done. The reviewer agrees that the events were probably related to study medication.

MCB 9905 INT CRF 8100: Arthralgia. A 49-year-old male received study medication from 21 April until May 18, 2000. He experienced severe arthralgia beginning on April 22. He was

hospitalized on —— and discharged on —— He was "on treatment and without pain" on May 12. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 9905 INT CRF 8303: Cholecystectomy. A 59-year-old male (history of cholelithiasis) received study medication from May 10 until June 8, 2000. On ——, he underwent laparoscopic cholecystectomy. He was discharged the following day with no complications. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 9905 INT CRF 8608: Intestinal obstruction. A 59-year-old male with (history of retroperiotoneal fibrosis) received study medication from April 8 until May 8, 2000. On April — he "suffered from" intestinal obstruction with abdominal pain and nausea. He was hospitalized and treated with intravenous fluids. The obstruction resolved spontaneously. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 9905 INT CRF 8885: Cerebrovascular accident (CVA), dysphagia. A 49-year-old male [history: diabetes, diabetic foot (amputation right foot), hypertension] received study medication from June 1, 2000 for 28 days. On June 10, he awoke with dysphagia. Five days later, speech was impaired and he had "slight face drop." He was hospitalized on ——, and CT scan showed a right internal lacunar capsular CVA; treatment was instituted. All laboratory tests were normal, and ECG showed a sinus rhythm. He was discharged on —— , recovered with sequelae. Investigator assessment: "not related" to study medication. *The reviewer agrees.*

MCB 9905 INT CRF 9165: Mouth ulceration. A 45-year-old male received study medication from March 31 until April 27, 2000. On May 5 (8 days after end of study), he experienced leg pain and was diagnosed with thrombophlebitis on May 8. He was hospitalized on —— due to worsening. He was anticoagulated. Tests revealed activated protein C resistance. He recovered on —— and was discharged. Investigator assessment: "not related" to study medication. *The reviewer agrees.*(Note this case is not included in tables in the Integrated Summary of Safety as it occurred after end of study.)

In the 52-week, Long-Term Core Study, serious adverse events were reported as follows:

- In the group treated with combination for 52 weeks, 14 serious adverse events were reported by 11 subjects (5.3%).
- In the group treated with alternating treatment of combination 4 weeks/calcipotriol 4 weeks, 5 serious adverse events were reported by 5 subjects (2.3%).
- In the group treated with combination for 4 weeks and calcipotriol for 48 weeks, 17 serious adverse events were reported by 13 subjects (6.3%).

Serious Adverse Events by SOC+ and Preferred Term: Long-Term Core Study *

System Organ Class Preferred Term	Number (%) of subjects with Serious Adverse Event		
	Combination once daily for 52 weeks N=207	Combination/Calcipotriol Alternating 4 weeks (once daily) N=213	Combination once daily for 4 weeks/ calcipotriol once daily for 48 weeks N=206
Any Serious Adverse Event	11 (5.3)	5 (2.3)	13 (6.3)
Cardiac Disorders			
Arrhythmia	0 (0.0)	1 (0.5)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.5)	0 (0.0)
Pericarditis	0 (0.0)	0 (0.0)	1 (0.5)
Endocrine disorders			
Hyperthyroidism	0 (0.0)	0 (0.0)	1 (0.5)
Eye disorders			
Blindness	0 (0.0)	0 (0.0)	1 (0.5)
Gastrointestinal disorders			
Diverticulum	1 (0.5)	0 (0.0)	0 (0.0)
Infections and infestations			
Urinary tract infection	1 (0.5)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.5)	0 (0.0)
Injury, poisoning and procedural complications			
Face injury	1 (0.5)	0 (0.0)	0 (0.0)
Tendon rupture	1 (0.5)	0 (0.0)	0 (0.0)
Foot fracture	0 (0.0)	0 (0.0)	1 (0.5)
Metabolism and nutrition disorders			
Dehydration	0 (0.0)	0 (0.0)	1 (0.5)
Musculoskeletal and connective tissue disorders			
Osteonecrosis	0 (0.0)	0 (0.0)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			
Bladder neoplasm	1 (0.5)	0 (0.0)	0 (0.0)
Ovarian neoplasm	1 (0.5)	0 (0.0)	0 (0.0)
Prostate cancer	1 (0.5)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	1 (0.5)
Pancreatic neoplasm	0 (0.0)	0 (0.0)	1 (0.5)
Nervous system disorders			
Convulsion	1 (0.5)	0 (0.0)	0 (0.0)
Headache	1 (0.5)	1 (0.5)	0 (0.0)
Loss of consciousness	1 (0.5)	0 (0.0)	0 (0.0)
Sleep apnea syndrome	1 (0.5)	0 (0.0)	0 (0.0)
Transient ischaemic attack	0 (0.0)	0 (0.0)	2 (1.0)
Pregnancy, puerperium and perinatal conditions			
Pregnancy	1 (0.5)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders			
Prostatitis	0 (0.0)	1 (0.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders			
Atelectasis	0 (0.0)	0 (0.0)	1 (0.5)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.5)
Skin and subcutaneous tissue disorders			
Weight control	0 (0.0)	0 (0.0)	1 (0.5)
Vascular disorders			
Hypertension	1 (0.5)	0 (0.0)	0 (0.0)
Aortic aneurysm	0 (0.0)	0 (0.0)	1 (0.5)

Phlebothrombosis	0 (0.0)	0 (0.0)	1 (0.5)

+System Organ Class
*Applicant's Appendix Table 5 (in Summary of Clinical Safety Section 2.7.4)

No serious adverse events were reported in the healthy volunteer studies or in the Non-Core Studies.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The following table presents the disposition of subjects for the Short-Term Core Studies.

Subject Disposition Short-Term Core Studies by Treatment Group (Applicant Table T4)

	Combination (n=2448) # (%)	Vehicle (n=470) # (%)	Calcipotriol (n=3197) # (%)	Betamethasone (n=1164) # (%)
Reasons for Withdrawal				
Unacceptable adverse event(s)	17 (0.7)	16 (3.4)	79 (2.5)	7 (0.6)
Death	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Unacceptable treatment efficacy	15 (0.6)	37 (7.9)	78 (2.4)	13 (1.1)
Exclusion criteria emerging during study	34 (1.4)	9 (1.9)	33 (1.0)	15 (1.3)
Lost to follow-up	24 (1.0)	5 (1.1)	45 (1.4)	15 (1.3)
Medical deterioration	5 (0.2)	1 (0.2)	6 (0.2)	1 (0.1)
Voluntary	16 (0.7)	5 (1.1)	28 (0.9)	12 (1.0)
Other reasons	18 (0.7)	7 (1.5)	17 (0.5)	6 (0.5)
Total withdrawn	115 (4.7)	66 (14.0)	252 (7.9)	58 (5.0)

7.1.3.2 Adverse events associated with dropouts

The highest rate of dropouts due to an adverse event was in the vehicle group (3.4%). Across treatment groups, most adverse events leading to discontinuation occurred in the Skin and subcutaneous tissue disorders category, and most of these events were reported for the calcipotriol group. (Note: Potential irritation of lesional and perilesional skin is a labeled event for the marketed formulation of calcipotriol ointment, Dovonex®). For subjects who received treatment with the combination product, the most common adverse event leading to discontinuation was "psoriasis" (three subjects; 0.1%). Erythema was the second most common adverse event leading to discontinuation for subjects who received treatment with the combination product (two subjects; 0.1%).

Of the 17 subjects in the combination group who discontinued due to adverse events, investigators considered 13 of those subjects to have had adverse events that were either possibly or probably related to treatment. The events were application site burning and psoriasis, skin burning sensation, urticaria, erythema/pain of skin, dermatitis bullous/erythema, arthralgia, inflammation, cushingoid, application site pruritus, and folliculitis.

Adverse Events Leading to Discontinuation by Treatment Group; Short-Term Core Studies *

	Number (%) of Subjects			
	Combination	Vehicle	Calcipotriol	Betamethasone

	N=2448	N=470	N=3197	N=1164
Number of Subjects with An Adverse Event Leading to Discontinuation	17 (0.7)	16 (3.4)	79 (2.5)	7 (0.6)
Number of Adverse Events	19	20	112	8
System Organ Class Preferred Term				
Cardiac Disorders				
Angina pectoris	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Endocrine disorders				
Cushingoid	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders				
Colitis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Colitis ulcerative	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Glossitis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Stomatitis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
General disorders and administration site conditions				
Application site burning	2 (0.1)	2 (0.4)	4 (0.1)	0 (0.0)
Application site pruritus	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Inflammation	1 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Application site erythema	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Oedema	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Oedema	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Infections and infestations				
Folliculitis	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pilonidal abscess	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eczema infected	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Influenza	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Localised infection	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Injury, poisoning and procedural complications				
Upper limb fracture	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blister	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Haemothorax	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Rib fracture	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders				
Athralgia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)				
Pharyngeal cancer stage Unspecified	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Nervous system disorders				
Burning sensation	0 (0.0)	3 (0.6)	7 (0.2)	1 (0.1)
Cerebrovascular disorder	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions				
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Psychiatric disorders				
Emotional distress	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Renal and urinary disorders				
Renal insufficiency	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				

