

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-563

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	23 September 2010
From	Jill Lindstrom, MD
Subject	Cross-Discipline Team Leader Review
NDA #	22-563
Applicant	Stiefel Laboratories, Inc.
Date of Submission	18 December 2009
PDUFA Goal Date	18 October 2010
Proprietary Name / Established (USAN) names	SORILUX (calcipotriene)
Dosage forms / Strength	Foam, 0.005%
Proposed Indication(s)	Topical treatment of plaque psoriasis in patients 18 and older
Recommended:	<i>Approval</i>

1. Introduction

SORILUX (calcipotriene) foam, 0.005%, is a topical drug product for which the applicant seeks approval under Section 505 (b) (2) of the Federal Food Drug and Cosmetic Act (hereafter, the Act) for the topical treatment of plaque psoriasis in patients [REDACTED] (b) (4) [REDACTED]. The active ingredient, calcipotriene, is a vitamin D analog which is currently marketed in the US in various topical dosage forms (cream, ointment, and solution) and as fixed-dose combination (with betamethasone dipropionate, in ointment and suspension). This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

During their development program, the applicant interacted with the Agency at three milestone meetings (PreIND [pIND], End of Phase 2 [EOP2], preNDA [pNDA]); in addition, they received written feedback on submissions to their IND. The applicant did not request a Special Protocol Assessment. The dates of the meetings are as follows:

pIND	7 Mar 05
EOP2	24 Oct 07
pNDA	21 Oct 09

The applicant articulated their intent to pursue a 505(b)(2) pathway for SORILUX foam at the pIND meeting, and identified Dovonex ointment as the listed drug. The applicant was informed of the need for both local and systemic comparative bioavailability data, obtained from well-controlled studies with clinical endpoints and pharmacokinetic studies, respectively. At the EOP2 meeting, the applicant stated that their listed drug, Dovonex ointment, was no longer commercially available. The applicant was informed that an adequate clinical bridge could potentially contribute to human long-term safety data needs

related to the moiety (but not to the vehicle). At the pNDA meeting, the applicant was requested to address the fact that one of the two phase 3 studies did not meet the prespecified efficacy criteria of $\alpha=0.05$.

The applicant seeks approval of their application under section 505(b)(2) of the Act. Their listed drug is Dovonex Ointment. Their clinical bridge consists of study CAL.201 and CAL.203, discussed in section 5 of this review. Through the clinical bridge, the applicant is relying on the Agency's finding of safety for Dovonex ointment, NDA 20-723, to satisfy systemic safety data needs in this application, specifically nonclinical genetic toxicology, carcinogenicity, and reproductive and developmental toxicology, and clinical systemic long-term safety. Dovonex ointment was withdrawn from marketing in the US in April 2007 for business reasons.

3. CMC

The drug substance, calcipotriene, is a synthetic vitamin D analog with the molecular formula $C_{27}H_{40}O_3$. It is a white to off-white crystalline powder or crystal. Calcipotriene is insoluble in water but soluble in propylene glycol, and is sensitive to light exposure.

The drug product, SORILUX (calcipotriene) foam, 0.005%, is a white, thermostabile, aqueous-based emulsion foam containing 50 mcg/gm of calcipotriene. The composition is described in the following table:

Ingredient	Function	Quantity (%w/w)
Calcipotriene	Active ingredient	0.005
Purified water	(b) (4)	(b) (4)
Propylene glycol		
Light mineral oil		
Polyoxyl 20 cetostearyl ether		
Cetyl alcohol		
Stearyl alcohol		
White petrolatum		
Isopropyl myristate		
Dibasic sodium phosphate, anhydrous		
dl- α -tocopherol		
Propane/butane/isobutene		

Source: adapted from CMC Review of NDA 22-563; Rajiv Agarwal, PhD, archived 9.7.10, pp 17-21.

The drug product is packaged in a one-piece seamless aluminum can (b) (4)

(b) (4) The applicant proposes to market a 60gm trade size. Stability data supports an expiry of 24 months.

The product does not contain any preservatives. The applicant stated that the product failed USP<51> Antimicrobial Effectiveness Test, as the product failed to show a 2-log reduction in *E. coli* and *S. aureus* at day 14, although 2-log reduction was seen by day 28.

Consultation was obtained from CMC-Microbiology, who identified that the microbial challenge on the final drug product had not been conducted in the final, pressurized drug product container. The applicant was requested to conduct additional USP<51> Antimicrobial Effectiveness Testing in which the challenge organisms were inoculated into the filled container just prior to sealing; when conducted using the final pressurized drug product container, the USP<51> Antimicrobial Effectiveness Test results of the drug product were acceptable. The CMC-Microbiology consultant, Dr. Robert Mello, recommended *Approval* of the application from a microbiology product quality standpoint.

