CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-563

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	**22-563**
Brand Name:	Sorilux®
Generic Name:	Calcipotriene
Dosage Form & Strength:	Foam, 0.005 %, applied twice daily
Indication:	Topical treatment of Plaque Psoriasis in patients (b) (4)
Applicant:	Stiefel**,** GSK
Submission:	505(b)(2), Standard
Submission Dates:	12/18/09
OND Division:	Dermatological and Dental Products
OCP Divisions:	Clinical Pharmacology 3
Primary Reviewer:	Seongeun Julia Cho, Ph.D.
Team Leader:	Dennis Bashaw, Pharm.D.

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1. EXECUTIVE SUMMARY

1.1 Recommendation

The clinical pharmacology information submitted in NDA 22-563 is acceptable from a Clinical Pharmacology perspective to support the approval of Sorilux in the subjects with mild to moderate plaque psoriasis aged 18 years and older, provided that a mutually agreement is reached between the sponsor and the Agency regarding the labeling language (b) (4)

(b) (4) following the communication with Division of Dermatology and Dental Products (DDDP), the sponsor submitted an updated pediatric development plan on Jun 30th, 2010, requesting a Partial Pediatric Waiver to conduct studies in subjects from birth to age 2 years and proposed to conduct clinical studies in subjects aged 2 to 11 years. The sponsor's pediatric development plan includes an open-label bioavailability study in this age group under maximum use conditions. We find the proposed Pediatric Development Plan acceptable from a clinical pharmacology perspective. The sponsor, however, is recommended to submit the study protocol prior to the initiation of the study for the Agency's review.

1.2 Post-Marketing Requirements (to be finalized after PeRC meeting on August 11th, 2010)

- Conduct PK study in patients aged 2 to 17 years under maximum use conditions

1.3 Summary of Clinical Pharmacology Findings

Calcipotriene foam is a new topical dosage form of calcipotriene with a proposed indication of the treatment of mild to moderate plaque psoriasis. The submission is a 505(b)(2) application with Dovonex Ointment, 0.005% (NDA 20-273, 1993 [Leo Pharma]) as a reference listed drug (RLD), which contains the same active ingredient, strength and route of administration as the new investigational drug. The sponsor intends to rely on the Agency's previous findings on the clinical safety of Dovonex ointment and conducted a comparative bioavailability study with an aim to provide systemic exposure data and to establish a clinical systemic safety bridge between Dovonex ointment and Calcipotriene foam.

In Study CAL.203, the bioavailability of calcipotriene foam, 0.005% was compared to that of Dovonex ointment, 0.005%, in a single-center, randomized, open-label phase 2 study in subjects with mild-to-moderate plaque psoriasis (5-10% Body Surface Area). The study enrolled 32 male and female subjects (Male: 19 Female: 13) age 12 years and older. Subjects were instructed to apply approximately 3.5 grams of study product per application twice a day (morning and evening) for 2 weeks, applying to all affected areas. Plasma levels of circulating calcipotriene were measured at the following time points:

- Prior to study product application on Days 1, 8, and 15
- At 1, 3, 6, and 10 hours after morning study product application on Day 8
- At 1 hour after morning study product application on Day 15

The plasma drug levels were measured using a HPLC/MS/MS with a lower limit of detection 10 pg/mL. Among 32 subjects, 6 subjects (one subject in the calcipotriene foam group and 5 subjects in the Dovonex treatment group) had measurable levels of calcipotriene at various time points during the study. Among these 6 calcipotriene-positive subjects, only one subject had calcipotriene levels above LOQ in 2 consecutive samples and was in the Dovonex ointment treatment group. Due to insufficient data to calculate pharmacokinetic parameters, computation of Cmax, Tmax, or AUC was not conducted. Therefore, a definite bioequivalence evaluation between two products per 80-125 % rule could not be made. However, it can be concluded that the systemic absorption of calcipotriene following twice daily application of 3.5 g of calcipotriene foam for 2 weeks is low and is not any higher than that of Dovonex ointment.

(b) (4)

While the systemic safety bridge in adults (>18 years) may be established by the above mentioned study results, there are two issues related to the pediatric indication (12 -17 years). Dovonex ointment is approved only for patients 18 years or older and as such the sponsor would not be able to reply on the safety information of Dovonex ointment for the development of Sorilux in pediatric patients. In addition, the sponsor enrolled only one subject in the pediatric age group in this study. While the plasma calcipotriene levels in this subject were similarly low (BLQ at all time points studied) as in the majority of adult subjects, a single subject evaluation in this age group is clearly inadequate to establish clinical safety bridge to the entire pediatric population and to obtain pediatric indication. Therefore, a post-marketing requirement is recommended to obtain systemic exposure data in patients aged 12 to 17 years.

The following is key demographic information and baseline characterization of the PK study for each treatment group, showing an imbalance in the number of subjects among age categories.

	Calcipotriene Foam	Dovonex Ointment
Number of Subjects	16	16
Age		
N	16	16
mean (std)	50.6 (18.3)	42.2 (13.9)
median	56.5	41.0
min, max	14.0, 80.0	19.0, 76.0
Age Category		
12 < 18 Years	1 (6%)	0 (0%)
18 < 65 Years	12 (75%)	15 (94%)
≥ 65 Years	3 (19%)	1 (6%)
Gender		
Male	10 (63%)	9 (56%)
Female	6 (38%)	7 (44%)

(b) (4)

a consult from Pediatric and Maternal Health Staff (PMHS) agrees with the Division's position based on the epidemiology and an abundance of pediatric psoriasis (see the comments below from a Memorandum by PMHS).

PMHS Reviewer Comment:
Based on the epidemiologic data and the limited number of approved topical treatments for plaque psoriasis in pediatric patients, especially those less than 12 years, requiring PREA studies in patients > 2 years appears appropriate as an adequate number of patients appear to be available and calcipotriene treatment may provide a meaningful therapeutic benefit as an alternative therapeutic option.

On Jun 30th, 2010, the sponsor submitted an updated pediatric development plan, which includes a request for Partial Pediatric Waiver to conduct studies in subjects from birth to age 2 years. The sponsor proposes the following clinical studies in subjects aged 2 to 11 years.

1. One open-label bioavailability study under maximum-use conditions in 25 evaluable subjects aged 2 through 11 years with moderate plaque psoriasis
2. One randomized, double-blind safety and efficacy study in 100 evaluable subjects aged 2 through 11 years with moderate plaque psoriasis

The proposed pharmacokinetic study plan appears reasonable. To note, however, is that the sponsor plans sparse blood sampling for pharmacokinetic analysis. Since the number of required subjects will depend on the sampling scheme and there was no detailed information submitted at this time, we recommend the sponsor submit the study protocol prior to the initiation of the study for the Agency's review.

2. QUESTION BASED REVIEW

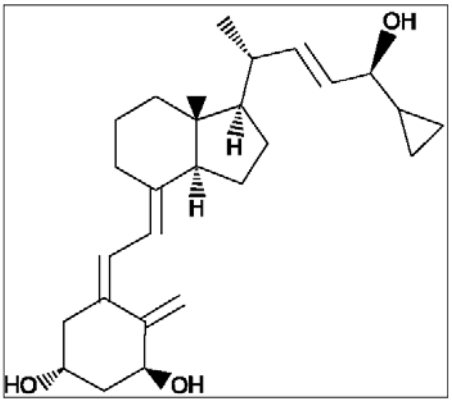
2.1 General Attributes

What are the proposed mechanisms of action of Sorilux?

One of the pathologic features of psoriasis is a shortened epidermal cell cycle. Normally, keratinocytes require 28 to 44 days to migrate from the basal cell layer of the epidermis to the stratum corneum. However, in subjects with psoriasis, this migration can be only 4 days (Weinstein and Van Scott 1965). Vitamin D3 and its analogs are believed to normalize the hyperproliferative changes that occur in psoriatic skin via inhibition of proliferation and stimulation of cell (keratinocyte) differentiation (Christophers and Mrowietz, 1999).