Epistaxis	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnoea	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders				
Psoriasis	3 (0.1)	0 (0.0)	9 (0.3)	2 (0.2)
Erythema	2 (0.1)	1 (0.2)	12 (0.4)	0 (0.0)
Dermatitis bullous	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain of skin	1 (0.0)	2 (0.4)	1 (0.0)	0 (0.0)
Skin burning sensation	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Urticaria	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Dermatitis exfoliativa	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Koebner phenomenon	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Pruritus	0 (0.0)	7 (1.5)	24 (0.8)	0 (0.0)
Purpura	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	3 (0.1)	0 (0.0)
Rash pruritic	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Skin desquamation	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Skin discomfort	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Skin fissures	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Skin inflammation	0 (0.0)	1 (0.2)	2 (0.1)	0 (0.0)
Skin irritation	0 (0.0)	0 (0.0)	16 (0.5)	2 (0.2)
Stasis dermatitis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Surgical and medical procedures				
Dental operation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vascular disorders				
Hemorrhage	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)

***Modified Applicant's Appendix Table 8 in Summary of Clinical Safety Section 2.7.4 (Additional source: Statistical Table 126 (M5, Vol. 67)**

Adverse Event Leading to Discontinuation by Treatment Frequency; Short-Term Core Studies (Combination Product Only)*

	Number (%) of subjects	
	Combination once daily N=1539	**Combination twice daily N=909**
Any Adverse Event Leading to Discontinuation	8 (0.5)	9 (1.0)
System Organ Class Preferred Term		
Endocrine disorders		
Cushingoid	0 (0.0)	1 (0.1)
General disorders and administration site conditions		
Application site burning	2 (0.1)	0 (0.0)
Application site pruritus	0 (0.0)	1 (0.1)
Inflammation	0 (0.0)	1 (0.1)
Infections and infestations		
Folliculitis	0 (0.0)	1 (0.1)
Pilonidal abscess	1 (0.0)	0 (0.0)
Injury, poisoining and procedural complications		
Upper limb fracture	1 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Athralgia	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders		

Epistaxis	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders		
Psoriasis	2 (0.1)	1 (0.1)
Skin burning sensation	1 (0.1)	0 (0.0)
Urticaria	1 (0.1)	0 (0.0)
Dermatitis bullous	0 (0.0)	1 (0.1)
Erythema	0 (0.0)	2 (0.2)
Pain of skin	0 (0.0)	1 (0.1)

***Applicant's Table T36**

7.1.3.3 Other significant adverse events

Other significant adverse events include those that relate to the effects of the product on calcium metabolism and on the hypothalamic-pituitary-adrenal (HPA) axis. Please see Section 7.1.7, "Laboratory Findings" and Section 7.1.12, "Special Safety Studies."

7.1.4 Other Search Strategies

The reviewer searched adverse event data for signs and symptoms associated with clinically significant hypercalcemia, e.g. anorexia, nausea, vomiting, constipation, depression and corticosteroid effect, e.g. infections, hyperglycemia, hypertension. The occurrence of these events was compared across treatment groups.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In all of the studies, information about adverse events was obtained by means of non-leading questioning of subjects and by recording of changes not reported by subjects but observed by the investigator.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded according to MedDRA version 6.1, and categorization appeared to be appropriate.

7.1.5.3 Incidence of common adverse events

The percentage of subjects reporting at least one adverse event was 27.1% in the combination group, 33.4% in the vehicle group, 33.0% in the calcipotriol group, and 28.3% in the betamethasone group.

In the Short-Term Core Studies, in the combination, vehicle and calcipotriol groups, the most commonly reported adverse events were in the Skin and subcutaneous tissue disorders category (8.5%, 14.5% and 14.2%, respectively), followed by Infections and infestations (8.1%, 8.1% and

9.0%, respectively). In the betamethasone group, the most commonly reported adverse events fell in the same two categories, but in the reverse order: 9.3% Infections and infestations and 6.7% Skin and subcutaneous tissue disorders.

In the Short-Term Core Studies, for the combination group, adverse events in the Skin and subcutaneous tissue disorders category that were reported for $\geq 1\%$ of subjects were pruritus, psoriasis, and rash scaly:

- Pruritus was reported for 3.1% of subjects in the combination group, 9.1% in the vehicle group, 5.7% in the calcipotriol group and 3.3% in the betamethasone group.
- Psoriasis was reported for 1.2% of subjects in the combination group, 1.1% in the vehicle group, 1.5% in the calcipotriol group and 1.2% in the betamethasone group.
- Rash scaly was reported for 1.2% of subjects in the combination group, 0.2% in the vehicle group, 1.3% in the calcipotriol group and 3.3% in the betamethasone group.

Comment: The reports of "psoriasis" included both worsening of treated plaques and the appearance and/or worsening of plaques on untreated areas, e.g. face, genitals, scalp. The higher rates of events suggestive of irritant effect in the vehicle and calcipotriol groups (e.g. pruritus, erythema, irritation) could suggest an irritant effect calmed/suppressed by the corticosteroid making for lower (and comparable) rates of this event in the combination and betamethasone groups. The potential for irritancy is addressed in the package insert for Dovonex® ointment:

- *The PRECAUTIONS section advises that, "Use of Dovonex may cause irritation of lesions and surrounding uninvolved skin."*
- *The "ADVERSE REACTIONS" section include the following discussion, "In controlled clinical trials, the most frequent adverse reactions reported for Dovonex were burning, itching and skin irritation, which occurred in 10-15% of patients. Erythema, dry skin, peeling, rash, dermatitis, worsening of psoriasis including development of facial/scalp psoriasis were reported in 1 to 10% of patients."*

7.1.5.4 Common adverse event tables

For the Short-Term Core Studies, the applicant pooled data from the once daily and twice daily combination treatment groups in the integrated analyses of safety data. Some analyses were repeated in which the frequency of combination treatment was considered, i.e. once daily and twice daily regimens. Data from the long-term study were generally considered separately (for some analyses, data from the first four weeks of the long-term study were pooled with other safety data, since all subjects received the combination ointment in the first four weeks of the long-term study). The calcipotriol and betamethasone pooled treatment groups represent each of those active ingredients in either the applicant's vehicle or marketed formulations.

"All Studies" includes data from the Short-Term Core Studies, data from the healthy volunteer studies, data from the Non-Core Studies, and data from the first four weeks of the Long-Term Core Study.

When all studies are considered, the most commonly reported adverse events in the combination and betamethsone groups were in the Infections and infestations system organ class, (7.6% and 9.3%, respectively) and Skin and subcutaneous tissue disorders (6.8% and 6.7%, respectively). In the vehicle and calcipotriol groups, the most commonly reported adverse events

were in the Skin and subcutaneous tissue disorders system organ class (14.5% and 14.2%, respectively) and Infections and infestations (8.1% and 9.0%, respectively).

Adverse Events Reported by ≥ 1% of Subjects by Preferred Term: All Studies (Applicant Table T25)

	Number (%) of subjects with Adverse Event			
	Combination N=3477	**Vehicle N=470**	**Calcipotriol N=3203**	**Betamethasone N=1164**
Any Adverse Event	835 (24.0)	157 (33.4)	1061 (33.1)	329 (28.3)
Preferred Term	**#of subjects (%)**			
Pruritus	88 (2.5)	43 (9.1)	183 (5.7)	38 (3.3)
Headache	84 (2.4)	12 (2.6)	76 (2.4)	44 (3.8)
Nasopharyngitis	73 (2.1)	9 (1.9)	77 (2.4)	34 (2.9)
Psoriasis	34 (1.0)	5 (1.1)	47 (1.5)	14 (1.2)
Rash scaly	30 (1.2)	1 (0.2)	40 (1.2)	0 (0.0)
Influenza	30 (0.9)	6 (1.3)	34 (1.1)	14 (1.2)
Upper respiratory tract infection	21 (0.6)	3 (0.6)	19 (0.6)	12 (1.0)
Arthralgia[+]	19 (0.5)	3 (0.6)	20 (0.6)	9 (0.8)
Erythema	16 (0.5)	5 (1.1)	54 (1.7)	3 (0.3)
Application site pruritus	13 (0.4)	6 (1.3)	24 (0.8)	10 (0.9)
Skin irritation	11 (0.3)	5 (1.1)	60 (1.9)	8 (0.7)
Pain	10 (0.3)	5 (1.1)	12 (0.4)	3 (0.3)
Burning sensation	9 (0.3)	6 (1.3)	30 (0.9)	3 (0.3)

*Occurred at ≥ 1% of subjects only in the tacalcitol group

Adverse Events Reported by ≥ 1% of Subjects by Preferred Term: Short-Term Core Studies (Applicant Table T22)

	Number (%) of subjects with Adverse Event			
	Combination N=2448	**Vehicle N=470**	**Calcipotriol N=3197**	**Betamethasone N=1164**
Any Adverse Event	663 (27.1)	157 (33.4)	1055 (33.0)	329 (28.3)
Preferred Term	**#of subjects (%)**			
Pruritus	75 (3.1)	43 (9.1)	183 (5.7)	38 (3.3)
Headache	69 (2.8)	12 (2.6)	75 (2.3)	44 (3.8)
Nasopharyngitis	56 (2.3)	9 (1.9)	77 (2.4)	34 (2.9)
Psoriasis	30 (1.2)	5 (1.1)	47 (1.5)	14 (1.2)
Rash scaly	30 (1.2)	1 (0.2)	40 (1.3)	0 (0.0)
Influenza	23 (0.9)	6 (1.3)	34 (1.1)	14 (1.2)
Upper respiratory tract infection	20 (0.8)	3 (0.6)	19 (0.6)	12 (1.0)
Arthralgia[+]	16 (0.7)	3 (0.6)	20 (0.6)	9 (0.8)
Erythema	15 (0.6)	5 (1.1)	54 (1.7)	3 (0.3)
Application site pruritus	13 (0.5)	6 (1.3)	24 (0.8)	10 (0.9)
Skin irritation	11 (0.4)	5 (1.1)	60 (1.9)	8 (0.7)
Pain	7 (0.3)	5 (1.1)	12 (0.4)	3 (0.3)
Burning sensation	6 (0.2)	6 (1.3)	30 (0.9)	3 (0.3)

[+]Occurred in ≥ 1% of subjects in the taclacitol group only

Comment: In the above analyses, for subjects who received combination treatment, adverse events generally occurred at lower or similar rates to comparators. "Rash scaly" was essentially limited to the combination and calcipotriol arms (one report in the vehicle group and none in the betamethasone group). This could suggest that this event reflects irritant effect of calcipotriol.