Facilities inspections for the drug substance and drug product were satisfactory from the perspective of both ONDQA and the Office of Compliance.

The CMC reviewer, Dr. Rajiv Agarwal, recommended *Approval* of this application.

4. Nonclinical Pharmacology/Toxicology

The applicant conducted eight non-clinical studies with SORILUX foam:

- 14-day repeat dose dermal toxicity study in rats
- 28-day repeat dose dermal toxicity study in rats
- 28-day repeat dose dermal toxicity study in minipigs
- 91-day repeat dose chronic dermal toxicity study in Sprague Dawley rats
- 90-day repeat dose chronic dermal toxicity study in Gottingen minipigs
- rabbit primary skin irritation study
- rabbit primary eye irritation study
- guinea pig dermal sensitization study

Findings included dose-dependent irritation and increases in calcium. Eye irritation in rabbits and dermal sensitization in guinea pigs was not observed.

The applicant is relying on the Agency's previous finding of safety for Dovonex ointment to supply the genetic toxicology, carcinogenicity, and reproductive and developmental toxicology safety data needs in their SORILUX foam application. Information from the Dovonex package insert on these topics has been incorporated into SORILUX labeling. Of note, information about non-clinical teratogenicity and non-clinical photocarcinogenicity from Dovonex ointment labeling are included in the relevant sections of the SORILUX package insert. Calcipotriene was not noted to be genotoxic or to impair fertility or reproductive performance.

There are no outstanding pharmacology-toxicology issues, and the pharmacology-toxicology reviewer, Dr. Carmen Booker, recommended *Approval* of this application.

5. Clinical Pharmacology/Biopharmaceutics

The applicant pursued a 505(b)(2) pathway for SORILUX foam and identified Dovonex® ointment as the listed drug product. Although both SORILUX foam and Dovonex

ointment are intended to deliver calcipotriene locally to the skin, systemic exposure occurs. To characterize the comparative bioavailability of their product and that of the listed drug, the applicant submitted data from two trials: CAL.201, entitled “A Multicenter, Randomized, Double-Blind Study of the Safety and Efficacy of Emulsion Formulation Calcipotriene Foam, 0.005%, versus Vehicle Foam, Dovonex® (calcipotriene) Ointment, 0.005%, and Vehicle Ointment in the Treatment of Mild-to-Moderate Plaque-type Psoriasis,” and CAL.203, entitled “A Randomized, Open-Label Study to Assess the Bioavailability of Emulsion Formulation Calcipotriene Foam, 0.005%, and Dovonex® (calcipotriene) Ointment, 0.005%, in Patients with Mild-to-Moderate Plaque-Type Psoriasis.”

One hundred and one subjects were enrolled in CAL.201. Key enrollment criteria included age ≥ 12 years, plaque psoriasis with 2%-10% body surface area (BSA) involvement, and Investigators Static Global Assessment (ISGA) score of mild (2) or moderate (3). Subjects applied test article twice daily for eight weeks. The proportions of subjects who achieved treatment success, defined as a score of clear (0) or almost clear (1) on the ISGA and a minimum of 2 grades improvement from baseline, are presented in the following table:

	SORILUX foam	Vehicle foam	Dovonex ointment	Vehicle ointment
# of subjects	36	36	20	9
Treatment successes	6 (17%)	1 (3%)	7 (35%)	0

Source: applicant’s NDA submission, mod 2.7.6, CSR CAL.201, 11.4.1.1

The point estimate for treatment success was higher for subjects receiving SORILUX foam than vehicle foam, but lower than Dovonex ointment. Adverse events were generally lower in the SORILUX foam arm than the Dovonex ointment arm. Based on these data, the bioavailability of calcipotriene in the skin is not likely greater with SORILUX foam than Dovonex ointment.

Thirty-two subjects enrolled in CAL.203. Enrollment criteria differed from CAL.201 in that subject needed BSA involvement of 5-10%. Subjects were to apply either 3.5 gms of SORILUX foam or Dovonex ointment twice daily, and plasma calcipotriene levels were assessed at baseline and on days 8 and 15. In the SORILUX foam group, one subject had detectable calcipotriene at one timepoint (one hour post dosing on d8), and in the Dovonex ointment group, six subjects had detectable calcipotriene at various timepoints. The low number of data points does not allow calculation of pharmacokinetic parameters; however, based on these data, the systemic bioavailability of calcipotriene is low and not greater with SORILUX foam than Dovonex ointment.