Sorilux is a new topical formulation of calcipotriene 0.005%, which is in an ethanol-free, aqueous-based emulsion formulation foam. Calcipotriene (Calcipotriol in Europe and Canada) is a synthetic vitamin D3 analog that is derived from naturally occurring vitamin D3 (Calcitriol, 1,25-dihydroxy vitamin D3). The effects of calcipotriene on skin cells are similar to those of vitamin D3. Calcipotriene binds to receptors on skin cells, including keratinocytes, and induces differentiation and suppresses proliferation of these cells.

What are physico-chemical properties of the drug substance?



Calcipotriene foam is a new topical dosage form of calcipotriene that has been developed for the treatment of plaque psoriasis, and contains the same active ingredient as Dovonex Ointment, 0.005% (NDA 20-273, 1993, Leo Pharma), which is selected as the reference listed drug (RLD) for this 505(b)(2) application.

The formulation of calcipotriene foam, which was used in all nonclinical and clinical studies, is shown in Table 1 (clinical formulation, Lot Number ZLS-C). The vehicle foam used as placebo in the phase 3 studies replaced calcipotriene with an additional 0.005% water to maintain proportionality of ingredients (Lot Number ZLP-C).

Table 1: Calcipotriene Foam Clinical Formulations

Component	Reference to Quality Standard	% (w/w) Clinical Placebo Formulation	% (w/w) Clinical Active Formulation	Function
Calcipotriene	In-house	N/A	0.005	Active
Purified Water	(b) (4)			
Propylene Glycol				
Light Mineral Oil				
Polyoxyl 20 Cetostearyl Ether				
Cetyl Alcohol				
Stearyl Alcohol				
White Petrolatum				
Isopropyl Myristate				
Dibasic Sodium Phosphate, Anhydrous				
Edatate Disodium				
dl-α-Tocopherol				
Lot Number(s)	N/A	ZLP-C	ZLS-C	

What are proposed indications and dosing regimen for Sorilux?

The sponsor-proposed indication is topical treatment of plaque psoriasis in patients (b) (4) (b) (4) with a dosage form of foam (aerosol) and the proposed dosing regimen is twice daily.

2.2 Clinical Pharmacology

What are the bases of the proposed dose and a dosage form of Sorilux?

Calcipotriene foam is a new topical dosage form of calcipotriene, and contains the same active ingredient, strength, and route of administration, as Dovonex Ointment, 0.005% (NDA 20-273, 1993, Leo Pharma), which is selected as the reference listed drug (RLD) for this 505(b)(2) application. The sponsor claims that the foam delivery system has certain advantages over the other currently marketed dosage forms, such as cream, ointment and lotion. The sponsor-claimed differences are (1) cream and ointment dosage forms have cosmetic disadvantages, and (2) lotions may be runny, leading to loss of active ingredient at the desired site of action. (3) In contrast, the foam is an aqueous and non-runny vehicle and a collapse of the foam structure upon application deposits the active ingredient directly on to the skin. (4) The sponsor also claims that (b) (4) contribute to the effectiveness of this new formulation of calcipotriene, especially in subjects with mild psoriasis.

The strength and the dosing regimen of calcipotriene foam is the same as Dovonex Ointment and other doses/dosing regimens were not studied by the current sponsor in this submission.

What are the design features of the clinical pharmacology and clinical studies used to support the dosing or claims?

This application is being submitted under 505(b)(2) using Dovonex Ointment (calcipotriene 0.005 %) as a reference drug. As such the clinical development program for calcipotriene foam consists of the followings:

- Four phase 1 studies in healthy volunteers to determine the irritation and allergenic potential of calcipotriene foam: a skin irritation study (U0267-101), a skin sensitization study (U0267-102), a phototoxicity study (U0267-103), and a photoallergy study (U0267-104).
- One phase 2 efficacy and safety study (CAL.201) and one bioavailability study (CAL.203) in subjects with mild-to-moderate plaque-type psoriasis to compare the bioavailability, efficacy, and safety of calcipotriene foam and the RLD, Dovonex Ointment.
- Two identically designed phase 3 studies (U0267-301 and U0267-302) comparing the safety and efficacy of calcipotriene foam and vehicle foam in subjects with mild-to-moderate plaque-type psoriasis.

(b) (4)

Reviewer's comments:
As stated above, the review team and PMHS determined that epidemiologic data on the number of pediatric patients with plaque psoriasis (b) (4)

As a part of a clinical safety bridge, the sponsor has compared the bioavailability of calcipotriene foam to the reference listed drug (RLD). The sponsor states that Dovonex (calcipotriene) Ointment, 0.005%, was selected as a RLD, because at the time of the inception of their clinical development program for calcipotriene foam, the majority of published calcipotriene nonclinical safety information and the longest market history were available for the ointment formulation.

Dovonex Ointment was used in a phase 2 study (CAL.201) as well as in a bioavailability study (CAL.203). After Stiefel had conducted these two studies (systemic bioavailability and phase 2 study), Dovonex Ointment was withdrawn in April 2007 from the United States and European markets, reportedly for business reasons. Alternatively, Dovonex Cream (calcipotriene 0.005%) is currently approved and marketed for the treatment of plaque-type psoriasis, and Dovonex Solution (calcipotriene 0.005%) is currently approved and marketed for scalp psoriasis. However, the cream and solution formulations

that are discussed in this submission were considered supplemental for safety purposes, as they are not the RLD.

To evaluate the potential for topically applied calcipotriene to affect systemic calcium metabolism, serum calcium concentrations were measured in Study CAL.203 and Study CAL.201. A summary of these studies and a review of the data are included in the pharmacodynamic section below.

The safety and efficacy of calcipotriene foam was evaluated in two phase 3 studies (U0267-301 and U0267-302). Two studies were identical in design and compared the efficacy of calcipotriene foam and vehicle foam in subjects with mild-to-moderate plaque-type psoriasis affecting 2% to 20% of BSA. Study U0267-301 enrolled 343 subjects and U0267-302 enrolled 330 subjects; both studies randomized subjects in a 2:1 ratio to calcipotriene foam and vehicle foam groups. The primary efficacy endpoint was the proportion of subjects who had an ISGA (Investigator's Static Global Assessment) score of clear or almost clear (0 or 1) at week 8 and a minimum improvement in the ISGA score of 2 grades from baseline to week 8.

What is the relative bioavailability of the proposed to-be-marketed formulation to the reference formulation?

The relative bioavailability of calcipotriene foam, 0.005%, compared to Dovonex ointment, 0.005%, was evaluated in a single-center, randomized, open-label phase 2 study in subjects with mild-to-moderate plaque psoriasis (5-10% Body Surface Area, (CAL.203). Thirty two male and female subjects (Male: 19 Female: 13) age 12 years and older were enrolled and randomized 1:1 (EF Calcipotriene Foam: Dovonex Ointment). The study consisted of 2 weeks of dosing. Subjects were instructed to apply approximately 3.5 grams of study product per application (twice a day (morning and evening) at approximately the same time each day) and cover all affected areas (except for the face and scalp). Plasma levels of circulating calcipotriene were measured at the following time points:

- Prior to study product application on Days 1, 8, and 15
- At 1, 3, 6, and 10 hours after morning study product application on Day 8 (The second daily application of study product on Day 8 occurred after the 10-hour blood sampling).
- At 1 hour after morning study product application on Day 15

Rationale for selecting Day 8 for frequent PK sampling:
The sponsor stated that in a previous PK study conducted with Dovonex ointment (using ^{14}C-labeled calcipotriene) and submitted in NDA 20-273, the mean Cmax was reached at 6 hours and plasma calcipotriene was no longer detected at 36 hours post-dosing. Although the exact half-life of calcipotriene had not been determined, the sponsor reasoned that steady-state would be reached by Day 8, which represents >5 half-lives, even in the case of $T_{1/2}$ of 36 hours.

Reviewer's comments

The sponsor's rationale for choosing Day 8 for steady-state PK evaluation appears to be reasonable.

The following is key demographic information and Baseline characterization for each treatment group.