Pruritus was most common in the vehicle group, followed by the calcipotriol group. This could suggest a vehicle effect, calmed by corticosteroid in the combination and betamethasone arms. Pruritus was the most common event in all treatment groups except betamethasone, where headache was the most common. Headache was the second most common event in all treatment groups except betamethasone, where pruritus was the second most common. Nasopharyngitis was the third most commonly reported event in all treatment groups.

Adverse Events Reported by ≥ 1% of Subjects by Preferred Term by Treatment Frequency; Short-Term Core Studies-Combination Product Only (Applicant Table 59)

Preferred Term	Combination once daily N=1539	Combination twice daily N=909
Total # of adverse events	**218**	**138**
Total # of subjects with an adverse event	**195 (12.7)**	**123 (13.5)**
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)

Comment: Headache and nasopharyngitis occurred at similar rates in both groups, as did psoriasis and "rash scaly." Pruritus occurred at a somewhat higher rate in the twice daily group. For the above analysis, Influenza and Upper respiratory tract infection were reported more often in subjects who had less frequent application of the combination product. Folliculitis occurred at a more than three times higher rate in the twice daily group compared to the once daily group.

Adverse Events Reported by ≥ 1% of Subjects in Any Treatment Group by Preferred Term: Long-Term Core Study by Treatment Group (Source: Applicant Table 52 of the study report)

Preferred Term	# (%) of subjects with Adverse Event		
	Combination once daily for 52 wks N=207	**Combination/calcipotriol once daily (4/4alt.) N=213**	**Combination /calcipotriol once daily (4/48) N=206**
Any adverse event	137 (66.2)	146 (68.5)	151 (73.3)
	#of subjects (%)		
Abdominal pain	0 (0.0)	3 (1.4)	0 (0.0)
Abscess	2 (1.0)	0 (0.0)	0 (0.0)
Angina pectoris	2 (1.0)	0 (0.0)	1 (0.5)
Anxiety	2 (1.0)	0 (0.0)	0 (0.0)
Application site burning	0 (0.0)	1 (0.5)	4 (1.9)
Application site pruritus	0 (0.0)	3 (1.4)	1 (0.5)
Arrhythmia	0 (0.0)	3 (1.4)	0 (0.0)
Arthralgia	7 (3.4)	12 (5.6)	5 (2.4)

Arthritis	2 (1.0)	1 (0.5)	2 (1.0)
Arthropod bite	2 (1.0)	1 (0.5)	0 (0.0)
Asthma	3 (1.4)	1 (0.5)	0 (0.0)
Back pain	5 (2.4)	12 (5.6)	9 (4.4)
Bronchitis	10 (4.8)	5 (2.3)	2 (1.0)
Burning sensation	5 (2.4)	8 (3.8)	10 (4.9)
Bursitis	2 (1.0)	2 (0.9)	0 (0.0)
Cellulitis	1 (0.5)	0 (0.0)	3 (1.5)
Conjunctivitis	2 (1.0)	4 (1.9)	3 (1.5)
Constipation	1 (0.5)	1 (0.5)	2 (1.0)
Cough	2 (1.0)	2 (0.9)	1 (0.5)
Cystitis	2 (1.0)	0 (0.0)	1 (0.5)
Depression	1 (0.5)	5 (2.3)	1 (.5)
Dermatitis	0 (0.0)	2 (0.9)	3 (1.5)
Contact dermatitis	1 (0.5)	1 (0.5)	2 (1.0)
Diarrhea	4 (1.9)	6 (2.8)	4 (1.9)
Dry skin	1 (0.5)	5 (2.3)	2 (1.0)
Dysmenorrhoea	2 (1.0)	0 (0.0)	2 (1.0)
Dyspepsia	2 (1.0)	2 (0.9)	1 (0.5)
Ear infection	4 (1.9)	2 (0.9)	0 (0.0)
Ear pain	0 (0.0)	0 (0.0)	2 (1.0)
Ecchymosis	2 (1.0)	1 (0.5)	0 (0.0)
Eczema	2 (1.0)	5 (2.3)	2 (1.0)
Erythema	2 (1.0)	5 (2.3)	7 (3.4)
Fatigue	2 (1.0)	2 (0.9)	3 (1.5)
Folliculitis	5 (2.4)	5 (2.3)	5 (2.4)
Fungal skin infection	1 (0.5)	1 (0.5)	2 (1.0)
Furuncle	1 (0.5)	3 (1.4)	1 (0.5)
Gastritis	2 (1.0)	1 (0.5)	2 (1.0)
Gastroenteritis	5 (2.4)	11 (5.2)	9 (4.4)
Gastrooesophageal reflux disease	1 (0.5)	0 (0.0)	2 (1.0)
Haemorrhoids	3 (1.4)	0 (0.0)	0 (0.0)
Hand dermatitis	2 (1.0)	1 (0.5)	0 (0.0)
Headache	9 (4.3)	12 (5.6)	12 (5.8)
Herpes simplex	2 (1.0)	2 (0.9)	1 (0.5)
Herpes zoster	2 (1.0)	0 (0.0)	0 (0.0)
Hypercholesterolaemia	0 (0.0)	0 (0.0)	3 (1.5)
Hypertension	6 (2.9)	5 (2.3)	2 (1.0)
Impetigo	0 (0.0)	1 (0.5)	2 (1.0)
Influenza	12 (5.8)	12 (5.6)	8 (3.9)
Influenza-like illness	2 (1.0)	2 (0.9)	1 (0.5)
Insomnia	2 (1.0)	0 (0.0)	0 (0.0)
Joint sprain	3 (1.4)	1 (0.5)	1 (0.5)
Limb injury	2 (1.0)	3 (1.4)	0 (0.0)
Localized infection	0 (0.0)	2 (0.9)	2 (1.0)
Lower respiratory tract Infection	3 (1.4)	5 (2.3)	5 (2.4)
Migraine	0 (0.0)	2 (0.9)	3 (1.5)
Muscle strain	1 (0.5)	3 (1.4)	0 (0.0)
Musculoskeletal pain	2 (1.0)	0 (0.0)	1 (0.5)
Myalgia	0 (0.0)	2 (0.9)	2 (1.0)
Nasopharyngitis	19 (9.2)	23 (10.8)	23 (11.2)
Nausea	2 (1.0)	4 (1.9)	3 (1.5)
Neck pain	4 (1.9)	1 (0.5)	2 (1.0)

Oedema peripheral	3 (1.4)	3 (1.4)	2 (1.0)
Otitis externa	1 (0.5)	3 (1.4)	0 (0.0)
Otitis media	0 (0.0)	1 (0.5)	2 (1.0)
Pain	4 (1.9)	2 (0.9)	1 (0.5)
Pain in extremity	3 (1.4)	2 (0.9)	2 (1.0)
Pain of skin	1 (0.5)	2 (0.9)	3 (1.5)
Pharyngitis	4 (1.9)	2 (0.9)	6 (2.9)
Pharyngolaryngeal pain	4 (1.9)	8 (3.8)	5 (2.4)
Pneumonia	0 (0.0)	1 (0.5)	2 (1.0)
Polymorphic light eruption	0 (0.0)	0 (0.0)	2 (1.0)
Post procedural pain	1 (0.5)	1 (0.5)	2 (1.0)
Pruritus	18 (8.7)	25 (11.7)	32 (15.5)
Psoriasis	19 (9.2)	20 (9.4)	21 (10.2)
Psoriatic arthropathy	1 (0.5)	1 (0.5)	4 (1.9)
Pyrexia	1 (0.5)	2 (0.9)	4 (1.9)
Rash erythematous	2 (1.0)	0 (0.0)	0 (0.0)
Respiratory tract infection	3 (1.4)	5 (2.3)	2 (1.0)
Rhinitis	2 (1.0)	3 (1.4)	3 (1.5)
Rhinitis allergic	3 (1.4)	0 (0.0)	2 (1.0)
Rhinitis infective	0 (0.0)	0 (0.0)	2 (1.0)
Rosacea	4 (1.9)	1 (0.5)	1 (0.5)
Sciatica	2 (1.0)	1 (0.5)	0 (0.0)
Seborrhoeic dermatitis	1 (0.5)	1 (0.5)	2 (1.0)
Sinusitis	3 (1.4)	9 (4.2)	5 (2.4)
Skin atrophy	4 (1.9)	1 (0.5)	2 (1.0)
Skin burning sensation	2 (1.0)	3 (1.4)	2 (1.0)
Skin depigmentation	3 (1.4)	0 (0.0)	0 (0.0)
Skin hyperpigmentation	1 (0.5)	0 (0.0)	3 (1.5)
Skin irritation	0 (0.0)	6 (2.8)	7 (3.4)
Skin papilloma	3 (1.4)	1 (0.5)	1 (0.5)
Sunburn	0 (0.0)	0 (0.0)	2 (1.0)
Tendonitis	2 (1.0)	0 (0.0)	0 (0.0)
Tinea versicolor	1 (0.5)	1 (0.5)	2 (1.0)
Tonsillitis	2 (1.0)	1 (0.5)	0 (0.0)
Tooth abscess	5 (2.4)	4 (1.9)	0 (0.0)
Tooth extraction	1 (0.5)	4 (1.9)	0 (0.0)
Tooth infection	1 (0.5)	3 (1.4)	2 (1.0)
Toothache	1 (0.5)	1 (0.5)	6 (2.9)
Tracheitis	0 (0.0)	0 (0.0)	2 (1.0)
Transient ischaemic attack	0 (0.0)	0 (0.0)	2 (1.0)
Upper respiratory tract infection	8 (3.9)	6 (2.8)	9 (4.4)
Urinary tract infection	2 (1.0)	3 (1.4)	4 (1.9)
Vertigo	2 (1.0)	2 (0.9)	3 (1.5)
Viral upper respiratory tract infection	1 (0.5)	1 (0.5)	4 (1.9)
Xerosis	2 (1.0)	2 (0.9)	1 (0.5)