Based on the low systemic bioavailability (6.6nM), the lack of significant increase in bioavailability relative to marketed products, and the lack of a postmarketing signal for pro-arrhythmic adverse events with use of the moiety, a thorough QT/QT_c study is not needed.

In Study CAL.203, only one subject was younger than 18 years of age; in Study CAL.201, no subjects were younger than 18 years of age.

The OCBP reviewer, Dr. Julia Cho, recommended *Approval* of this application for use in adults and with a postmarketing requirement to conduct a pharmacokinetic study in pediatric subjects.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The applicant submitted data from two pivotal trials, Study CAL.301 and CAL 302 to establish the effectiveness of their product applied twice daily for 8 weeks in the treatment of psoriasis. These trials were multi-center, prospective, randomized, double-blind, parallel group studies with two arms, active and vehicle. The population enrolled was subjects 12 years of age and older with plaque psoriasis, a score of mild or moderate on the ISGA scale at baseline, and between two and twenty percent BSA of involvement (excluding face and scalp).

The applicant attended an EOP2 meeting on 24 October 2007, at which the following comments were made regarding the design of the phase 3 trials as presented in the briefing document:

As presented in the briefing package, the study designs (population, endpoints, and evaluations) for the proposed Phase 3 trials appear to be acceptable.

- To ensure that the results are not driven by the primary method of data imputation, the sponsor should propose a sensitivity analysis using an alternate method of imputing missing data.
- The Agency recommends incorporating multiplicity control for the set of key secondary endpoints.

The applicant did not request a special protocol assessment, and no agreement letter was issued.

The primary efficacy measure was the ISGA, assessed over all treatable areas excluding face and scalp. The primary timepoint was at 8 weeks, and the primary endpoints was the proportion of subjects with treatment success, defined as an ISGA 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. The efficacy results from the pivotal trials are presented in the table below:

	Study CAL.301		Study CAL.302	
	SORILUX (N=223)	Vehicle (N=113)	SORILUX (N=214)	Vehicle (N=109)
ISGA score of clear or almost clear (0 or 1) and a 2-grade improvement from baseline	31 (14%)	3 (7%)	58 (27%)	17 (16%)
p-value*	0.058		0.016	

Source: adapted from Statistical Review and Evaluation NDA 22-563; Carin Kim, PhD, archived 8.26.10, p 18.

In Study CAL.301, the success rate of SORILUX versus vehicle for the primary endpoint failed to be significant at the 0.05 level. However, sensitivity analyses of the primary endpoint (missing data imputed with LOCF, and a reviewer's sensitivity analysis) reached significance at the 0.05 level (see Statistical Review and Evaluation NDA 22-563; Carin Kim, PhD, archived 8.26.10, pp 13, 24-25).

The results of the secondary endpoints for the cardinal symptoms of psoriasis, erythema, scaling and plaque thickness, are presented in the following table:

	Study CAL.301			Study CAL.302		
	SORILUX (N=223)	Vehicle (N=113)	p-value	SORILUX (N=214)	Vehicle (N=109)	p-value
Erythema ¹	41 (18%)	11 (10%)	0.03	67 (31%)	22 (20%)	0.03
Scaling ¹	48 (22%)	12 (11%)	0.01	72 (34%)	20 (18%)	<0.01
Plaque thickness ²	30 (13%)	5 (4%)	<0.01	42 (20%)	12 (11%)	0.05

¹success defined as scoring 0 or 1 with at least a 2-grade improvement

²success defined as scoring 0

Source: adapted from adapted from Statistical Review and Evaluation NDA 22-563; Carin Kim, PhD, archived 8.26.10, p 14.

The reader is referred to the reviews of Dr. Carin Kim and Dr. Melinda McCord for additional analyses, including post hoc explorations of the data and sensitivity analyses.

In summary, although the results of the pivotal trials are not robust, the totality of the data demonstrates that SORILUX is superior to vehicle in the treatment of psoriasis. I concur with the conclusions of the clinical and statistical reviewers, Dr. Melinda McCord and Dr. Carin Kim, respectively, that the data support a determination of efficacy; both Dr. McCord and Dr. Kim recommended *Approval* of the application..

8. Safety

The 120-day safety update was reviewed, and did not identify new safety signals.

The safety database is adequate. In the pooled safety analysis set, which included subjects from studies CAL201, CAL.301, and CAL.302 (vehicle-controlled studies of 8-weeks duration), 473 subjects were exposed to SORILUX foam dosed BID, including 437 subjects in the pivotal trials.