	Calcipotriene Foam	Dovonex Ointment
Number of Subjects	16	16
Age		
N	16	16
mean (std)	50.6 (18.3)	42.2 (13.9)
median	56.5	41.0
min, max	14.0, 80.0	19.0, 76.0
Age Category		
12 < 18 Years	1 (6%)	0 (0%)
18 < 65 Years	12 (75%)	15 (94%)
≥ 65 Years	3 (19%)	1 (6%)
Gender		
Male	10 (63%)	9 (56%)
Female	6 (38%)	7 (44%)

All 32 subjects enrolled in the study completed the study. Using a HPLC/MS/MS bioanalytical assay with a lower limit of detection 10 pg/mL, 6 out of the 32 subjects had measurable levels of calcipotriene at various time points during the study, all of which were below 25 ng/mL. Among 6 subjects with detectable calcipotriene levels, one subject was in the calcipotriene foam group and the other 5 subjects were from the Dovonex treatment group. Among all 6 calcipotriene-positive subjects, only one subject had calcipotriene levels above LOQ in 2 consecutive samples and was in the Dovonex ointment treatment group.

Due to insufficient data to calculate pharmacokinetic parameters, computation of Cmax, Tmax, or AUC was not conducted. Therefore, bioequivalence determination could not be made. However, this reviewer concludes that the systemic absorption of calcipotriene following twice daily application of 3.5 g of calcipotriene foam (7 g daily) for 2 weeks is low and is not any higher than that found in the Dovonex ointment treatment group.

Does the submission contain sufficient clinical pharmacology information to adequately address clinical systemic safety bridge to RLD?

As described above, the sponsor conducted a comparative bioavailability study using calcipotriene foam and Dovonex ointment (RLD) to establish a clinical systemic safety bridge. The data submitted in the application demonstrate that the systemic absorption following the use of calcipotriene foam is not higher than that following the use of Dovonex ointment. It should be noted, however, that Dovonex ointment was approved

for patients 18 years or older, (b) (4) Given the approved age population for Dovonex ointment, the safety and effectiveness of Dovonex in pediatric patients have not been established (per Dovonex ointment 0.005% label) and therefore the sponsor can not rely on safety findings of Dovonex for their product in this age group.

As an alternative approach, the systemic safety of calcipotriene foam in this 505(b)(2) application may be established in the following two steps: (1) clinical safety bridge based on comparative bioavailability to Dovonex ointment among patients 18 years or older and, (2) relative bioavailability of calcipotriene foam in adolescent patients (12 to 17 years) compared to that of 18 years or older. As for the patients 18 years or older, it can be concluded that the systemic absorption of calcipotriene is not higher than that of Dovonex ointment, based on the data summarized above. However we can not adequately determine if the systemic absorption in 12 to 17 years is similar to that in adults because the study CAL.203 had only one subject in this age group. This clearly poses an issue of insufficient information for pediatric safety, as the outcome of one single patient cannot be extrapolated to represent the responses of the entire adolescent patient population. That being said, the calcipotriene levels of that one patient (14 yo) were BLOQ at all time points tested, similar to those in the majority of adult patients.

For a comparison purpose, the age demographics in phase 3 studies are shown below. Again, the number of pediatric subjects in both phase 3 studies is small, representing 1-2 % of studied subjects.

Demographics:

Phase 3 study (U0267-301) Per Protocol Analysis Set

	EF Calci Foam (n=188)	Vehicle Foam (n=93)	Total (n=281)
Age			
n	188	93	281
mean (sd)	48.6 (14.5)	48.9 (13.6)	48.7 (14.2)
median	48	48	48
min, max	15, 89	17, 78	15, 89
p-value	0.983		
Age Category, n(%)			
12 - < 18	4 (2%)	1 (1%)	5 (2%)
18 - < 65	161 (86%)	78 (84%)	239 (85%)
>= 65 years	23 (12%)	14 (15%)	37 (13%)
p-value	0.646		

Phase 3 study (U0267-302) Per Protocol Analysis Set

	EF Calci Foam (n=176)	Vehicle Foam (n=85)	Total (n=261)
Age			
n	176	85	261
mean (sd)	48.0 (14.5)	47.6 (17.1)	47.9 (15.3)
median	48	47	47
min, max	12, 82	16, 80	12, 82
p-value	0.762		
Age Category, n(%)			
12 - < 18	2 (1%)	2 (2%)	4 (2%)
18 - < 65	149 (85%)	67 (79%)	216 (83%)
>= 65 years	25 (14%)	16 (19%)	41 (16%)
p-value	0.337		

Another point of consideration is the range of BSA involvement of patients in the study. Because the evaluation of systemic absorption of topical products is one of the safety measures, in order to rely on the findings of the systemic adverse events of the RLD, the systemic exposure for calcipotriene foam should be compared to that of Dovonex ointment under maximal use conditions consistent to Phase 3 trials and in the proposed labeling. In the study CAL.203, the BSA range evaluated was 5-10 %, while in two phase 3 studies, the range was 2-20 %. Based on the comparative bioavailability data summarized above, the extent of systemic absorption in patients up to 10 % BSA can be concluded to be similar between calcipotriene foam and Dovonex. While a definite comparison can not be made for BSA higher than 10 %, which consists of ~14 % of subjects in phase 3 trials, it is reasonable to assume that when the systemic exposure between the test and reference products is similar up to 10 % BSA, it is not likely that the systemic absorption of two products will be different at higher BSA involvement. In addition, the mean percent BSAs of the calcipotriene treatment group in Phase 3 studies were 6.3-6.4 %, which is not different from the mean 6.5 % in Study CAL.203. Therefore, it can be concluded that systemic exposure to calcipotriene foam is comparable to that of Dovonex ointment.

Have pharmacodynamic markers been adequately explored?

One of the known potential systemic side effects of vitamin D analogues is its impact on calcium metabolism. Use of high doses of topical calcipotriene ointment (>100 g/week) has been shown to result in mild increases in 24-hr urine calcium concentrations, and

doses of >300 g/week have resulted in increases in serum calcium concentrations, while exposures to calcipotriene ointment or cream up to 50 g/week have shown no significant changes in serum calcium concentrations or calcium urine excretions. In the study CAL.203, the sponsor monitored serum calcium concentrations at Screening, Day 1, Day 8, and Day 15. The mean and median values of serum calcium and albumin-adjusted serum calcium were comparable between two groups and were within the normal range (table below). At an individual level, there were 10 subjects who had albumin-adjusted serum calcium that were lower than the normal range at Screening and/or Baseline. Four of these subjects (2 in each treatment arm) had lower than normal levels after initiating study dosing as well, but similar to Screening and/or Baseline values.

Reviewer's comments

One of potential concerns of systemic exposure to calcipotriene is its effects on calcium metabolism and increased blood calcium levels. In this study, none of the albumin-adjusted calcium levels measured at Screening, Day 1, Day 8, and Day 15 were higher than the normal range. There is one caveat, however, in concluding no effects of calcipotriene foam on the plasma calcium level, based on these results; many subjects in the study (10 out of 32) had Screening/Baseline calcium levels lower than the normal range, so even with some degrees of elevation in calcium following the drug use, the laboratory values would still be within the normal range. Nonetheless, a further examination of potential causal relationship between calcium effects vs. calcipotriene systemic exposure will not be meaningful, because, as described above, the majority of the plasma concentrations of calcipotriene in this study were BLQ.