Comment: Since 2 of the 3 treatment arms at times received only calcipotriol treatment in the long-term study, it is reasonable to conclude that the group that was treated only with the combination product likely had the highest mean exposure to corticosteroid over the study period:

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

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

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

From the table above of adverse events (which considers events that were reported at ≥ 1% in any treatment group in the long-term study), the following adverse events were reported at a higher rate in subjects who received only the combination product: abscess, angina pectoris, anxiety, arthropod bite, asthma, bursitis, cystitis, dyspepsia, ear infection, ecchymosis, haemorrhoids, hand dermatitis, herpes simplex, herpes zoster, hypertension, influenza, influenza-like illness, insomnia, joint sprain, musculoskeletal pain, neck pain, pain, pain in extremity, rash erythematous, rosacea, sciatica, skin atrophy skin depigmentation, skin papilloma, tendonitis, tonsillitis, tooth abscess, and xerosis. Corticosteroid effect may be causative or contributory for some of these events. For example, use of topical corticosteroids has been associated with local events such as infections (e.g. abscess, folliculits, herpes simplex), ecchymosis, atrophy and depigmentation. Additionally, absorption of topical corticosteroids can be sufficient to make for systemic exposure, and manifestations could include anxiety, hypertension, infection.

All subjects were exposed to calcipotriol over the course of the 52-week study. Events that occurred in all treatment groups and that have reported to occur in the setting of hypercalcemia (which can follow sufficient systemic exposure to topical calcipotriol) include: athralgia, arthritis, back pain, conjunctivitis, constipation, depression, dyspepsia, fatigue, headache, hypertension, nausea, pain, pain in an extremity, and pruitus.

It is noted to that papillomas were reported in all treatment groups.

A lesional/perilesional adverse event was generally defined as an adverse event located ≤ 2 cm from the lesional border.

Lesional/Perilesional Adverse Events Reported by ≥ 1% of Subjects in Any Treatment Group: Short-Term Core Studies (Applicant Table T26)

	Number (%) of subjects with Adverse Event			
	Combination N=2448	**Vehicle N=470**	**Calcipotriol N=3197**	**Betamethasone N=1164**
Any Adverse Event	213 (8.7)	76 (16.2)	419 (13.1)	85 (7.3)
Preferred Term	**#of subjects (%)**			
Pruritus	69 (2.8)	41 (8.7)	170 (5.3)	31 (2.7)
Rash scaly	29 (1.2)	0 (0.0)	38 (1.2)	0 (0.0)
Psoriasis+	13 (0.5)	3 (0.6)	28 (0.9)	6 (0.5)
Application site pruritus	12 (0.5)	6 (1.3)	24 (0.8)	10 (0.9)
Erythema	9 (0.4)	4 (0.9)	36 (1.1)	2 (0.2)
Skin irritation	9 (0.4)	5 (1.1)	51 (1.6)	8 (0.7)
Burning sensation	6 (0.2)	5 (1.1)	25 (0.8)	3 (0.3)

+Occurred in ≥ 1% of subjects in the tacalcitol group only

For subjects who reported lesional/perilesional adverse events in the Short-Term Core Studies, the median time to onset was 7 days for combination, 3 days for vehicle, 7 days for calcipotriol and 5 days for betamethasone.

Lesional/Perilesional Adverse Events Reported by ≥ 1% of Subjects in Any Treatment Group: Long-Term Core Study (Applicant Table T28)

Preferred Term	**Combination od N=207**	**Combination od/calcipotriol od 4wk/alt. N=213**	**Combination od 4 wks/calcipotriol od 48 wks N=206**
Any adverse event	43 (20.8))	61 (28.6)	75 (36.4)
	#of subjects (%)		
Pruritus	15 (7.2)	22 (10.3)	28 (13.6)
Psoriasis	7 (3.4)	10 (4.7)	10 (4.9)
Skin atrophy	4 (1.9)	1 (0.5)	2 (1.0)
Folliculitis	3 (1.4)	3 (1.4)	2 (1.0)
Burning sensation	3 (1.4)	8 (3.8)	10 (4.9)
Skin depigmentation	3 (1.4)	0 (0.0)	0 (0.0)
Ecchymosis	2 (1.0)	0 (0.0)	0 (0.0)
Erythema	2 (1.0)	4 (1.9)	7 (3.4)
Hand dermatitis	2 (1.0)	1 (0.5)	0 (0.0)
Pain of skin	1 (0.5)	2 (0.9)	3 (1.5)
Skin burning sensation	1 (0.5)	3 (1.4)	2 (1.0)
Skin hyperpigmentation	1 (0.5)	0 (0.0)	3 (1.5)
Application site burning	0 (0.0)	1 (0.5)	4 (1.9)
Application site pruritus	0 (0.0)	3 (1.4)	1 (0.5)
Skin irritation	0.(0.0)	6 (2.8)	7 (3.4)

For subjects who reported lesional/perilesional adverse events in the long-term study, the median time to the event was 85 days in the combination group, 67 days in the combination

4weeks/calcipotriol 4 weeks (alt.) group and 6 days in the combination 4weeks/calcipotriol 48 weeks group.

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)

There were no reports of striae or hypertrichosis in the Short-Term Core Studies. In Section 2.7.4.2.1.4.2 of the Summary of Clinical Safety, the applicant indicates that the one papilloma reported in the combination group, was not lesional/perilesional.

Local Events Possibly Related to Use of Topical Corticosteroid: Long-Term Study (Source: Table 96 Integrated Summary of Safety)

Preferred Term	**Combination od N=207**	**Combination od/calcipotriol od 4wk/alt. N=213**	**Combination od 4 wks/calcipotriol od 48 wks N=206**
Any adverse event			
	#of subjects (%)		
Skin atrophy	4 (1.9)	1 (0.5)	2 (1.0)
Telangiectasia	0 (0.0)	1 (0.5)	0 (0.0)
Ecchymosis	2 (1.0)	1 (0.5)	0 (0.0)
Purpura	1 (0.5)	0 (0.0)	1 (0.5)
Skin hypopigmentation*	3 (1.4)	0 (0.0)	0 (0.0)
Skin hyperpigmentation	1 (0.5)	0 (0.0)	1 (0.5)
Skin striae	0 (0.0)	1 (0.5)	0 (0.0)
Hypertrichosis	1 (0.5)	0 (0.0)	1 (0.5)
Rash pustular	1 (0.5)	1 (0.5)	0 (0.0)
Skin folliculitis	5 (2.4)	5 (2.3)	5 (2.4)
Furuncle	1 (0.5)	3 (1.4)	1 (0.5)
Celliuitis	1 (0.5)	0 (0.0)	3 (1.5)
Papilloma	3 (1.4)	1 (0.5)	1 (0.5)

*The events in the table were reported as "skin depigmentation."

In Section 2.7.4.2.1.4.3 of the Summary of Clinical Safety, the applicant indicates that only one papilloma was reported as occurring in lesional/periliesional skin, and this report was from the "combination/calcipotriol 4/4 alt." group.

7.1.5.5 Identifying common and drug-related adverse events

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. There are three areas of particular interest as relates to the applicant's product:

1. Local tolerance

The occurrence of irritation would largely be considered attributable to the calcipotriol, since the marketed ointment is known to potentially cause irritation. As a corticosteroid, betamethasone may be associated with several local adverse events. In the submission, the applicant has identified such events as being: skin atrophy, telangiectasia, ecchymosis, purpura, skin hypo- or depigmentation, skin hyperpigmentation, skin striae, hypertrichosis, rash pustular, skin folliculitis, furuncle, cellulitis and papilloma.

Comment: The applicant's categorizations, are generally acceptable to the reviewer. However, in the reviewer's opinion, hyperpigmentation is not generally the pigmentary change that is typically associated with topical corticoseriods (hypo- or depigmentation are more what is thought to be seen). Also, the occurrence of skin infections would not necessarily be limited to bacterial processes. Lastly, it is not clear that papillomas are classic steroid effects. However, assessment for the development of papillomas could be a potentially important event, given the findings in the pre-clinical photocarcinogenicity study and the uncertainty regarding how those results might apply to humans.

An independent board of three dermatologists was created specifically for the long-term study to assess adverse events that might be associated with long-term use of topical corticosteroids ("Independent Adjudication Panel). It is not clear why the applicant chose this approach in the long-term study. However, the reviewer looked for the occurrence of the same adverse events in the long-term study that the applicant had identified as being of particular interest in the short-term studies.

2. Adverse events related to systemic corticosteroid effect.

While emphasis has been placed on the assessment for the potential for the product to cause HPA axis suppression, there are other possible metabolic/systemic adverse events that could reflect corticosteroid effect, e.g. hyperglycemia, hypertension, weight gain.