There were no deaths, and no serious adverse events (SAE) attributable to study drug. The most frequently reported adverse events in the SORILUX arm were application site erythema (2%) and application site irritation (2%). Collection of adverse event data and assessment of local tolerance did not reveal unexpected safety signals.

The reader is referred to the clinical review by Dr. Melinda McCord for discussion of the safety database.

No postmarketing commitments or requirements to address safety concerns (outside of PREA) are warranted.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. Calcipotriene is not a new molecular entity.

10. Pediatrics

(b) (4)

The safety database is inadequate to establish the safety of SORILUX foam in pediatric patients aged 12 to 17 years. In the PK study CAL.203, only one subject was younger than 18 years of age. In phase 2 study CAL.201, no subjects were younger than 18 years of age. In the pivotal trials CAL.301 and CAL.302, ten subjects were less than 18 years of age at enrollment, and of these only six were exposed to SORILUX foam.

(b) (4)

Available prevalence data indicate that plaque psoriasis is not rare in children. In addition, a non-steroidal treatment would offer a meaningful therapeutic alternative to the current therapeutic armamentarium.

Additional studies are needed to establish the safety of SORILUX foam in children prior to extension of the indication to the pediatric age group, however the efficacy of SORILUX foam can be extrapolated from adult data. Plaque psoriasis occurs in both children and adults, and although the disease prevalence varies with age, the pathophysiology is understood to be the same across all ages. Additionally, there are not known age-related factors that would make the disease either more or less responsive to treatment in pediatric patients (although there are unique factors in children that may

increase their risk for adverse events, or increase the significance of those adverse events should they occur). Therefore it is scientifically appropriate to extrapolate efficacy from the adult population to the pediatric population, but the safety of the product will need to be established for the pediatric age group 2-16 years of age.

The application was presented to the Pediatric Review Committee (PeRC) on July 21, 2010. The committee concurred with the Division's recommendation to grant a partial waiver for pediatric patients aged 0 to 2, and a deferral for pediatric patients aged 2 to 16. The committee agreed with the plan to conduct PK/PD studies in children 2 through 11 and adolescents 12 through 16 with psoriasis, and a vehicle-controlled safety and efficacy study in subjects 2-^(b)₍₄₎ years of age with psoriasis, detailed as follows:

1. The applicant should conduct a PK/PD study in a minimum of 20 evaluable pediatric subjects with psoriasis aged 12 through 16.
2. The applicant should conduct a PK/PD study in a minimum of 25 evaluable pediatric subjects with psoriasis aged 2 through 11.
3. The applicant should conduct a vehicle-controlled study of the safety and efficacy of their product in pediatric subjects with psoriasis aged 2 to ^(b)₍₄₎ years of age with a minimum of 100 evaluable subjects exposed to active.

The subjects in these studies should have careful monitoring of serum and urine parameters of calcium homeostasis.

11. Other Relevant Regulatory Issues

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted, other than a single subject who used a prohibited medication; sensitivity analysis in which the data for that subject was excluded did not find the data for that subject to be influential, however.

DDMAC found the tradename SORILUX to be non-promotional. DMEPA found the tradename SORILUX not vulnerable to name confusion that could lead to medication errors, and acknowledged it as acceptable.

12. Labeling

Professional and patient labeling were reviewed, and negotiations regarding their content are ongoing at the time of close of this review. An outstanding issue is utility of the initially-proposed figures in patient labeling; the applicant indicated that they intend to provide photographs to replace the line-drawn figures to better convey the steps involved for patients when using the product.

The trade dress as initially proposed by the applicant presented a risk for medication errors due to its similarity to that for Veltin. The applicant submitted revised trade dress in response to the Agency's comments; the revised color scheme is acceptable and resolved this concern.

13. Recommendations/Risk Benefit Assessment

I concur with the recommendations of the multi-disciplinary review team for approval of NDA 22-563, SORILUX foam, pending agreement of the applicant with the recommended labeling revisions. I find that the applicant constructed an adequate clinical bridge to the listed drug, Dovonex ointment, for the purposes for which the application relies on the FDA finding of safety for the listed drug. The risk-benefit ratio for this product is appropriate for the indication of topical treatment of psoriasis in adults. Postmarketing risk management beyond professional labeling, prescription status, and routine pharmacovigilance is not needed. However to fulfill the requirements of PREA, the applicant will need to study the safety and effectiveness of SORILUX foam in pediatric subjects aged 2 to 16 years of age.

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/s/

JILL A LINDSTROM
09/24/2010