Table 14.3.11: Summary of Albumin Adjusted Calcium (mg/dL)

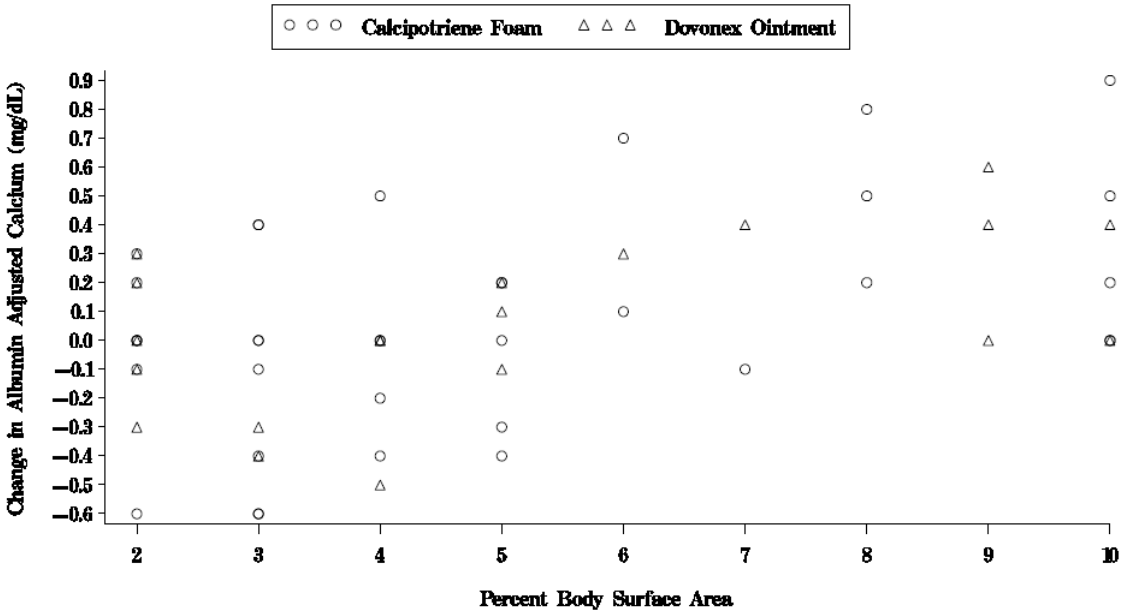
	Calcipotriene Foam	Dovonex Ointment
Number of Subjects	16	16
Screening		
n	16	16
mean (std)	8.5 (0.41)	8.7 (0.37)
median	8.5	8.7
min, max	7.7, 9.1	8.0, 9.4
Baseline		
n	16	16
mean (std)	8.8 (0.24)	8.8 (0.39)
median	8.9	8.9
min, max	8.4, 9.2	7.9, 9.5
Day 8		
n	16	16
mean (std)	8.8 (0.38)	8.8 (0.25)
median	8.8	8.9
min, max	8.2, 9.7	8.2, 9.2
Day 15/End of Treatment		
n	16	16
mean (std)	8.9 (0.31)	8.8 (0.26)
median	8.9	8.9
min, max	8.2, 9.7	8.3, 9.1

Table 14.3.12: Out of Range Laboratory Results

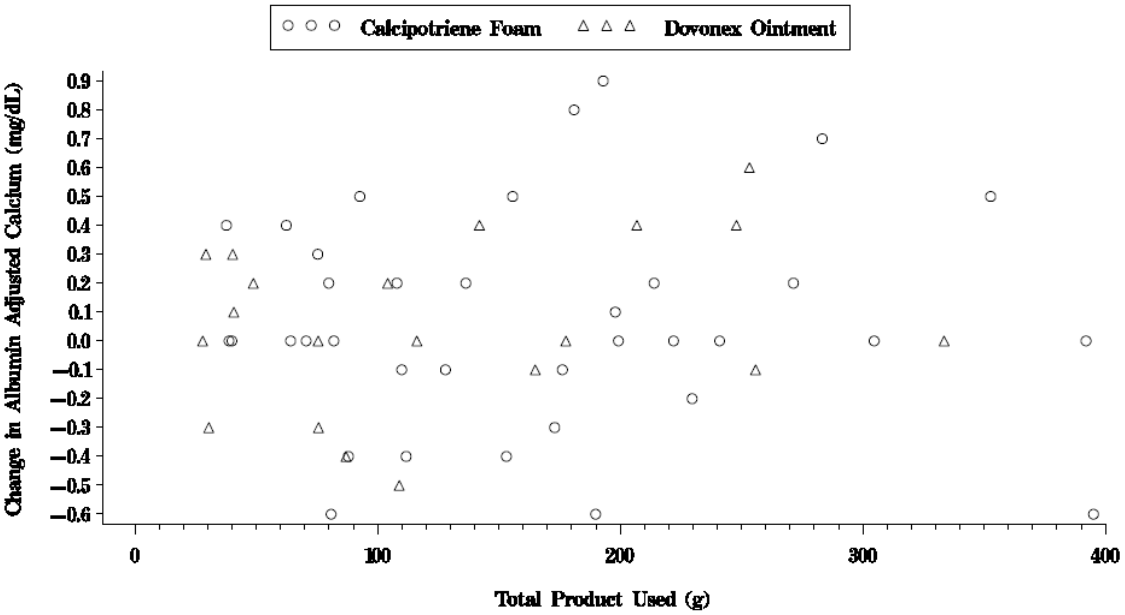
Site-Subject	Actual Treatment	Visit	Test Name	Test Result *		Normal Range
101-3001	Calcipotriene Foam	Screening	Adjusted Calcium	7.7	L	8.4-10.6
101-3004	Calcipotriene Foam	Screening	Adjusted Calcium	7.9	L	8.4-10.6
101-3005	Dovonex Ointment	Screening	Adjusted Calcium	8.0	L	8.4-10.6
101-3006	Calcipotriene Foam	Screening	Adjusted Calcium	8.2	L	8.4-10.6
101-3007	Calcipotriene Foam	Screening	Adjusted Calcium	8.3	L	8.4-10.6
101-3011	Dovonex Ointment	Baseline	Adjusted Calcium	8.3	L	8.4-10.6
		Day 8	Adjusted Calcium	8.2	L	8.4-10.6
101-3013	Calcipotriene Foam	Screening	Adjusted Calcium	8.2	L	8.4-10.6
		Day 8	Adjusted Calcium	8.2	L	8.4-10.6
		Day 15	Adjusted Calcium	8.2	L	8.4-10.6
101-3014	Dovonex Ointment	Screening	Adjusted Calcium	8.3	L	8.4-10.6
101-3018	Calcipotriene Foam	Screening	Adjusted Calcium	8.5	L	9.2-10.7
		Baseline	Adjusted Calcium	9.0	L	9.2-10.7
		Day 8	Adjusted Calcium	8.9	L	9.2-10.7
		Day 15	Adjusted Calcium	8.8	L	9.2-10.7
101-3029	Dovonex Ointment	Screening	Adjusted Calcium	8.2	L	8.4-10.6
		Baseline	Adjusted Calcium	7.9	L	8.4-10.6
		Day 15	Adjusted Calcium	8.3	L	8.4-10.6

The following analyses are intended to evaluate albumin-adjusted calcium levels in serum as a function of BSA or amounts of drug used, as a surrogacy for systemic absorption of calcipotriene.

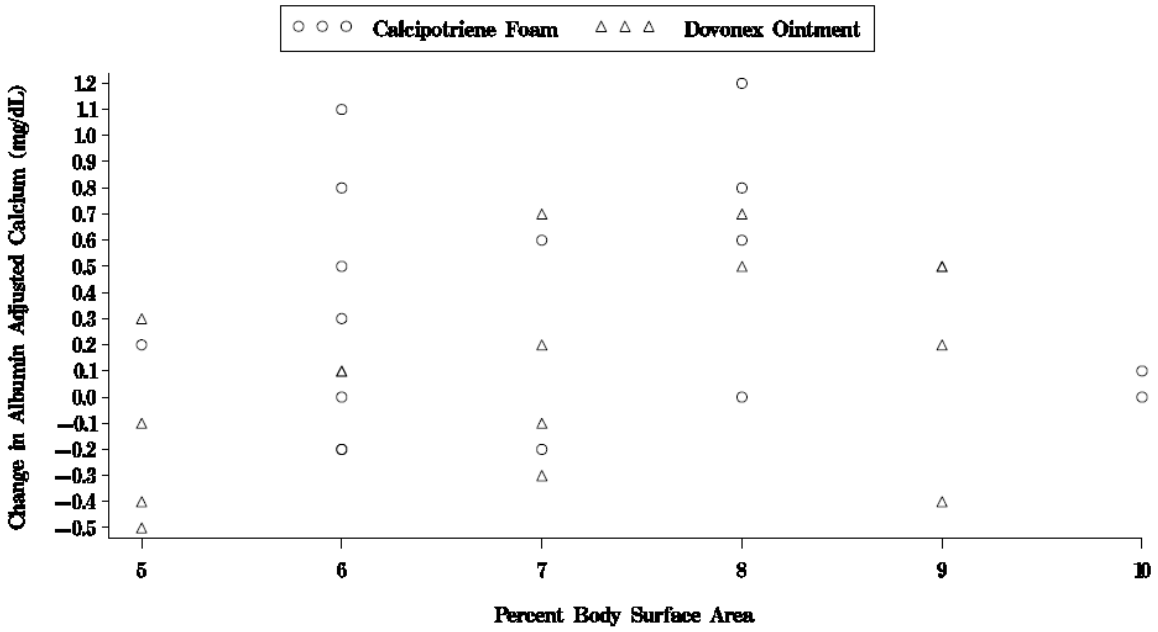
CAL201
Change from Baseline to Week 8 Albumin Adjusted Calcium
by Treatment and Percent BSA at Baseline
Intent–to–Treat Analysis Set