3. Adverse events related to systemic absorption of calcipotriol (hypercalcemia).

The mnemonic "stones, bones, abdominal moans, and psychic groans" is sometimes employed to describe the constellation of signs and symptoms of hypercalcemia of certain severities.[13] Clinical manifestations may vary according to the severity of the elevation. Mild hypercalcemia may be symptomatic. Signs and symptoms can include nephrolithiasis, bone pain, arthritis,

nausea, vomiting, anorexia, constipation, abdominal pain, confusion, lethargy, fatigue, muscle weakness, hypertension, arrhythmias, keratitis, conjunctivitis.[14,15]

HPA Axis testing is discussed in Section 7.1.12, "Special Safety Studies," and the calcium testing is discussed in Section 7.1.7, "Laboratory Findings."

In the Short-Term Core Studies, treatment-related adverse events were reported by 9.0% of subjects in the combination group, 14.7% of subjects in the vehicle group, 13.3% of subjects in the calcipotriol group, and 7.6% of subjects in the betamethasone group. For all treatment groups, Skin and subcutaneous disorders was the most common system organ class for which treatment-related events were reported.

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)

The following table presents events reported as treatment-related that were reported more for the combination-treated subjects in the Short-Term Core Studies than the other treatment groups, but did not rise to a level of ≥ 1% (i.e. a more conservative assessment of treatment-related events). The table only includes events that had at least two reports (Source: Statistical Table 76 Integrated Summary of Safety):

	Number (%) of subjects with Adverse Event			
	Combination N=2448	**Vehicle N=470**	**Calcipotriol N=3197**	**Betamethasone N=1164**
Preferred Term	**#of subjects (%)**			
Folliculitis	16 (0.7)	0 (0.0)	4 (0.3)	0 (0.0)
Herpes simplex	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Blood calcium increased	2 (0.1)	1 (0.2)	0 (0.0)	1(0.1)
Rash papular	8 (0.3)	2 (0.4)	2 (0.1)	0 (0.0)
Skin hypopigmentation	5 (0.2)	0 (0.0)	3 (0.1)	2 (0.2)
Skin atrophy	3 (0.1)	0 (0.0)	2 (0.1)	2 (0.2)
Ecchymosis	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Post inflammatory pigmentation change	2 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Skin disorder	2 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
Telangiectasia	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

The adverse events in the above table are all consistent with the established profiles of each active ingredient in the product. One interpretation of the data presentation above data is that the combination product appears to more often be associated with treatment-related adverse events. In the table below, the reviewer considered these same events as they were reported for all

treatment groups, i.e. not just those that were reported as being treatment-related (Source: Statistical Table 54):

	Number (%) of subjects with Adverse Event			
	Combination N=2448	**Vehicle N=470**	**Calcipotriol N=3197**	**Betamethasone N=1164**
Preferred Term	**#of subjects (%)**			
Folliculitis	19 (0.8)	1 (0.2)	17 (0.5)	6 (0.5)
Herpes simplex	6 (0.2)	1 (0.2)	9 (0.3)	0 (0.0)
Blood calcium increased	3 (0.1)	1 (0.2)	1 (0.0)	0 (0.1)
Rash papular	8 (0.3)	2 (0.4)	2 (0.1)	2 (0.2)
Skin hypopigmentation	6 (0.2)	0 (0.0)	4 (0.1)	2 (0.2)
Skin atrophy	3 (0.1)	1 (0.2)	2 (0.1)	2 (0.2)
Ecchymosis	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Post inflammatory pigmentation change	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Skin disorder	3 (0.1)	1 (0.2)	1 (0.0)	0 (0.0)
Telangiectasia	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Not only were some events reported in treatment groups other than the combination group, they were sometimes reported at a similar frequency. One possible explanation for this is that some of the local events that were reported as treatment-related possibly occurred in the treatment area, increasing the impression that the event was treatment-related.

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were conducted beyond those described in other sections of the review.

7.1.6 Less Common Adverse Events

Short-Term Core Studies

In the following table, the reviewer considered adverse events that occurred at the highest rate in the combination group in the Short-Term Core Studies:

Source: Table 54 Integrated Summary of Safety

	Number (%) of subjects with Adverse Event			
	Combination N=2448	**Vehicle N=470**	**Calcipotriol N=3197**	**Betamethasone N=1164**
Preferred Term	**#of subjects (%)**			
Mouth ulceration	3 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Abdominal discomfort	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Odynophagia	2 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Malaise	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cholelithiasis	2. (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Folliculitis	19 (0.8)	1 (0.2)	17 (0.5)	6 (0.5)
Cystitis	5 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Labyrinthitis	2 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Tinea cruris	2 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)

Muscle strain	4 (0.2)	0 (0.0)	1 (0.0)	1 (0.1)
Back injury	2 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Skeletal injury	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Psoriatic arthropathy	4 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)
Dysmenorrhea	6 (0.2)	0 (0.0)	1 (0.0)	1 (0.1)
Nasal congestion	5 (0.2)	0 (0.0)	3 (0.1)	0 (0.0)
Rhinitis allergic	3 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Rhinorrhea	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ecchymosis	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Acne	3 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Hyperhidrosis	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Telangiectasia	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Comment: Many of the events seem to also occur only in the calcipotriol treatment group, raising the question of whether calcipotriol is driving the occurrence of these events.

Long-Term Core Study

Similar to what was done with the Short-Term Core Studies, the following table presents adverse events that occurred at the highest rate in the groups that received only the combination product. Subjects in this group would have had the most potential exposure to corticosteroid over the treatment period. Only events that were reported more than once are included in the table.

Source: Table 82 Integrated Summary of Safety

Preferred Term	**Combination once daily for 52 wks** **N=207**	**Combination calcipotriol 4/4 alt.** **N=213**	**Combination/ calcipotriol once daily 4/48** **N=206**
	#of subjects (%)		
Angina pectoris	2 (1.0)	0 (0.0)	1 (0.5)
Haemorrhoids	3 (1.4)	0 (0.0)	0 (0.0)
Dyspepsia	2 (1.0)	2 (0.9)	1 (0.5)
Pain	4 (1.9)	2 (0.9)	1 (0.5)
Influenza like illness	2 (1.0)	2 (0.9)	1 (0.5)
Xerosis	2 (1.0)	2 (0.9)	1 (0.5)
Influenza	12 (5.8)	12 (5.6)	8 (3.9)
Bronchitis	10 (4.8)	5 (2.3)	2 (1.0)
Tooth abscess	5 (2.4)	4 (1.9)	0 (0.0)
Ear infection	4 (1.9)	2 (0.9)	0 (0.0)
Abscess	2 (1.0)	0 (0.0)	0 (0.0)
Cystitis	2 (1.0)	0 (0.0)	1 (0.5)
Herpes simplex	2 (1.0)	2 (0.9)	1 (0.5)
Herpes zoster	2 (1.0)	0 (0.0)	0 (0.0)
Tonsillitis	2 (1.0)	1 (0.5)	0 (0.0)
Joint sprain	3 (1.4)	1 (0.5)	1 (0.5)
Arthropod bite	2 (1.0)	1 (0.5)	0 (0.0)
Neck pain	4 (1.9)	1 (0.5)	2 (1.0)
Pain in extremity	3 (1.4)	2 (0.9)	2 (1.0)
Bursitis	2 (1.0)	2 (0.9)	0 (0.0)

Musculoskeltal pain	2 (1.0)	0 (0.0)	1 (0.5)
Tendonitis	2 (1.0)	0 (0.0)	0 (0.0)
Skin papilloma	3 (1.4)	1 (0.5)	1 (0.5)
Achrochordon	1 (0.5)	0 (0.0)	0 (0.0)
Basal cell carcinoma	1 (0.5)	0 (0.0)	0 (0.0)
Sciatica	2 (1.0)	1 (0.5)	0 (0.0)
Anxiety	2 (1.0)	0 (0.0)	0 (0.0)
Insomnia	2 (1.0)	0 (0.0)	0 (0.0)
Asthma	3 (1.4)	1 (0.5)	0 (0.0)
Rhinitis allergic	3 (1.4)	0 (0.0)	2 (1.0)
Cough	2 (1.0)	2 (0.9)	1 (0.5)
Rosacea	4 (1.9)	1 (0.5)	1 (0.5)
Skin atrophy	4 (1.9)	1 (0.5)	2 (1.0)
Skin depigmentation	3 (1.4)	0 (0.0)	0 (0.0)
Ecchymosis	2 (1.0)	1 (0.5)	0 (0.0)
Hand dermatitis	2 (1.0)	1 (0.5)	0 (0.0)
Rash erythmatous	2 (1.0)	0 (0.0)	0 (0.0)
Hypertension	6 (2.9)	5 (2.3)	2 (1.0)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Particular concerns about systemic adverse events relate to the active ingredients in the applicant's product. Laboratory monitoring in the applicant's development program was largely limited to assessment for the potential effect on calcium metabolism (from calcipotriol) and on the HPA axis (betamethasone).

Serum calcium, serum albumin, and albumin-corrected serum calcium were assessed in subjects with psoriasis in MCB 9905 INT, MCB 9904 INT and MCB 9802 INT. Only serum calcium was measured in MCB 0201 FR; therefore, calcium results from this study were not pooled with those from the other three studies.

HPA axis testing was investigated in study MCB 0201 FR and in a subset of subjects in the long-term study, MCB 0102 INT. Maximal-use conditions applied in study MCB 0201 FR, while "as needed" use was the case in study, MCB 0102 INT, probably more reflective of real-world use.

Standard safety laboratory testing (hematology, chemistry and urinalysis) was done in psoriasis subjects in only one study MCB 0201 FR (the HPA axis study) and in that study, only 12 subjects received treatment with the combination product. Standard safety laboratory testing was done in four healthy volunteer studies: MCB 9801 NL, MCB 9901 NL, MCB 9902 FR, and MCB 9903 DE. However, healthy volunteers represent a different population from those with psoriasis, and it is unclear to what extent results from these could be applied to subjects with psoriasis, since percutaneous absorption of topical products could differ in skin affected by psoriasis compared to normal skin. Further, subjects received only a single dose of study product in studies MCB 9801 NL and MCB 9902 FR and, dosing was therefore not in line with the proposed multi-dose regimen. MCB 9903 DE was an intra-individual comparison study in which subjects received the combination product and betamethasone ointment (as well as

vehicle), and it is unclear to what extent this might confound interpretation of any abnormal lab results.

This section of the review will address only the calcium testing.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Studies reviewed for systemic tolerance as pertains to calcium metabolism were those in which the serum calcium, serum albumin were collected. The serum calcium, serum albumin, and albumin-corrected serum calcium data were pooled across studies for comparable dosing groups, i.e. data from once daily treatment were pooled as were data from twice daily treatment. In this review, references to pooled data refer to data from the three studies MCB 9905 INT, MCB 9904 INT and MCB 9802 INT. Dosing of the combination product in those studies was as follows:

- MCB 9905 INT: once and twice daily for 4 weeks
- MCB 9904 INT: twice daily for 4 weeks (then 4 weeks of calpciptriol ointment)
- MCB 9802 INT: twice daily for 4 weeks

All studies required a minimum score for extent of 2 in at least one body region using the PASI scoring scale, i.e. psoriasis affecting at least 10% of arms, and/or 10% of trunk and/or 10% of legs.

Comment: Most of the calcium data is from subjects treated twice daily; however, treatment durations are comparable (i.e. four weeks), it is reasonable that these data could be extrapolated and applied to a population who would dose less frequently.

Per a communication from the applicant dated October 12, 2005, they used the following formula to calculate the albumin-corrected serum calcium:

Corrected calcium= total serum calcium (mmol/) = [0.02 x (40 – serum albumin (g/L)].

7.1.7.3 Standard analyses and explorations of laboratory data

Baseline disease data are presented below. Mean extent of baseline disease was similar across studies.

Mean Baseline Disease (PASI)

Study	Combination once daily	Combination twice daily	Calicpotriol twice daily	Betamethasone twice daily	Vehicle
9905	9.9	10.6	10.8	N/A	10.4
9904	N/A	10.8	10.9	10.5	N/A
9802	N/A	10.9	10.8	10.7	10.5

Sources: Table 11 (study report for 9905); Table 10 (study 9904); Table 8 (study 9802)
N/A=not applicable

Mean amount of exposure to study product over the four-week treatment period is presented in the following table. The reviewer considers the mean amount of exposure to the combination product to have been generally similar across studies, when the product was applied twice daily.

Mean Amount of Study Product Used (g)*

Study	Combination once daily	Combination twice daily	Calicpotriol twice daily	Betamethasone twice daily	Vehicle
9905	76.2[+]	156.0	166.8	N/A	152.8
9904	N/A	143.1	163.0	144.5	N/A
9802	N/A	146.6	148.8	138.9	155.0

Sources: Table 14 (study report for 9905); Table 45 (study 9904); Table 38 (study 9802)
*For study 9904, this reflects the amount used in the first 4 weeks
[+]For blinding purposes, subjects in this group also applied vehicle once daily (mean amount: 72.1g)

Calcium Testing

Mean albumin-corrected serum calcium values were similar across treatment arms at baseline and at the end of treatment. For all treatment groups, mean calcium values were in the normal range at the end of four weeks of treatment irrespective of frequency of treatment. Specifically,

- In the combination group, the mean albumin-corrected serum calcium was 2.36 mmol/L (range: .90 to 2.80) at baseline and 2.36 mmol/L (range 1.87 to 2.81) at the end of treatment.
- In the calcipotriol group, the mean albumin-corrected serum calcium was 2.36 mmol/L at baseline (range: 2.00 to 2.68) and 2.36 mmol/L (range 2.03 to 2.69) at the end of treatment.
- In the betamethasone group, the mean albumin-corrected serum calcium was 2.35 mmol/L at baseline and 2.34 mmol/L at the end of treatment.
- In the vehicle group, the mean albumin-corrected serum calcium 2.36 mmol/L at baseline and 2.36 mmol/L at the end of treatment.

Comment: According to Listing 21, reference ranges for albumin-corrected serum calcium in study 9905 were 2.07-2.54 or 2.13-2.53 (depending on study site), and reference ranges were provided for each result reported. For study 9904, the upper limit for the reference range was stated to be 2.54 on p. 230 of the study report; however, in the data listing Table III.34, 2.54 was sometimes flagged as a being "high," i.e. outside of the normal range (e.g. subjects 6199 and 6257). No reference range could be found for study 9802.

When frequency of treatment was considered, the mean albumin-corrected serum calcium in the combination group once daily was 2.37 mmol/L at baseline and 2.38 mmol/L at the end of treatment. The mean albumin-corrected serum calcium in the combination group twice daily was 2.36 mmol/L at baseline and 2.36 mmol/L at the end of treatment.

Applicant Table T41: Changes in Albumin-Corrected Serum Calcium for Baseline to End of Treatment

	Combination N=1060	Vehicle N=316	Calcipotriol N=901	Betamethasone N=678
Mean value (SD) at baseline (mmol/L)	2.36 (0.09)	2.36 (0.09)	2.36 (0.09)	2.35 (0.09)
Mean value (SD) at EOT (mmol/L)	2.36 (0.09)	2.36 (0.09)	2.36 (0.09)	2.34 (0.09)
Actual change[1] (mmol/L)				
Mean (SD)	0.00 (0.09)	0.00 (0.09)	0.00 (0.09)	-0.01 (0.09)
Min, Max	-0.47, 0.37	-0.25, 0.27	-0.29, 0.30	-0.41, 0.20
Ratio[2]				
Mean[3] (SD)[4]	1.00 (3.70)	1.00 (3.78)	1.00 (3.65)	1.00 (3.35)
Min, Max	0.80, 1.18	0.90, 1.12	0.89, 1.13	0.84, 1.09
Number of subjects assessed[5]	1030	304	872	659

SD: standard deviation EOT: end of treatment with combination ointment for study 9904 INT) Min, Max: Minimum, Maximum
[1] Actual change from baseline to EOT
[2] Ratio of EOT value to baseline value
[3] Geometric mean
[4] SD as percentage of mean
[5] Number of subjects for whom both baseline and EOT values were available

Applicant Table T42: Changes in Albumin-Corrected Serum Calcium for Baseline to EOT (ISSp. 120)

	Combination once daily N=151	Combination twice daily N=909
Mean value (SD) at baseline (mmol/L)	2.37(0.09)	2.36 (0.09)
Mean value (SD) at EOT (mmol/L)	2.38 (0.10)	2.36 (0.09)
Actual change[1] (mmol/L)		
Mean (SD)	0.01 (0.08)	0.00 (0.08)
Min, Max	-0.22, 0.28	-0.47, 0.37
Ratio[2]		
Mean[3] (SD)[4]	1.0 (3.63)	1.00 (3.71)
Min, Max	0.91, 1.13	0.80, 1.18
Number of subjects assessed[5]	144	886

SD: standard deviation EOT: end of treatment with combination ointment for study 9904 INT) Min, Max: Minimum, Maximum
[1] Actual change from baseline to EOT
[2] Ratio of EOT value to baseline value
[3] Geometric mean
[4] SD as percentage of mean
[5] Number of subjects for whom both baseline and EOT values were available

Comment: The Medical Officer reviewed all albumin-corrected serum calcium data from studies

- *MCB 9905 INT: once and twice daily dosing*
- *MCB 9904 INT: twice daily dosing*
- *MCB 9802 INT: twice daily dosing*

These studies were conducted in the population of interest, i.e. subjects with psoriasis and, laboratory data included serum albumin to permit calculation of the corrected levels. Only subjects who had normal baseline albumin-corrected serum calcium levels were considered in

the reviewer's analysis (these numbers were as provided by the applicant in the individual study reports.)

As previously stated, according to Listing 21, reference ranges for albumin-corrected serum calcium in study 9905 were 2.07-2.54 or 2.13-2.53 (depending on study site), and reference ranges were provided for each specimen. For study 9904, the upper limit for the reference range was stated to be 2.54 on p. 230 of the study report; however, in the data listing Table III.34, 2.54 was sometimes flagged as a being "high." No reference range could be found for study 9802. Therefore, the reviewer conservatively considered the upper limit for the reference range to be 2.53. Only study 9904 included a dosing arm that corresponds to the applicant's proposed once daily dosing.

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)

Sources: Listing 21 (study 9905), Table III.34 (9904) and Table III.17 (9802)

Hypercalcemia between 2.63 and 3 mmol per L may be considered mild and levels in this range may not make for any symptoms.[16] Calcium levels generally normalized at follow-up testing, for subjects who had such testing. However, follow-up testing did not appear to have been done in most subjects.

For study 9905, a higher percentage of subjects treated once daily with the combination product had elevated corrected calcium levels as compared to twice-daily treated subjects. However, the significance of this comparison is not clear, since in the same study, a slightly higher percentage of vehicle-treated subjects had elevated corrected calcium levels when compared to the twice daily group. There were no other data from subjects who received once daily dosing for comparison.

For study 9802, the data were reviewed for trends towards elevation of calcium from baseline, even though the end-of-treatment values remained within the reference range. (Study 9802 was the only study that contained all four comparators.) The numbers of subjects who had elevations in their calcium from baseline to end-of-treatment but whose values remained within normal limits are presented below.