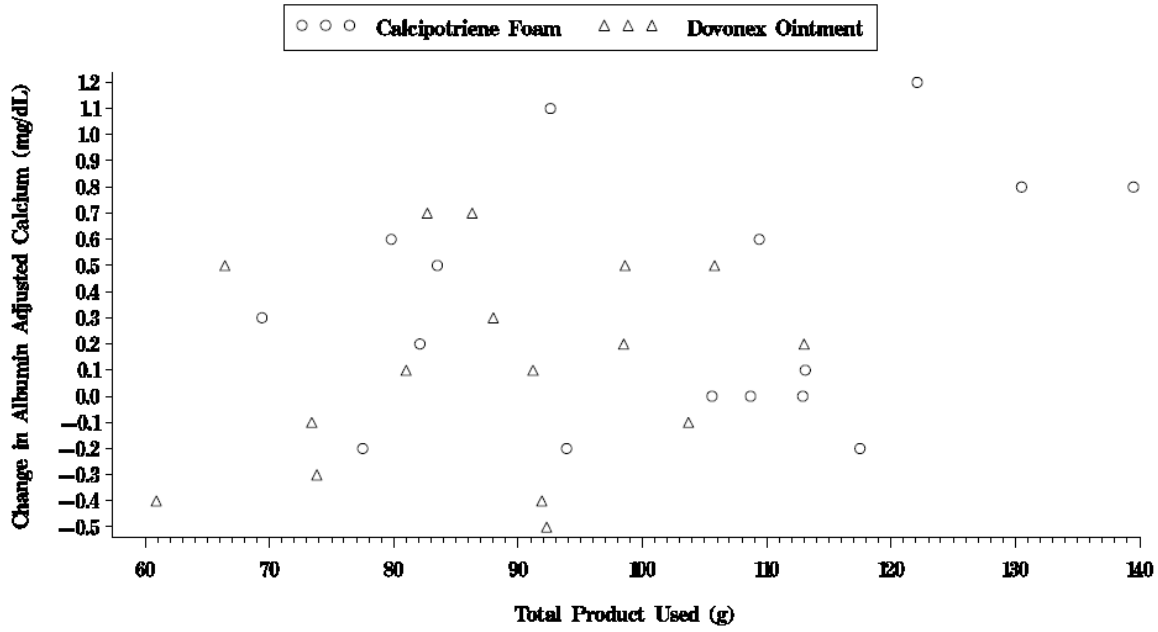
CAL201
Change from Baseline to Week 8 Albumin Adjusted Calcium
by Treatment and Total Product Used
Intent–to–Treat Analysis Set



CAL203
Change from Baseline to Day 15 Albumin Adjusted Calcium
by Treatment and Percent BSA at Baseline
Intent–to–Treat Analysis Set



CAL203
Change from Baseline to Day 15 Albumin Adjusted Calcium
by Treatment and Total Product Used
Intent–to–Treat Analysis Set



Reviewer's comments

Results from CAL.201 showed a trend of increased calcium changes with increasing BSA. Data from CAL.203 did not show this trend, probably due to a smaller sample size. There were less clear relationships between serum calcium changes and the total product used in either study. There were no signals suggestive of differential effects on calcium metabolism by calcipotriene foam vs. Dovonex ointment in relation to the amount of drug used or BSA. These data are consistent with the PK results that systemic exposures of calcipotriene foam and Dovonex ointment are not significantly different.

What is the effect of food on the bioavailability of Sorilux?
Not applicable

What are the single and multiple dose PK parameters?

The study was conducted following twice daily application for two weeks to meet one of the components required for the maximal use conditions. No additional data from a single dose PK study are needed for this drug product.

2.3 Intrinsic factors

What intrinsic factors (gender, age, ethnicity, or disease) affect exposure or response?

Pediatrics

As mentioned in the above section, the safety and effectiveness of Dovonex have not been established in pediatric patients, and as such the systemic safety bridge of calcipotriene foam in this age group should be established within the calcipotriene foam treatment group by comparing the blood levels of the drug in pediatric patients (12 to 17 years) to those of adults. As noted above, in the PK study in this application, there was only one subject in the adolescent age group (12 to 17 years). The date from this study are clearly inadequate to make a conclusion on systemic absorption potential in pediatrics since the outcome of one single patient cannot represent the responses of the entire pediatric patient population.

Renal or hepatic impairments
Not applicable

2.4 Extrinsic factors

Drug interactions

Drug interaction potential with calcipotriene was not evaluated in this application. Considering low systemic exposure to calcipotriene following the use of calcipotriene foam, no clinically meaningful systemic drug interaction is anticipated.

2.5 Analytical section

Were the active moieties identified and measured in the plasma in the clinical pharmacology study?

Yes.

What analytical method was used to determine drug concentrations and was the analytical assay method adequately validated?

The sponsor has developed and validated a method for the determination of calcipotriene concentrations in human plasma using high-performance liquid chromatography (HPLC) with mass spectrometric (MS/MS) detection. The method is applicable for measuring calcipotriene concentrations ranging from 10.0 to 2000.0 pg/mL using 1.0 mL of human plasma for extraction.

Human plasma samples containing calcipotriene with tacalcitol as the internal standard (IS) and heparin as the anticoagulant were processed by liquid/liquid extraction, followed by a normal phase solid-phase extraction (SPE) clean-up on an amino column. The extracts were reconstituted and analyzed by reverse-phase high-performance liquid chromatography using a (b) (4) column maintained at 35°C. The mobile phase was nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds were detected using a tandem quadrupole mass spectrometer (MS/MS). Calcipotriene and the internal standard were detected as lithium adducts with lower limit of detection at 10 pg/mL.

The correlation coefficients of the calcipotriene plasma calibration curves were not less than 0.9997 for the concentration range of 10.0 to 2000.0 pg/mL. The overall precision (%CV) of the back-calculated standard concentrations ranged from 0.7% to 8.5% for calcipotriene for all three validation runs. The overall accuracy (%DEV) of the mean back-calculated values ranged from -3.5% to 1.9% for calcipotriene over the same period.

Calibration Curve Parameters for Calcipotriene in Human Plasma

Analytical Run	Analysis Date	Coefficient (A)	Exponent (B)	Correlation Coefficient
AR01	06/09/06	5.885E-04	0.9822	0.9997
AR02	06/16/06	7.354E-04	0.9696	0.9999
AR03	06/16/06	7.666E-04	0.9807	0.9999
	Mean	6.968E-04	0.9775	0.9998

Back-Calculated Calibration Standard Data and Statistics for Calcipotriene in Human Plasma

Analytical Run	Standard Concentration (pg/mL)									
	10.0		20.0	50.0	100.0	250.0	500.0	1000.0	2000.0	
AR01	9.82	10.0	22.1	48.9	91.9	248.1	487.9	1022.4	2021.4	2046.8
AR02	10.0	10.3	20.0	49.4	97.3	244.5	507.1	1003.1	1916.6	2121.6
AR03	10.4	a	18.7	51.0	100.3	246.8	502.2	1032.7	1996.5	1960.5
Mean	10.1		20.3	49.8	96.5	246.5	499.1	1019.4	2010.6	
SD	0.24		1.72	1.10	4.26	1.82	9.98	15.03	71.12	
%CV	2.4		8.5	2.2	4.4	0.7	2.0	1.5	3.5	
%DEV	1.0		1.5	-0.4	-3.5	-1.4	-0.2	1.9	0.5	

Interday Precision

For the QC samples prepared in human plasma, the interday precision of the method was determined. The %CV for the 30.0, 250.0 and 1600.0 pg/mL calcipotriene QC samples was (b) (4)

Interday Accuracy

The interday accuracy of the method was determined by comparing the mean concentrations with the theoretical concentrations of the compounds in the QC samples. For calcipotriene in human plasma, the interday mean %DEV values ranged from -8.7% to -1.5% from their expected values for the three validation runs at the three QC sample concentrations.

Intraday Precision

For the QC samples prepared in human plasma, the intraday precision of the method was determined from the %CV of the mean of six replicates of the three QC sample concentrations in each of the three validation runs. For the 30.0, 250.0 and 1600.0 pg/mL calcipotriene QC samples, the %CV ranged from 1.4% to 6.6% for all three validation runs.

Intraday Accuracy

The intraday accuracy of the method was determined by comparing the mean concentrations with the theoretical concentrations of the compound in the QC samples. For calcipotriene in human plasma, the intraday mean %DEV values ranged from -12.3% to -1.0% from their expected values for the three QC sample concentrations for all three validation runs.

Lower Limit of Quantitation (LLOQ)
The LLOQ was set at 10.0 pg/mL for calcipotriene in human plasma. At that level, the %CV (n = 6) of the concentrations was 11.2%. The deviation of the mean of the 10.00 pg/mL calibration standards from their theoretical value was -6.8%

Freeze/Thaw Stability
The stability of plasma samples exposed to 4 cycles of freezing (-70°C) and thawing (room temperature) prior to analysis was tested. The mean values for the calcipotriene QC samples remained within ±11.0 %DEV from theoretical for all three levels at -70°C.

Thawed Sample Stability
The stability of plasma samples exposed to thawed, room temperature storage conditions prior to analysis was tested by extracting and analyzing triplicate QC samples at each concentration level after storage at room temperature for 27 hours. The mean %DEV values for the calcipotriene QC samples ranged from -5.6% to -9.5% from theoretical for all three levels.

Frozen Sample Stability
The stability of frozen samples was tested by extracting triplicate QC samples at each concentration after storage for 41 days at -70°C. The mean %DEV values for the calcipotriene QC samples remained within ±9.1% from theoretical for all three levels.

3. DETAILED LABELING RECOMMENDATIONS

Sections related to Clinical Pharmacology only are listed below.

~~Strikethrough text~~ means deletion of the sponsor's proposed text. Underscored blue text means recommended addition.

1 INDICATIONS AND USAGE

SORILUX is (b) (4) indicated for the topical treatment of (b) (4) plaque psoriasis in patients aged (b) (4) 18 and older.

7 DRUG INTERACTIONS

No drug interaction studies were conducted with SORILUX.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

Calcipotriene is a synthetic vitamin D3 (b) (4) that has a similar receptor binding affinity as natural vitamin D3. However, the exact mechanism of the action contributing to the clinical efficacy in the treatment of psoriasis is unknown (b) (4)

12.2 Pharmacodynamics

(b) (4)

12.3 Pharmacokinetics

The systemic absorption of calcipotriene in psoriatic patients was evaluated at steady state following application of SORILUX or calcipotriene ointment. In the SORILUX treatment group, (b) (4) showed calcipotriene plasma concentrations below the limit of quantitation (10 pg/mL), while in the calcipotriene ointment treated group, 5 out of 16 subjects had measurable calcipotriene plasma concentrations at various time points. All measurable plasma calcipotriene concentrations were below 25 pg/mL. (b) (4)

The systemic disposition of caldipotriene is expected to be similar to that of the naturally occurring vitamin (b) (4) Absorbed calcipotriene is known to be converted to inactive metabolites within 24 hours of application (b) (4) and the metabolism occurs via a similar pathway to the natural hormone (b) (4)

4. APPENDIX

4.1 Sponsor's proposed labeling

4.2 OCP filing form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22,563**	**Brand Name**	**Sorilux**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Calcipotriene**
Medical Division	**DDDP**	**Drug Class**	**Vit D analogue**
OCP Reviewer	**Julia Cho**	**Indication(s)**	**Plaque Psoriasis**
OCP Team Leader	**Dennis Bashaw**	**Dosage Form**	**Foam, 0.005 %**
Pharmacometrics Reviewer	**NA**	**Dosing Regimen**	**Applied twice daily**
Date of Submission	**12/18/09**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review		**Sponsor**	**Stiefel, GSK**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**10/21/10**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**1**	**1**	**CAL.203**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				

Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**1**	**1**	
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**	**1**	

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	All clinical studies were conducted with the final formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?		x		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-			x	Since most plasma concentrations were

	submission discussions, submitted in the appropriate format (e.g., CDISC)?				below the detection limit, data were presented only in a tabular format
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			BSA of patients enrolled in the PK study is 5-9%, while patients in phase 3 studies have a wider range of BSA (2-20%) with a mean value of 6.3%.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		x		(b) (4)
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __ __yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

- We noticed that the study population in the PK study does not sufficiently represent the age group of 12-18 years. The adequacy of data will be a review issue (b) (4)

4.3 Individual Study Review

Study Protocol CAL.203

Title of Study:
A Randomized, Open-Label Study to Assess the Bioavailability of Emulsion Formulation Calcipotriene Foam, 0.005%, and Dovonex® Ointment, 0.005%, in Patients with Mild to Moderate Plaque-Type Psoriasis

Development Phase: Phase 2

Study Objectives: To evaluate the bioavailability of Calcipotriene Foam, 0.005% and Dovonex® (calcipotriene) Ointment, 0.005% (Dovonex Ointment), as measured by circulating plasma levels of calcipotriene in subjects with mild-to moderate plaque-type psoriasis.

Methodology:
This was a single-center, randomized, open-label, Phase 2 study of the bioavailability of EF Calcipotriene Foam and Dovonex Ointment in subjects with mild-to-moderate plaque-type psoriasis. Approximately 30 male and female subjects age 12 years and older were enrolled and randomized 1:1 (EF Calcipotriene Foam: Dovonex Ointment). The study consisted of 2 weeks of dosing. Subjects were instructed to apply approximately 3.5 grams of study product per application and cover all affected areas (except for the face and scalp). Subjects were instructed to apply the study product twice a day (morning and evening) at approximately the same time each day.
A blood sample was taken within 1 hour prior to the first application of study product. Additional blood samples were collected on Day 8 and Day 15. On Day 8, blood samples were taken within 1 hour pre-dose and 1, 3, 6, and 10 hours post-dose. The second daily application of study product on Day 8 occurred after the 10-hour blood sampling. On Day 15, blood samples were collected within 1 hour pre-dose and 1 hour post-dose.

Number of Subjects Enrolled: 32
Gender: 19 Males, 13 Females, aged 14 to 80 years
Ethnicity (Race): Caucasian: 25; Hispanic or Latino: 4; Asian: 1; Black: 1; Native Hawaiian/Other Pacific Islander: 1

Main Criteria for inclusion: Male or female subjects at least 12 years old and in good general health with mild-to-moderate plaque-type psoriasis as defined by an Investigator's Static Global Assessment (ISGA) score of 2 or 3 involving 5% to 10% of total Body Surface Area (BSA), excluding face and scalp.

Key demographic information and Baseline characterization

	Calcipotriene Foam	Dovonex Ointment
Number of Subjects	16	16
Age		
N	16	16
mean (std)	50.6 (18.3)	42.2 (13.9)
median	56.5	41.0
min, max	14.0, 80.0	19.0, 76.0
Age Category		
12 < 18 Years	1 (6%)	0 (0%)
18 < 65 Years	12 (75%)	15 (94%)
≥ 65 Years	3 (19%)	1 (6%)
Gender		
Male	10 (63%)	9 (56%)
Female	6 (38%)	7 (44%)
Total Extent of Psoriasis (%)		
N	16	16
mean (std)	7.1 (1.5)	7.0 (1.5)
median	6.5	7.0
min, max	5.0, 10.0	5.0, 9.0
Investigator's Static Global Assessment Score		
Clear	0	0
Almost Clear	0	0
Mild (score of 2)	6 (38%)	6 (38%)
Moderate (score of 3)	10 (63%)	10 (63%)
Severe (score of 4)	0	0

Reviewer's comments:
Among 16 patients in calcipotriene foam-treated group, there was only one patient under 18 years (14 years old; Subject number 101-3018, Female, Caucasian, BSA 6%). It is impractical to assume that the results from this one patient can be a representative of the whole patient population between 12 to 18 years. Therefore, the data from this study are inadequate to support clinical safety bridge in pediatric population.