Combination twice daily N=293	**Calicpotriol twice daily N=293**	**Betamethasone twice daily N=295**	**Vehicle N=104**
140 (47.8)	131 (44.7)	139 (47.1)	46 (44.2)

While a higher rate of subjects appeared to have upward trends in calcium levels in the combination group, the reviewer considers the rates to be similar across treatment groups.

HPA Axis Testing

These studies are discussed in Section 7.1.12, "Special Safety Studies."

Other Laboratory Testing

Other laboratory testing is discussed in Section 7.1.12, as these labs were obtained in the HPA axis study.

7.1.7.3.1 Analyses focused on outliers or shifts from normal to abnormal

In the applicant's analysis, in studies 9905 INT, 9904 INT and 9802 INT (irrespective of frequency of treatment), the numbers of subjects who had shifts from normal to high in albumin-corrected calcium were

- 24 of 1060 (2.3%) in the combination group
- 9 of 316 (2.8%) in the vehicle group
- 22 of 901 (2.4%) in the calcipotriol group
- 6 of 678 (0.9%) in the betamethasone group

When frequency of treatment was considered, the numbers of subjects who had shifts from shifts from normal to high in albumin-corrected calcium were

- 9 of 151 (6.0%) for subjects treated once daily with the combination product
- 15 of 909 (1.7%) for subjects treated twice daily with the combination product

In study MCB 0201 FR, all serum calcium values were categorized as normal both at baseline and at end of treatment. Albumin levels were not obtained in this study.

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations were preformed.

7.1.7.5 Special assessments

The potential for the product to impact calcium metabolism and to suppress the HPA-axis are discussed in the review.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In subjects with psoriasis, vital signs were assessed only in study 0201 FR (HPA axis study) and did not include respirations. Vital signs were measured in five healthy volunteer studies (including respirations).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

All median and mean values were within normal limits. There were no clinically relevant changes from baseline to end of treatment for any variables.

7.1.8.3 Standard analyses and explorations of vital signs data

All median and mean values were within normal limits. There were no clinically relevant changes from baseline to end of treatment for any variables.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were conducted.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

MCB 0201 FR (the HPA-axis study) was the only study in subjects with psoriasis in which electrocardiograms were obtained. Only 12 subjects received treatment with the applicant's product in that study.

Per Section 2.4.2.3 of the Non-clinical Overview, calcipotriol and betamethasone dipropionate had no effect on arterial blood pressue, ECG, heart rate or cardiac conduction times including the QT interval when orally administered to "telemetrised" dogs; however, it is not clear that similar testing was conducted with the combination product.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The data from study MCB 0201 FR were reviewed.

7.1.9.3 Standard analyses and explorations of ECG data

The PR intervals for one combination-treated subject (#9) and one betamethasone-treated subject (#24) were slightly increased at visit 4 to 206 and 211 ms respectively (upper reference limit is 200ms). One betamethasone-treated subject (#17) had a long Bazett corrected QT interval at baseline and end of treatment. None of these findings was considered to be clinically significant.

Comment: When hypercalcemia is at a level sufficient to affect the electrocardiogram, shortening of the QT interval is reported as a manifestation; however, the PR interval may be prolonged. [17,18] *Albumin levels were not measured, so albumin-corrected total calcium could*

not be determined. However, per Listing 16.2.3.2.3 total calcium levels for these 3 subjects at the end-of treatment were: 2.33 mmol/L (#9), 2.5 (#17) and 2.48 (#24). While reference ranges were not found in the data listing 16.2.3.2.3, it is noted that these values are within the reference ranges discussed in Section 7.1.7.3 for corrected calcium.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were conducted.

7.1.10 Immunogenicity

This section is not applicable to the applicant's product.

7.1.11 Human Carcinogenicity

In Section 2.5.5.2 of the Clinical Overview, the applicant indicates that a dermal photo(co)carcinogenicity study was conducted with calcipotriol in the marketed scalp solution vehicle in the hairless mouse. Topical administration of the solution at a dose of 30 mcg/kg (7.5 mcg/mL) produced a "very slight increase in UV-induced tumor onset" in the male mouse. The significance of these findings for humans is unclear. The concentration of calcipotriol in the combination ointment is the same as in the marketed scalp solution; therefore, these data from the studies conducted with the solution may apply to the combination ointment.

In the Clinical Overview (Section 2.5.1.7), the applicant indicates that the intent of a ultraviolet (UV) transmission study that they conducted was to verify that UV transmission is not enhanced by the new ointment vehicle as compared to the scalp solution vehicle, to be able to relate the non-clinical data from the scalp solution to the combination ointment product. The study evaluated UV transmission properties of the combination ointment in healthy human skin.

Comment: The following wording is found in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" of the "PRECAUTIONS" section in the current package insert for Dovonex ointment:

"Patients that apply Dovonex to exposed portions 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.

Similar wording will need to be included in the package insert for the combination product.

7.1.12 Special Safety Studies

This section includes a discussion of the studies in which HPA axis testing was done, the topical safety studies, and a UV penetration study.

HPA axis testing was done in MCB 0201 FR and MCB 0102 INT. Additionally, study MCB 0102 INT was intended to assess the long-term safety of the combination product.

The topical safety studies are:

- MCB 0202 FR/PC 1644: repeat insult patch test sensitization study
- MCB 0203 FR/CPCAD CPC-3169: 21-day cumulative irritation test
- MCB 0204 FR/CPCAD CPC-3186: Photo-allergy study
- MCB 0101 FR: Photo-toxicity study

A fifth study, MCB 0306 UK, was conducted to evaluate the UV light penetration potential of the combination ointment.

MCB 0201 FR: "Effect of Calcipotriol/Betamethasone Dipropionate Ointment Compared to Betamethasone Dipropionate Ointment on the HPA Axis in Patients with Psoriasis Vulgaris" (April 15, 2003-January 13, 2004)

Note: The final version of the protocol is dated April 3, 2003. The study dates were April 15, 2003-January 13, 2004. The protocol was submitted for Agency review in a correspondence dated May 29, 2003 (i.e. the study was already underway).

Study design: single-center, prospective, randomized, active-controlled, double-blind, two-arm, parallel group

Objective: The objective of the study was to compare the effect of once daily use of the combination product with that of Diprosone® ointment, a marketed betamethasone dipropionate ointment, on the hypothalamic-pituitary-adrenal (HPA) axis in subjects with psoriasis vulgaris.

Methodology: The study duration was 6 weeks (for each subject), consisting of a two-week run-in period followed by a four-week treatment phase. Subjects presented for four visits: two during screening (Visits 1 and 2) and two during the treatment phase on Day 0 (Visit 3) and Day 28 (Visit 4; end-of-treatment). At the investigator's discretion, a follow-up visit was conducted two weeks post-treatment if a serious adverse event or a non-serious adverse event classified as possibly/probably related to the study medication or not assessable was ongoing.

History, physical, routine laboratory examinations, and ECG's were done at Visit 1. Adrenal function was assessed one week prior to treatment by a rapid standard dose ACTH (Synacthen®) stimulation test at Visit 2. The test consisted of blood sampling at 8:00 AM for a baseline serum cortisol (normal considered to be 10 to 22.4µg/dL) followed by an intravenous bolus injection of 250 µg Synacthen®. Blood samples were taken 30 and 60 minutes later for assessment of the serum cortisol levels. Normal HPA axis function was defined by:

- a serum cortisol concentration, obtained at 30 or 60 minutes after Synacthen® injection , above 18µg/dL,
- the rise in serum cortisol concentrations from baseline to 30 or 60 minutes after Synacthen® injection of at least 7µg/dL

Comments: 1) Synacthen ® is not marketed in the United States. From literature and internet searches: Synacthen® is tetatracosactrin, a synthetic corticotropin composed of the first 24 amino acids of ACTH. Per Section 9.2 of the study report, the applicant considers Synacthen ® to be equivalent to Cortrosyn® to be supported by the "identical recommendations of use and interpretations of what constitutes a normal HPA axis response following

administration." In review of the protocol (submitted to IND 62, 993; review dated May 4, 2004), the Clinical Pharmacology/Biopharmaceutics Reviewer concluded that, "Based on the response of the sponsor and careful review of the product literatures, the reviewer concurs that the two products may be considered equivalent for HPA axis suppression test purpose."

2) For purposes of this review, normal HPA axis functioning will be defined by a serum cortisol concentration above 18μg/dL 30 minutes after Synacthen® injection. At the pre-NDA meeting, the applicant was advised that the Agency considers this to be the most relevant criterion.

Subjects were to have been withdrawn if baseline laboratory results suggested adrenal suppression of possible clinical significance according the definitions in the Inclusion/ Exclusion Criteria below.

At Day 0 (Visit 3), a PASI assessment was performed, and subjects were equally randomized to one of two treatment arms:

- the applicant's combination ointment or
- Diprosone® ointment.

Subjects received four 100 g tubes of study product and were instructed to use one tube of product per week. Study drug was to have been applied to all lesions once daily for up to four weeks for a total of 28 applications (non-occlusively).

On Day 28 (± 2 days), PASI, history, physical, laboratory examinations, and ECG's were repeated. Additionally, adrenal function was again assessed by the ACTH (Synacthen) stimulation test. If laboratory tests suggested HPA axis suppression of "possible clinical significance," a follow-up visit was to be performed 6 weeks after the subject's last visit and was to include a Synacthen® stimulation test.