Test Product, Dose, Batch Number: EF Calcipotriene Foam, 0.005%, 3.5 grams applied topically twice daily, 2 weeks, batch number XEF-C
Reference Therapy, Batch Number: Dovonex (calcipotriene) Ointment, 0.005%, 3.5 grams applied topically twice daily, 2 weeks, batch number T2657

Pharmacokinetic Criteria for evaluation:
Plasma levels of circulating calcipotriene were measured at the following time points:

Prior to study product application on Days 1, 8, and 15
At 1, 3, 6, and 10 hours after morning study product application on Day 8
At 1 hour after morning study product application on Day 15

Cmax, Tmax, and AUC(0–10) at Day 8 were calculated. Trough plasma levels of calcipotriene were to be determined 1 hour before dosing on Days 1, 8, and 15.

Albumin-adjusted serum calcium levels were obtained to evaluate the effect of EF Calcipotriene Foam and Dovonex ointment on calcium metabolism.

Analytical Method:
Human plasma samples containing calcipotriene with tacalcitol as the internal standard (IS) and heparin as the anticoagulant were processed by liquid/liquid extraction, followed by a normal phase solid-phase extraction (SPE) clean-up on an amino column. The extracts were reconstituted and analyzed by reversed-phase high-performance liquid chromatography using a (b) (4) column maintained at 35°C. The mobile phase was nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds were detected using a tandem quadrupole mass spectrometer (MS/MS). Calcipotriene and the internal standard were detected as lithium adducts with lower limit of detection at 10 pg/mL.

Study Results:

Pharmacokinetics Results:
Table below provides the plasma calcipotriene levels detected during the study. Thirty-two subjects were enrolled with 16 in each treatment group. All subjects completed the study. Using a HPLC/MS/MS bioanalytical assay with a lower limit of detection10 pg/mL, 6 out of the 32 subjects had measurable levels of calcipotriene at various time points during the study following treatment for 2 weeks (all below 25 ng/mL). Therefore, pharmacokinetic parameters including Cmax, Tmax, and AUC were not computed.

Table 5: Plasma Concentrations (pg/mL) of Calcipotriene

		Subject Number															
Calcipotriene Foam																	
Day	**Time**	**3001**	**3004**	**3006**	**3007**	**3010**	**3012**	**3013**	**3016**	**3018**	**3019**	**3021**	**3023**	**3026**	**3028**	**3030**	**3032**
1	Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
8	Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
	1 hr	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	10.3	BQL	BQL	BQL
	3 hr	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
	6 hr	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
	10 hr	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
15	Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
	1 hr	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Dovonex Ointment																	
Day	**Time**	**3002**	**3003**	**3005**	**3008**	**3009**	**3011**	**3014**	**3015**	**3017**	**3020**	**3022**	**3024**	**3025**	**3027**	**3029**	**3031**
1	Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
8	Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
	1 hr	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	16.4	BQL	BQL	BQL
	3 hr	BQL	BQL	BQL	BQL	BQL	18.3	BQL	BQL	BQL	BQL	BQL	BQL	24.1	BQL	BQL	BQL
	6 hr	BQL	BQL	BQL	BQL	12.4	17.3	BQL	BQL	19.3	BQL	BQL	BQL	BQL	BQL	BQL	BQL
	10 hr	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
15	Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
	1 hr	BQL	BQL	BQL	BQL	BQL	11.9	BQL	BQL	BQL	11.7	BQL	BQL	BQL	BQL	BQL	BQL

Note: BQL is Below the Quantifiable Limit < 10.0 pg/mL

Efficacy Results: There were no efficacy evaluations in this study.

Safety Results: Median daily product usage in subjects receiving EF Calcipotriene Foam was 6.80 g and that in subjects receiving Dovonex Ointment was 5.55 g. The number of missed applications and the mean %BSA affected were similar for both groups.
One subject (EF Calcipotriene Foam group) reported an adverse experience during the study: a sinus infection of mild severity that was assessed by the investigator to be unrelated to study product. No deaths, other SAEs, or other significant AEs were reported during the conduct of the study. One subject became pregnant during the study and delivered a normal baby 219 days after applying the last dose of study product.

Serum calcium levels were measured in all subjects at Screening, Day 1, Day 8, and Day 15. The mean and median values of serum calcium and albumin-adjusted serum calcium were comparable between two treatment groups and were within the normal range. At an individual level, there were 10 subjects who had albumin-adjusted serum calcium that were lower than the normal range at Screening and/or Baseline. Four of these subjects (2 in each treatment arm) had continued lower-than-normal levels after initiating study dosing, but similar to Screening and/or Baseline values.

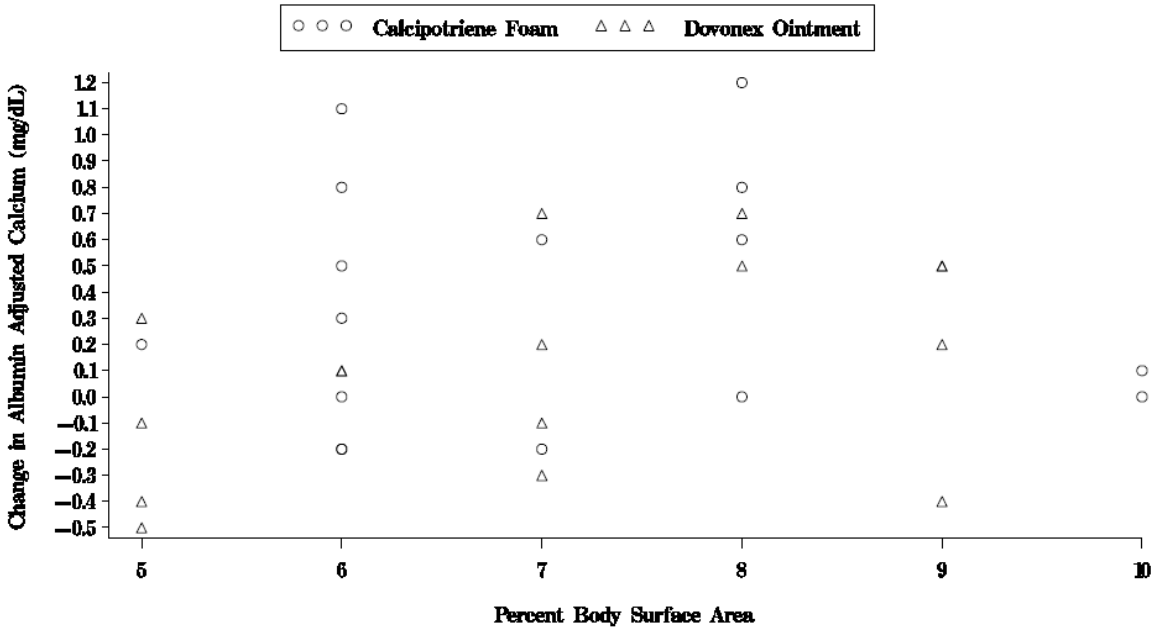
Reviewer's comments
One of potential concerns of systemic exposure to calcipotriene is its effects on calcium metabolism and increased blood calcium levels. In this study, none of the albumin-adjusted calcium levels measure at Screening, Day 1, Day 8, and Day 15 were higher than the normal range. There is one caveat, however, in concluding no effects of calcipotriene foam on the plasma calcium level, based on these results; many subjects in the study (10 out of 32) had Screening/Baseline calcium levels lower than the normal range, so even with some degrees of elevation in calcium following the drug use, the laboratory values would still be within the normal range. Nonetheless, a further analysis

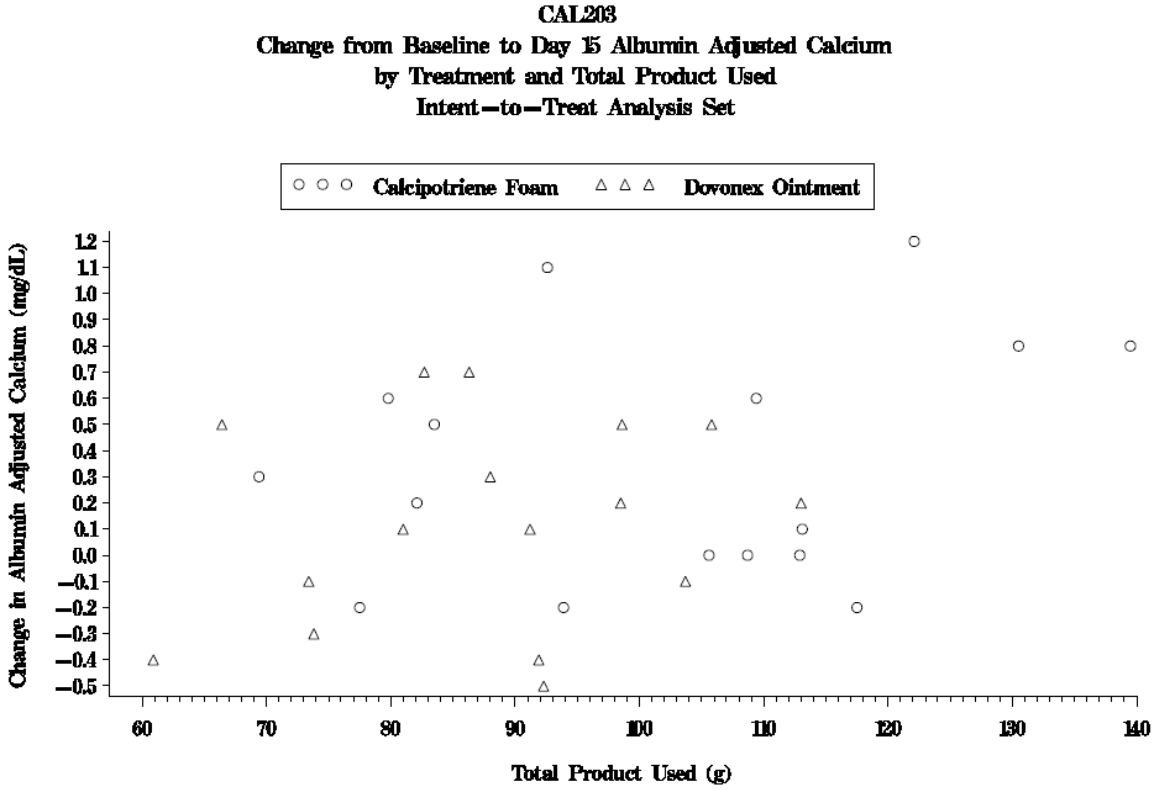
of exposure-calcium changes will not be meaningful, because the majority of the plasma concentrations of calcipotriene in this study were BLQ.

Table 14.3.12: Out of Range Laboratory Results

Site-Subject	Actual Treatment	Visit	Test Name	Test Result *		Normal Range
101-3001	Calcipotriene Foam	Screening	Adjusted Calcium	7.7	L	8.4-10.6
101-3004	Calcipotriene Foam	Screening	Adjusted Calcium	7.9	L	8.4-10.6
101-3005	Dovonex Ointment	Screening	Adjusted Calcium	8.0	L	8.4-10.6
101-3006	Calcipotriene Foam	Screening	Adjusted Calcium	8.2	L	8.4-10.6
101-3007	Calcipotriene Foam	Screening	Adjusted Calcium	8.3	L	8.4-10.6
101-3011	Dovonex Ointment	Baseline	Adjusted Calcium	8.3	L	8.4-10.6
		Day 8	Adjusted Calcium	8.2	L	8.4-10.6
101-3013	Calcipotriene Foam	Screening	Adjusted Calcium	8.2	L	8.4-10.6
		Day 8	Adjusted Calcium	8.2	L	8.4-10.6
		Day 15	Adjusted Calcium	8.2	L	8.4-10.6
101-3014	Dovonex Ointment	Screening	Adjusted Calcium	8.3	L	8.4-10.6
101-3018	Calcipotriene Foam	Screening	Adjusted Calcium	8.5	L	9.2-10.7
		Baseline	Adjusted Calcium	9.0	L	9.2-10.7
		Day 8	Adjusted Calcium	8.9	L	9.2-10.7
		Day 15	Adjusted Calcium	8.8	L	9.2-10.7
101-3029	Dovonex Ointment	Screening	Adjusted Calcium	8.2	L	8.4-10.6
		Baseline	Adjusted Calcium	7.9	L	8.4-10.6
		Day 15	Adjusted Calcium	8.3	L	8.4-10.6

CAL203
Change from Baseline to Day 15 Albumin Adjusted Calcium
by Treatment and Percent BSA at Baseline
Intent-to-Treat Analysis Set





Reviewer's comments

When albumin-adjusted calcium changes were compared per BSA or total drug amount used, there were no trends suggestive of differential effects on calcium metabolism by calcipotriene foam vs. Dovonex ointment. These data are consistent with the PK results that systemic exposures of calcipotriene foam and Dovonex ointment are not significantly different.

Conclusion:

The pharmacokinetics of Calcipotriene Foam and Dovonex Ointment showed no significant difference in the systemic exposure and accumulation of calcipotriene when drugs were administered twice daily for two weeks to subjects 18 years of age and older with mild-to-moderate plaque-type psoriasis.

Table 2 Study Flow Chart

Parameter	Screening	Day 1 Visit[2]	Day 8 Visit (± 1 day)	Day 15 Visit (± 2 days)
Written informed consent/assent	X			
Signed HIPAA Authorization Form	X			
Medical history/review of systems	X	X		
Vital Signs measurements: temperature, blood pressure, pulse		X		
Height and weight measurement		X		
Complete skin examination (% BSA involvement)	X[1]	X		
Investigator's Static Global Assessment (Appendix 2)		X		
Blood sample for AST (SGOT), ALT (SGPT), alkaline phosphatase, and bilirubin	X[1]			
Urine pregnancy test (as applicable)		X		X
Randomize subject		X		
Blood sample for serum albumin and calcium level	X[1]	X	X[3]	X
Blood sample for bioavailability within 1 hour prior to morning study product application		X	X	X
Blood sample for bioavailability 1 hour after morning study product application			X	X
Blood sample for bioavailability 3, 6, and 10 hours after study product application			X[4]	
Concomitant medications query	X	X	X	X
Adverse experience query			X	X
Weigh 3.5 g study product to be applied during visit (morning application)		X	X	X
Weigh and dispense study product container		X	X[5]	
Collect and weigh study product container			X	X

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22563	ORIG-1	STIEFEL LABORATORIES INC	CALCIPOTRIEN FOAM 0.005%

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/s/

SEONGEUN CHO
08/26/2010

EDWARD D BASHAW
08/26/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22,563**	**Brand Name**	**Sorilux**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Calcipotriene**
Medical Division	**DDDP**	**Drug Class**	**Vit D analogue**
OCP Reviewer	**Julia Cho**	**Indication(s)**	**Plaque Psoriasis**
OCP Team Leader	**Dennis Bashaw**	**Dosage Form**	**Foam, 0.005 %**
Pharmacometrics Reviewer	**NA**	**Dosing Regimen**	**Applied twice daily**
Date of Submission	**12/18/09**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review		**Sponsor**	**Stiefel, GSK**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**10/21/10**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**1**	**1**	**CAL.203**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**1**	**1**	
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**	**1**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	All clinical studies were conducted with the final formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have		x		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	Since most plasma concentrations were below the detection limit, data were presented only in a tabular format
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			BSA of patients enrolled in the PK study is 5-9%, while patients in phase 3 studies have a wider range of BSA (2-20%) with a mean value of 6.3%.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		x		(b) (4)
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __ __yes____

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

- We noticed that the study population in the PK study does not sufficiently represent the age group of 12-18 years. (b) (4)

Seongeun Julia Cho

Reviewing Clinical Pharmacologist Date

E. Dennis Bashaw

Team Leader/Supervisor Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

SEONGEUN CHO
02/12/2010

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02/12/2010