Inclusion Criteria:

1. Male or non-pregnant, not-breast-feeding female volunteers aged at least 18 years old
2. Patients with psoriasis vulgaris on trunk and/or limbs amenable to topical treatment, with lesions involving between 15 to 30% of the body surface area on trunk and/or limbs,
3. Patients with normal HPA axis function defined by:
   - serum cortisol concentration , obtained at 30 or 60 minutes after Synacthen® injection, above 18 μg/dL,
   - a rise in serum cortisol concentrations from baseline (T0) to 30 or 60 minutes after Synacthen® injection of at least 7μg/dL,
4. Females of child bearing potential who have had a negative pregnancy test taken at visit 1 and must use adequate contraception during the entire study,
5. Written informed consent by patient,
6. Registered with the French Social Security in agreement with the French law…on biomedical experimentation,
7. Able to comply with protocol requirements.

Exclusion Criteria:

1. History of serious allergy, asthma, allergic skin rash or sensitivity to any medication (including ACTH, Synacthen®) or to any component of the formulations being tested,
2. Concomitant medical or dermatological disorders(s) which might preclude accurate evaluation of the psoriasis,
3. Erythrodermic, exfoliative or pustular psoriasis,

4. Have not undergone the specified washout periods before day 0 for the following topical or systemic medications:
   - topical (Vitamin-D analogues, topical retinoids, salicylic acid preparations) and systemic antipsoriatic treatments (immunosuppressors: methotrexazte, cyclosporine, PUVA, UVB, retinoids) 2 weeks
   - topical or inhaled corticosteroids 4 weeks (apart form WHO group I on the skin folds and/or genitals and/or face and WHO group I/II on the scalp)
   - systemic corticosteroids 12 weeks
   - estrogenic therapy (for women only), or any other medication known to affect cortisol levels or HPA axis integrity 4 weeks
   - enzymatic inductors (barbiturates, phenytoin, rifampicin) 4 weeks
   - systemic or topical cytochrome P450 inhibitors (ketoconazole) 4 weeks
   - hypoglycemic sulfonamides 4 weeks
   - antidepressive medications 4 weeks
5. Have foreseen an intensive solar exposure during the study (UV radiation, etc.) or have been exposed within two weeks preceding the screening visit,
6. Have evidence of adrenal pathology of possible clinical significance from the baseline cortisol level (8:00 AM) i.e. level strictly below 10µg/dL or above 22.4 µg/dL,
7. Present a depressive delusion,
8. History of chronic alcohol or drug abuse,
9. Clinical signs or symptoms of Cushing's disease or Addison's disease,
10. Suffer from diabetes
11. Irregular sleep schedules or patients that work night shifts or with any clinically significant abnormality following review of screening laboratory tests (blood and urine samples) and full physical examination,
12. Present a positive laboratory test for Hepatitis B, surface antigen (HbsAg), HIV 1 and 2 antibodies and HCV antibody,
13. Undergo or have donated blood within 1 month prior to the screening
14. In the judgment of the investigator, are likely to be non-compliant or uncooperative during the study,
15. Freedom has been restricted by judicial or administrative decision or who are under legal guardianship
16. Could not be contacted in case of emergency.

RESULTS

The study enrolled 24 subjects, all of whom completed the study. Subjects were randomized to one of the two treatment arms. Per Section 9.72 of the study report, a sample size of 24 subjects was chosen as this was "generally in keeping with the numbers selected for the 19 previous studies reported in this area since 1981."

Comment: For HPA axis testing, a minimum of 30 evaluable subjects who received treatment with the study medication is generally recommended. However, the study was already underway when the protocol was submitted.

No subjects discontinued the study.

Demographic Characteristics

Twelve subjects were enrolled in each treatment arm, and treatment arms were comparable with respect to demographic characteristics. There were 11 male and 13 female subjects. The mean age was 44.0 years (45.1 years for the combination group and 42.8 for the Diprosone group). One subject was Asian; all others were Caucasian.

Baseline Characteristics

The percentage of body surface area involvement on the trunk and/or limbs ranged from 15 to 30%, and the distribution was similar between treatment arms. The average percentage body surface involvement was 22.1% in the combination group and 23.5% in the Diprosone® group. Mean PASI score was slightly higher in the Diprosone® treatment arm than in the combination arm: 14.33 vs. 11.92, respectively.

Extent of Exposure

Mean amount of study product used over the four-week treatment course was 215.79 g in the combination group (range: 63.7 to 393.9) and 207.39 g in the Diprosone® group (range: 106.3 to 348.8).

Vital Signs

There were no clinically significant changes in blood pressure at the end of treatment. Mean systolic blood pressure was 133.7 in the combination group and 130.3 in the betamethasone group at baseline and 130.7 and 133.4, respectively at end of treatment (Statistical Table 153). Mean diastolic blood pressure was 76.7 in the combination group and 74.8 in the betamethasone group at baseline and 75.3 and 77.4, respectively at end of treatment (Statistical Table 154). Values were within normal limits for all but two subjects: #14 (combination) had a blood pressure of 162/99 at the end of treatment (135/86 at baseline), and #8 (Diprosone) had a blood pressure of 149/92 at the end of treatment (151/83 at baseline). Values were not re-checked. It cannot be known what significance to attach to an isolated elevated reading.

Laboratory Evaluations

There were no clinically significant changes in laboratory parameters. Sporadic abnormal values were reported, but none were considered clinically significant. End-of-treatment fasting glucose levels were within the reference range for all but one subject (#3) whose level was elevated; however, the fasting glucose level was also elevated at baseline for this subject (end-of-treatment value was lower than baseline value). Baseline and end-of-treatment urine specimens were negative for glucose for all subjects.

The results of the HPA axis testing are presented in the following table.

Results of HPA-Axis Testing (Sources Listings 16.2.1.1.3, 16.2.1.3.2)

Subject#/ sex	% BSA baseline/ EOT+	Approx. Exposure (g) Over 4 weeks	Baseline 30 minute Post-stimulation cortisol mcg/dL (T30)	EOT 30 minute Post-stimulation cortisol mcg/dL (T30)
Combination Treatment				
1 /F	20/22	63.7	25.83	27.79
2 /F	16/16	196.4	26.70	27.43
3 /F	29/29	277.6	28.84	25.33
7/F	30/30	149.8	30.33	33.08
9 /M	22/22	265.1	27.64	26.45
12 /F	23/23	238.2	26.88	25.25
14 /F	15/19	328.9	35.94	28.08
16/M	30/30	163.9	23.88	*
19 /M	22/22	267.4	23.01	21.27
20 /F	16/16	99.8	20.80	24.96
21 /M	18/18	144.8	20.33	21.74
22 /M	24/24	276.1	28.33	24.53
Diprosone Treatment				
4 /M	22/30	275.5	20.94	20.76
5 /M	26/26	182.1	28.77	27.68
6 /M	22/18	106.3	24.71	23.44
8 /M	29/29	131.0	22.46	30.40
10 /M	23/23	163.3	26.88	29.24
11 /F	29/29	348.8	19.60	24.86
13 /F	29/29	341.2	15.54	7.57
15 /M	20/20	201.2	27.72	26.45
17 /F	30/30	301.0	24.24	27.32
18 /F	22/22	116.2	22.43	23.59
23 /F	15/15	177.3	20.00	15.87
24 /F	1515	146.8	27.61	28.59

+EOT= end of treatment

*End-of-treatment (Day 28) blood sampling, physical examination and urinalysis were delayed for subject #16 in the combination arm because the subject had the flu. These evaluations were performed one month after the end-of-treatment visit and did not include the Synacthen® test.

Comment: One Diprosone-treated subject (#23) who had normal HPA axis test results at baseline showed evidence of suppression at the end-of-treatment. Under the conditions of the study, no subjects who received treatment with the combination product showed evidence of HPA axis suppression.

Four subjects were enrolled in violation of Exclusion Criterion 6, which required exclusion of subjects who had baseline cortisol levels (8:00 AM) "strictly below 10µg/dL or above 22.4 µg/dL." However, only one of these subjects (#13) was considered to have shown evidence suggestive of adrenal pathology by the criteria that will be applied in this review. Cortisol values for these four subjects (and assigned treatment group) were:

Subject #/treatment group	Baseline cortisol	Post-stimulation cortisol (T30*)
#10/Diprosone	23.01	26.88
#11/Diprosone	8.22	19.6
#13/Diprosone	9.6	15.54
#21/Combination	8.01	20.33

*T30= 30 minutes post-stimulation

ECG

The PR intervals subjects for subjects 9 and 24 were slightly increased at visit 4 (206 and 211 ms, respectively; upper reference limit is 200ms). Subject 17 had a long Bazett correctecd QT interval at baseline and end of treatment. None of these findings was considered to be clinically significant.

Efficacy

The mean change in the PASI at the end of treatment compared to baseline was assessed as a secondary endpoint. PASI scores decreased by 9.3 in the combination group and 8.2 in the Diprosone® group. The difference between the two treatments was not significant (p=0.5331).

MCB 0102 INT: Repeated Courses of Calcipotriol/Betamethasone Dipropionate in Psoriasis Vulgaris

Study design: international (Europe and Canada), multi-center, prospective, randomized, double-blind, 3-arm, parallel group 52-week safety study

Study period: start of patient enrollment: August 23, 2002 to April 20, 2004

Objectives: The primary objective was to determine the safety of treatment regimens involving repeated courses of combination ointment over 52 weeks. Efficacy assessments were secondary.

Methodology: Subjects with psoriasis vulgaris of the trunk and/or limbs were randomized to one of three treatment groups (1:1:1):

- *Group 1*: 52 weeks of once daily combination treatment use as required
- *Group 2*: 4 weeks of once daily treatment with the combination ointment as required followed by 4 weeks of once daily treatment with calcipotriol ointment as required; this sequence was repeated for a total of 52 weeks (4/4 alt.)
- *Group 3*: 4 weeks of once daily treatment with the combination ointment as required followed by 48 weeks of once daily calcipotriol ointment treatment as required (4/48)

Subjects were assessed every four weeks.

Main Criteria for Inclusion: