

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-563

OTHER REVIEW(S)

SEALD LABELING REVIEW

This review identifies aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 22563
APPLICANT	Stiefel Laboratories, Incorporated
DRUG NAME	SORILUX (calcipotriene) Foam
SUBMISSION DATE	December 21, 2009
PDUFA DATE	October 21, 2010
SEALD REVIEW DATE	October 5, 2010
SEALD LABELING REVIEWER	Debbie Beitzell, BSN

Outlined below are the following outstanding labeling issues that must be corrected before SEALD sign-off and the final draft labeling is approved. Issues are listed in the order mandated by the regulations or guidance.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), “none” is stated. If clearly inapplicable sections are omitted from the FPI, “not applicable” is stated. In addition, “not applicable” is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

Highlights (HL):

- **Highlights Limitation Statement:** None
- **Product Title Line:** The product strength should not be in the product title and needs deleted. The product title should contain only the drug names, dosage form, route of administration, and, if applicable, controlled substance symbol. See 21 CFR 201.57 (a)(2).
- **Initial U.S. Approval:** None
- **Boxed Warning:** Not Applicable
- **Recent Major Changes:** Not Applicable
- **Indications and Usage:** None
- **Dosage and Administration:** None
- **Dosage Forms and Strengths:** None

SEALD LABELING REVIEW

- **Contraindications:** None
- **Warnings and Precautions:** None
- **Adverse Reactions:** A list of the most frequently occurring adverse reactions must be included under this heading, not adverse events. Adverse event terminology must be deleted and replaced with adverse reaction information. See 21 CFR 201.57 (a)(11).
- **Drug Interactions:** Not Applicable
- **Use in Specific Populations:** Not Applicable
- **Patient Counseling Information Statement:** None
- **Revision Date:** Revision date is the month/year that the application is approved. The review division enters this information upon approval. Do not leave blank. See 21 CFR 201.57 (a)(15).
- Table of Contents (TOC): None

Full Prescribing Information:

Boxed Warning: Not Applicable

1 Indications and Usage: None

2 Dosage and Administration: None

3 Dosage Forms and Strengths: None

4 Contraindications: None

5 Warnings and Precautions: None

6 Adverse Reactions: This section must describe adverse reactions, not adverse events. Adverse event terminology must be deleted from this section and replaced with adverse reaction information. See 21 CFR 201.57 (c)(7).

7 Drug Interactions: None

SEALD LABELING REVIEW

- 8 Use in Specific Populations:** None
- 9 Drug Abuse and Dependence:** Not Applicable
- 10 Overdosage:** None
- 11 Description:** None
- 12 Clinical Pharmacology:** None
- 13 Nonclinical Toxicology:** None
- 14 Clinical Studies:** None
- 15 References:** Not Applicable
- 16 How Supplied/Storage and Handling:** None
- 17 Patient Counseling Information:** None

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/s/

DEBRA C BEITZELL

10/06/2010

Review memo sent to DDDP on 10/5/10.

LAURIE B BURKE

10/06/2010

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: 1684-1: A Pharmacokinetics/Pharmacodynamics trial of calcipotriene foam under maximal use conditions in pediatric subjects age 12 through 16 with plaque psoriasis

PMR/PMC Schedule Milestones:

Protocol Submission Date:	<u>04/2011</u>
Study Initiation Date:	<u>N/A</u>
Study Completion Date:	<u>06/2013</u>
Final Study Report Submission Date:	<u>01/2014</u>
Other: _____	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

There is insufficient data provided by the sponsor for subjects ages 12 through 16. Therefore additional studies are required under PREA. Since the adult studies are completed and Sorilux is ready for approval, then a deferral of PREA studies is appropriate.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

(b) (4)

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this PMC

5. What type of study or clinical trial is required or agreed upon (describe)?

Pharmacokinetics/Pharmacodynamics trial of calcipotriene foam under maximal use conditions in 20 evaluable pediatric subjects with plaque psoriasis age 12 through 16 years. Evaluate the effect of the product on calcium metabolism in all subjects.

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)
Pediatric

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

JEANNINE M HELM
10/05/2010

TATIANA OUSSOVA
10/05/2010

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: 1684-3 A vehicle-controlled trial of the safety and efficacy of calcipotriene foam in pediatric subjects age 2 through 11 with plaque psoriasis

PMR/PMC Schedule Milestones:

Protocol Submission Date:	<u>09/2011</u>
Study Initiation Date:	<u>N/A</u>
Study Completion Date:	<u>06/2013</u>
Final Study Report Submission Date:	<u>01/2014</u>
Other: _____	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

There is insufficient data provided by the sponsor for subjects ages 2 through 11. Therefore additional studies are required under PREA. Since the adult studies are completed and Sorilux is ready for approval, then a deferral of PREA studies is appropriate.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

A PREA requirement has been established for the evaluation of calcipotriene foam for the topical treatment of psoriasis in subjects age 2 through 11. The adverse event data and laboratory assessment demonstrate the safety of calcipotriene foam for the treatment of mild to moderate plaque psoriasis in subjects aged 18 years and older. There is insufficient clinical pharmacology and safety data to support labeling in patients under age 18.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

5. What type of study or clinical trial is required or agreed upon (describe)?

Vehicle-controlled trial of the safety and efficacy of calcipotriene foam in 100 evaluable pediatric subjects with plaque psoriasis age 2 through 11 years. Evaluate the effect of the product on calcium metabolism in all subjects.

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)
Pediatrics

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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/s/

JEANNINE M HELM
10/05/2010

TATIANA OUSSOVA
10/05/2010

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: 1684-2: A Pharmacokinetics/Pharmacodynamics trial of calcipotriene foam under maximal use conditions ages 2 through 11

PMR/PMC Schedule Milestones:

Protocol Submission Date:	<u>04/2011</u>
Study Initiation Date:	<u>N/A</u>
Study Completion Date:	<u>09/2013</u>
Final Study Report Submission Date:	<u>03/2014</u>
Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

There is insufficient data provided by the sponsor for subjects ages 2 through 11. Therefore additional studies are required under PREA. Since the adult studies are completed and Sorilux is ready for approval, then a deferral of PREA studies is appropriate.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

A PREA requirement has been established for the evaluation of calcipotriene foam for the topical treatment of psoriasis in subjects age 2 through 11. The adverse event data and laboratory assessment demonstrate the safety of calcipotriene foam for the treatment of mild to moderate plaque psoriasis in subjects aged 18 years and older. There is insufficient clinical pharmacology and safety data to support labeling in patients under age 18.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this PMC

5. What type of study or clinical trial is required or agreed upon (describe)?

Pharmacokinetics/Pharmacodynamics trial of calcipotriene foam under maximal use conditions in 25 evaluable pediatric subjects with plaque psoriasis age 2 through 11 years. Evaluate the effect of the product on calcium metabolism in all subjects.

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)
Pediatric

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
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/s/

JEANNINE M HELM
10/05/2010

TATIANA OUSSOVA
10/05/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 022563	NDA Supplement #: N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Sorilux™ Established/Proper Name: calcipotriene Dosage Form: Foam Strengths: 0.005%		
Applicant: Stiefel Laboratories, Inc.		
Date of Receipt: December 21, 2009		
PDUFA Goal Date: October 21, 2010	Action Goal Date (if different): October 7, 2010	
Proposed Indication(s): Topical treatment of plaque psoriasis in patients (b) (4)		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Dovonex (calcipotriene) Ointment, 0.005% -NDA 020273	-Nonclinical safety data: single-dose toxicity, repeat-dose toxicity, genotoxicity, reproductive and developmental toxicity, carcinogenicity, photocarcinogenicity and dermal carcinogenicity studies - Long-term safety data

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant bridged to Dovonex Ointment with a well controlled Phase 2 study with clinical endpoints (CAL.201) and a systemic bioavailability study (CAL. 203). The bridge demonstrated the bioequivalence of calcipotriene and the listed drug, the non-superior efficacy of calcipotriene foam compared to the listed drug, and no greater incidence of adverse events for calcipotriene foam compared to the listed drug. To establish that the pharmacologic effects and systemic exposure were similar for calcipotriene foam and the listed drug in non-clinical testing, a 90-day repeat -dose dermal toxicity study was conducted including a group treated with Dovonex ointment. Based on the establishment of an adequate clinical bridge, Stiefel is relying on Agency findings of safety for Dovonex Ointment involving single dose toxicity, repeat-dose toxicity, genotoxicity, reproductive and developmental toxicity, carcinogenicity and photocarcinogenicity.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
 YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
 YES NO
If "NO," proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Dovonex (calcipotriene) Ointment, 0.005%	020273	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
 N/A YES NO
*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".
 If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:
 a) Approved in a 505(b)(2) application?
 YES NO
If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?
 YES NO
If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES NO
If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO
If "YES", please list which drug(s) and answer question d) i. below.
If "NO", proceed to question #9.

Name of drug discontinued from marketing: Dovonex (calcipotriene) Ointment, 0.005%

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO
(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication, topical treatment of plaque psoriasis in patients (b) (4), and a new dosage form, from ointment to foam.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

NDA 020554 Dovonex (calcipotriene) Topical Cream, 0.005%
NDA 020611 Dovonex (calcipotriene) Topical Solution, 0.005%
Approved generics are listed in the Orange Book

PATENT CERTIFICATION/STATEMENTS
--

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number:

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number: 4,866,048

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/

JEANNINE M HELM

09/15/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: August 20, 2010

To: Jeannine Helm, DDDP

From: Lynn Panholzer, PharmD, DDMAC
Sheetal Patel, PharmD, DDMAC

Re: NDA# 022563
Sorilux™ (calcipotriene) Foam, 0.005%

As requested in your consult dated February 5, 2010, DDMAC has reviewed the draft labeling for Sorilux™ (calcipotriene) Foam, 0.005%. DDMAC's comments are based on the proposed substantially complete, mark-up, version of the labeling found in the DDDP eRoom titled "NDA 022563 Sorilux Team draft_labeling 8_3_2010 Mtg #1.doc" from August 4, 2010.

DDMAC's comments are provided directly in the attached marked-up copy of the labeling.

If you have any questions about DDMAC's comments on the PI please contact Lynn Panholzer at 6-0616 or at Lynn.Panholzer@fda.hhs.gov. If you have any questions about our comments on the PPI please contact Sheetal Patel at 6-5167 or at Sheetal.Patel@fda.hhs.gov.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

LYNN M PANHOLZER
08/20/2010

SHEETAL PATEL
08/20/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 17, 2010

TO: Jeannine Helm, Regulatory Project Manager
Melinda McCord, M.D., Medical Officer
Division of Dermatologic and Dental Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-563

APPLICANT: Stiefel, a GSK Company
20 T. W. Alexander Drive
Research Triangle Park, NC 27709
Jeffrey S. Troughton, MS, RAC
Associate Director, Regulatory Affairs
Main: (919) 990-6000
Office: (919) 990-6206
Mobile: (919) 450-6616
Fax: (919) 990-6978
jtroughton@stiefel.com

DRUG: Sorilux (calcipotriene)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Topical treatment of plaque psoriasis in patients (b) (4)

CONSULTATION REQUEST DATE: March 23, 2010

DIVISION ACTION

GOAL DATE: October 1, 2010

PDUFA DATE: October 21, 2010

I. BACKGROUND:

The conduct of Protocol #U0267-302 entitled “A Multicenter, Randomized, Double-Blind, Phase 3 Study of the Safety and Efficacy of Emulsion Formulation Calcipotriene Foam, 0.005%, versus Vehicle Foam in Subjects with Plaque-type Psoriasis” was inspected.

Protocol #U0267-302 was a randomized, double-blind study comparing Emulsion Formulation (EF) Calcipotriene Foam to vehicle foam in subjects with plaque-type psoriasis. The primary objectives of this study were to evaluate the safety and efficacy of EF Calcipotriene Foam compared to vehicle foam in subjects with plaque-type psoriasis.

These clinical sites were selected on the basis of high numbers of treatment responders.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site 011: James A Solomon, M.D. Advanced Dermatology & Cosmetic Surgery 725 W Granada Blvd, # 44 Ormond Beach, FL 32174 Ph: (386) 898- 0547, FAX: (386) 898-0551, drjsolomon@leavittmgt.com	U0267-302/ 25/	18-21 May 2010	NAI
Site 005: Kimberly Grande, M.D. The Skin Wellness Center, PC 10215 Kingston Pike #200 Knoxville, TN 37922 Ph: (865) 584-8580, FAX: (865) 694-1949	U0267-302/ 36/	2-4 Jun 2010	NAI
Site 002 Sunil Dhawan, M.D. East Bay Dermatology Medical Group, Inc. 2557 Mowry Ave., Suite 34 Fremont, CA 94538 Ph: (510) 797-4111 or (408) 957-7676	U0267-302/ 18/	12-14 July 2010	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
 EIR has not been received from the field and complete review of EIR is pending.

1. Site 011

James A Solomon, M.D.
Advanced Dermatology & Cosmetic Surgery
725 W Granada Blvd, # 44
Ormond Beach, FL 32174

a. What was inspected: At this site, 49 subjects were screened for the study, 25 were randomized, and 22 completed the study. The records of 15 subjects were audited, including, but not limited to, consent forms, case report forms and corresponding source documents, sponsor and IRB correspondence, adverse event reporting, financial disclosure forms, and test article accountability records.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The data appear acceptable in support of the respective application.

2. Site 005

Kimberly Grande, M.D.
The Skin Wellness Center, PC
10215 Kingston Pike #200
Knoxville, TN 37922

a. What was inspected: At this site, 36 subjects were enrolled, four withdrew, and one subject was excluded for noncompliance. All subject records were audited with respect to informed consent. Of the 36 enrolled subjects, the records of 24 subjects were reviewed, which included but was not necessarily limited to parameters such as case report forms and corresponding source documents, sponsor/monitor correspondence, inclusion/exclusion criteria, adverse events, and test article accountability.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The data appear acceptable in support of the respective application.

3. Site 002

Sunil Dhawan, M.D.
East Bay Dermatology Medical Group, Inc.
2557 Mowry Ave., Suite 34
Fremont, CA 94538

- a. **What was inspected:** At this site, 19 subjects were screened, 18 were enrolled, and 17 completed the study. The records of all 18 enrolled subjects were audited for the following parameters which included, but were not limited to, case report forms and corresponding source documents, sponsor/monitor correspondence, consent forms, and study questionnaires.
- b. **General observations/commentary:** A Form FDA 483 was issued. Inspection revealed that Subject 1292 was enrolled and completed the study despite taking metoprolol, a protocol-prohibited concomitant medication. There were four subjects (#s 1039, 1044, 1045, and 1048) whose visits to the clinic were outside of the protocol-specified timeframes. In addition, Subjects 1048 and 1038 were taking clonidine and glucosamine, respectively; however, the dosages of these concomitant medications as stated in the source documents were not accurately reflected in their respective case report forms.
- c. **Assessment of data integrity:** The review division may wish to consider excluding the data from Subject 1292 since this subject was taking a protocol-prohibited medication. Otherwise, the deviations noted immediately above would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Solomon, Grande, and Dhawan were inspected in support of this NDA. Although regulatory violations were noted at Dr. Dhawan's site, the findings are unlikely to impact data integrity; however, the review division may wish to consider excluding data from Subject 1292 because of the use of a protocol-prohibited medication as described above. Otherwise, the study appears to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/

ROY A BLAY
08/18/2010

TEJASHRI S PUROHIT-SHETH
08/18/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 16, 2010
To: Susan Walker, M.D., Director
Division of Dermatology and Dental Products (DDDP)

Through: Mary Willy, PhD, Deputy Director
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Sorilux (calcipotriene) Foam, 0.005%

Application Type/Number: NDA 22-563

Applicant/sponsor: Stiefel Laboratories, Inc.

OSE RCM #: 2010-423

1 INTRODUCTION

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Sorilux (calcipotriene) Foam, 0.005%.

On December 18, 2009 Stiefel Laboratories, Inc., submitted an Original New Drug Application, NDA 22-563, for Sorilux (calcipotriene) Foam, 0.005%. Sorilux (calcipotriene) Foam, 0.005% is a topical dosage form of calcipotriene that is indicated for the topical treatment of plaque psoriasis in patients aged 18 and older.

2 MATERIAL REVIEWED

- Draft Sorilux (calcipotriene) Foam, 0.005% Prescribing Information (PI) submitted December 21, 2009, and provided by the Review Division to DRISK on August 5, 2010.
- Draft Sorilux (calcipotriene) Foam, 0.005% Patient Package Insert (PPI) submitted on December 21, 2009, and provided by the Review Division to DRISK on August 5, 2010.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured consistency with DRISK's June 2010 recommendations for Olux-E (clobetasol prionate) Foam, 0.05%
- addressed comments from the DMEPA Label and Labeling Review, dated August 11, 2010

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please send these comments to the Applicant and copy DRISK on the correspondence. Let us know if DDDP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

Please let us know if you have any questions.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

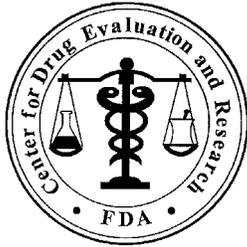
Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22563	ORIG-1	STIEFEL LABORATORIES INC	CALCIPOTRIEN FOAM 0.005%

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/s/

LATONIA M FORD
08/16/2010
Sorliux PPI DRISK Review

MARY E WILLY
08/16/2010
I concur



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 4, 2010

To: Susan Walker, MD, Director
Division of Dermatology and Dental Products

Through: Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Zachary Oleszczuk, PharmD, Acting Team Leader
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Sorilux (Calcipotriene) Foam
0.005%

Application Type/Number: NDA 022563

Applicant: Stiefel Laboratories, Inc.

OSE RCM #: 2010-166

***** This document contains proprietary and confidential information that should not be released to the public.*****

INTRODUCTION

This review responds to a request from the Division of Dermatology and Dental Products (DDDP) for DMEPA assessment of the container labels, carton labeling, insert labeling, and patient package insert labeling for Sorilux (Calcipotriene) Foam for their vulnerability to medication errors.

1 PRODUCT INFORMATION

Sorilux (calcipotriene 0.005%) is an antipsoriatic foam which is applied in a thin layer to affected skin twice daily. It is indicated for the topical treatment of plaque psoriasis in patients (b) (4). Sorilux will be available in a 60 gram can which can be inverted to dispense a small amount of foam into the cap of the can or directly on the affected area of the skin. The container is stored at room temperature and the product will be distributed through retail, inpatient, long-term care, and clinic pharmacy settings.

2 METHODS AND MATERIALS

DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted container labels (see Appendix A), carton labeling (see Appendix B), on December 18, 2009 and package insert labeling (no image) and patient package insert (no image) on May 7, 2010.

DMEPA also compared these container labels and carton labeling to Veltin*** (Clindamycin Phosphate and Trentinoin) Gel container labels (see Appendix C) and carton labeling (see Appendix D) because of concern for tradedress similarity.

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the labels and labeling noted that the route of administration should be included on the principal display panel of the container labels and carton labeling and that the patient package insert could be improved to help minimize the risk of Sorilux being administered by a wrong route of. Section 3.1, Comments to the Division, contains our recommendations for the package insert labeling, patient package insert labeling, and general tradedress for discussion during the labeling meetings. Section 3.2, Comments to the Applicant contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We can meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Janet Anderson, OSE Regulatory Project manager, at 301-796-0675.

3.1 COMMENTS TO THE DIVISION

1. In section 8.1 *Pregnancy*, the package insert contains the abbreviation ‘µg’. The abbreviation ‘µg’ appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations (<http://www.ismp.org/tools/errorproneabbreviations.pdf>) because it has been confused for ‘mg’. The Agency launched a campaign on June 14, 2006, warning healthcare practitioners and consumers not to use error prone abbreviations, acronyms, dose designations, or symbols. As part of the campaign, FDA agreed not to use such error prone designations in their approved product labeling. Thus, we request you revise the units of measure to use ‘mcg’ for micrograms throughout the labels and labeling.
2. The *Dosage and Administration* section of the highlights is should provide more specific instruction on how to apply the product to the affected area to help minimize the risk of inappropriate application. (b) (4)

3. The Warnings and Precautions section of the package insert includes a warning to “Avoid excessive exposure of the treated areas to natural or artificial sunlight”. However, this statement does not appear in the patient package insert. Revise the patient package insert to include a warning to avoid excessive exposure to natural or artificial sunlight.
4. The patient package insert using drawings of pictures to illustrate techniques for applying Sorilux. Since these techniques are vital to applying the product correctly, DMEPA recommends using actual photographs of humans and the actual product.
5. The first step in the patient package insert instructs patients to “break the tiny plastic piece at the base of the can’s rim by gently pushing back (away from the piece) on the nozzle” when using this product for the first time. Including a picture of the tiny plastic piece and how to break it would be helpful for patients.
6. DMEPA noted that the manufacture’s tradedress for this product is nearly identical to the manufacture’s tradedress for another product, Veltin*** currently under review. DMEPA has included the images of this product in Appendices C and D for comparison. The color scheme and presentation of information is almost identical. Both products are topical products and topical products are typically stored in an isolated part of the pharmacy from other medications. Although these products will not likely be stored directly next to each other on a shelf, the similar packaging in an isolated part of the pharmacy in addition to possible similar size container could lead to product selection errors or restocking errors. DMEPA has postmarketing evidence that similar tradedress has contributed to errors of restocking wrong product selection. DMEPA recommends differentiating the two products by the use of different colors or some other means.

3.2 COMMENTS TO THE APPLICANT

1. The description of Sorilux on the container labels and carton labeling uses the abbreviation ‘µg’. The abbreviation ‘µg’ appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because it has been confused for ‘mg’. The Agency launched a campaign on June 14, 2006, warning healthcare practitioners and consumers not to use error prone abbreviations, acronyms, dose designations, or symbols. As part of the campaign, FDA agreed not to use such error prone designations in their

approved product labeling. Thus, we request you revise the units of measure to use 'mcg' for micrograms throughout the labels and labeling.

2. The dosage form, 'Foam', on the container label and carton labeling appears on a different line the active ingredient 'calcipotriene'. The dosage form and active ingredient should appear on the same line. The presentation should appear as follows:

Sorilux
(calcipotriene) Foam,
0.005%

3. The principal display panel of the container labels and carton labeling do not state that this product is for topical use only. 21 CFR 201.100(b)(3) states that the route of administration should be present, if the product is not for oral use. To comply with 21 CFR 201.100(b)(3) add the statement 'For topical use only' on the principal display panel of the container labels and carton labeling.
4. Delete the 'V VersaFoam' logo that appears on the container label and carton labeling. The logo has greater prominence than the proprietary name.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

ZACHARY A OLESZCZUK
08/11/2010

DENISE P TOYER
08/11/2010

CAROL A HOLQUIST
08/12/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022563 BLA#	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE- N/A
Proprietary Name: Sorilux [™] Established/Proper Name: calcipotriene Dosage Form: Foam Strengths: 0.005%		
Applicant: Stiefel Laboratories, Inc.		
Date of Application: December 18, 2009 Date of Receipt: December 21, 2009		
PDUFA Goal Date: October 21, 2010		
Filing Date: February 19, 2010	Date of Filing Meeting: February 9, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5		
Proposed indication: Topical treatment of plaque psoriasis in patients (b) (4)		
Type of Original NDA:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	
Collaborative Review Division (if OTC product):		
List referenced IND Number(s): IND 071198		

Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes , explain in comment column.				
If affected by AIP , has OC/DMPQ been notified of the submission? If yes , date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
022185	Taclonex Scalp® Topical Suspension	NDF		May 9, 2011	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>				X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: Three years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA</i> efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X X X X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			X	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>		X		Signed pediatric certification requested by telephone, 5/21/2010.
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			DSI: 3.25.2010

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date: October 24, 2007 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting? Date: October 21, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 9, 2010

BLA/NDA/Supp #: 022563

PROPRIETARY NAME: Sorilux™

ESTABLISHED/PROPER NAME: calcipotriene

DOSAGE FORM/STRENGTH: Foam/0.005%

APPLICANT: Stiefel Laboratories, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Topical treatment of plaque psoriasis in patients (b) (4)

BACKGROUND: Regulatory Background: This is a 505(b)(2) submission. The applicant plans to rely on the Agency’s previous findings of safety by referencing nonclinical safety data and published literature. The referenced listed drug is Dovonex (calcipotriene) Ointment, 0.005% (NDA 020273). The applicant states that the application “adheres to comments” provided during the Pre-NDA meeting held on Oct. 21, 2009 regarding which formulation of their product they intend to market.

EOP2 meeting: October 24, 2007

Pre-NDA meeting: October 21, 2009

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeannine M. Helm	Y
	CPMS/TL:	Barbara J. Gould/Margo Owens	Y
Cross-Discipline Team Leader (CDTL)	Jill Lindstrom		Y
Clinical	Reviewer:	Melinda McCord	Y
	TL:	Jill Lindstrom	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Microbiology (<i>for antimicrobial products)</i>	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Seoguen (Julia) Cho	Y
	TL:	Edward Dennis Bashaw	Y
Biostatistics	Reviewer:	Mat Soukup	Y
	TL:	Mohamed Alosh	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carmen Booker	N
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Rajiv Agarwal	N
	TL:	Shulin Ding Moo Jhong Rhee	Y N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Felicia Duffy	N
	TL:	Zachary Oleszczuk	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

Comments:	
------------------	--

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: Quality Microbiology Consult will be requested.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Susan J. Walker, M.D.	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Other Submit consults for Quality Microbiology and for DSI, Clinical Site Inspections

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

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

/s/

JEANNINE M HELM
06/04/2010

MARGO L OWENS
06/04/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 1, 2010

To: Susan Walker, M.D., F.A.A.D., Director
Division of Dermatology and Dental Products (DDDP)
Office of New Drugs (OND)

Through: Mark Avigan, M.D., C.M., Director
Division of Pharmacovigilance I (DPV I)
and
Ida-Lina Diak, Pharm.D., Safety Evaluator Team Leader, DPV I

From: Tracy M. Salaam, Pharm.D., Safety Evaluator, DPV I

Subject: Cardiac arrhythmia

Drug Name(s): Calcipotriene

Application Type/Number: See below
Applicant/sponsor: See below

OSE RCM #: 2010-1042

PRODUCTS COVERED IN THIS REVIEW				
Generic Name and formulation	Brand Name	Applicant/Sponsor	NDA or ANDA number	FDA Approval Date
Calcipotriene foam 0.005%	Sorilux	Stiefel Laboratories, Inc	22563	<i>Approval Pending</i>
Calcipotriene ointment 0.005%	Generic	Glenmark Generics	90633	March 24, 2010
Calcipotriene cream 0.005%	Dovonex	Leo Pharmaceuticals	20554	July 22, 1996
Calcipotriene solution 0.005%	Dovonex and generics	Leo Pharmaceuticals, Tolmar, Hi Tech Pharma, Nycomed US	20611, 77029, 77579, 78305	March 3, 1997
Calcipotriene 0.005% and Betamethasone 0.064% ointment	Taclonex	Leo Pharmaceuticals	21852	January 9, 2006
Calcipotriene 0.005% and Betamethasone 0.064% suspension	Taclonex Scalp	Leo Pharmaceuticals	22185	May 9, 2008
<i>Calcipotriene ointment 0.005%</i>	<i>Dovonex</i>	<i>Leo Pharmaceuticals</i>	<i>20273</i>	<i>Discontinued</i>

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EXECUTIVE SUMMARY

In response to receipt of an original NDA 505(b)(2) application for calcipotriene 0.005% foam (Sorilux, NDA 22563) and a QT/QTc study waiver request from the sponsor, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Pharmacovigilance I (DPV I) search the Adverse Event Reporting System (AERS) database for cases of cardiac arrhythmias associated with calcipotriene. The purpose of this review is to determine if a postmarketing signal exists for cardiac arrhythmia and to provide DPV's opinion regarding the sponsor's claim that no further assessment of cardiac repolarization is necessary to assure the safety of this drug.

Based on the lack of post-marketing cases in both the AERS database and the literature, the data do not suggest a compelling safety signal for cardiac arrhythmias with the use of calcipotriene formulations at this time. We are mindful of the fact that the absence of reporting does not necessarily mean the absence of a signal and that the AERS database is subject to substantial under-reporting. However, we identified only three cases of adverse events related to arrhythmia in the AERS database and none in the literature associated with calcipotriene; atrial fibrillation and ventricular fibrillation (1), supraventricular tachycardia (1), and atrial fibrillation (1). The information provided in these cases was either limited in scope or confounded by other factors, and an association between cardiac arrhythmia and calcipotriene cannot be concluded.

Since this review did not identify any new post-marketing safety signals associated with calcipotriene and cardiac arrhythmias, DPV I has no recommendations for labeling enhancements. Based solely on the data we reviewed, we feel that further assessment of cardiac repolarization is not indicated at this time; however, DPV will continue to monitor the AERS database for reports of cardiac arrhythmias associated with calcipotriene use to determine the need for any regulatory action in the future.

1 INTRODUCTION

In response to receipt of an original NDA 505(b)(2) application for calcipotriene 0.005% foam (Sorilux, NDA 22563) and a QT/QTc study waiver request from the sponsor, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Pharmacovigilance I (DPV I) search the Adverse Event Reporting System (AERS) database for cases of cardiac arrhythmias associated with calcipotriene. The purpose of this review is to determine if a postmarketing signal exists for cardiac arrhythmia and to provide DPV's opinion regarding the sponsor's claim that no further assessment of cardiac repolarization is necessary to assure the safety of this drug.

1.1 BACKGROUND

DDDP received an original NDA 505(b)(2) application for calcipotriene 0.005% foam (Sorilux, NDA 22563) from Stiefel Laboratories, Inc.. On May 7, 2010, the sponsor requested a waiver to conduct a thorough QT/QTc study due to negligible systemic exposure and no evidence of effects of the moiety on cardiac repolarization according to the literature.

Electrical impulses control the mechanical activity of the heart, which cause a coordinated contraction and relaxation of cardiac muscle, thereby pumping blood throughout the entire body.

Cardiac arrhythmia occurs when the rhythm of the heart fails.¹ Cardiac arrhythmias can lead to significant morbidity and mortality, with estimates of 300,000 to 350,000 sudden cardiac deaths annually in the United States, and “in most cases it is assumed that the underlying cause of sudden death is ventricular tachyarrhythmia.”^{2, 3}

“Cardiac arrhythmias arise from abnormalities of impulse generation, conduction, or both.”⁴ Common causes of cardiac arrhythmias include genetic predisposition, developmental abnormalities of the heart, heart diseases such as cardiomyopathy or cardiac ischemia, metabolic abnormalities like abnormal potassium, calcium or magnesium concentrations, dysfunction of cardiac ion channels, and various medications.¹ Cardiac arrhythmias can also arise from excessive alcohol, caffeine, or nicotine intake, excessive exercise, illicit drug use, or stress.⁵ The four main types of cardiac arrhythmias are premature (extra) beats; supraventricular arrhythmias (i.e. atrial fibrillation or flutter, paroxysmal supraventricular tachycardia (PSVT), and Wolff-Parkinson-White (WPW) syndrome); ventricular arrhythmias (i.e. ventricular tachycardia or ventricular fibrillation); and bradyarrhythmias.⁵

1.2 REGULATORY HISTORY

Calcipotriene foam 0.005% is not available in the US market but DDDP is currently reviewing the calcipotriene foam 0.005% original NDA application for the treatment of psoriasis in patients (b) (4). FDA has approved five other topical formulations of calcipotriene for the treatment of psoriasis (calcipotriene ointment, calcipotriene cream, calcipotriene solution, calcipotriene + betamethasone ointment, and calcipotriene + betamethasone suspension).

1.3 PREVIOUS OSE REVIEWS

There have been no previous OSE reviews conducted for cardiac arrhythmia associated with calcipotriene.

1.4 PRODUCT LABELING

The currently approved calcipotriene product labels do not list cardiac arrhythmia as an adverse event. See Appendix A for the labeling information.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

We identified potential cases of cardiac arrhythmia utilizing the following inclusion criteria:

- Inclusions: Cases with a diagnosis of a specific arrhythmia (with or without electrocardiogram (EKG)/ Holter monitor findings)
- Exclusions: Cases that reported non-specific symptoms without confirmation from an EKG/ Holter monitor (i.e. tachycardia, syncope).

2.2 AERS SELECTION OF CASES

On May 14, 2010, we searched the AERS database for all reports of arrhythmia associated with calcipotriene, using the following search criteria:

- Drug terms: calcipotriene, Dovonex[®], and Taclonex[®] and all associated trade, active ingredient, and verbatim names
- MedDRA adverse event search terms:
 - Cardiac arrhythmias (SMQ)
 - Torsades de pointes / QT prolongation (SMQ)

Appendix B provides a listing of all preferred terms used in the search strategy.

- Time period: Approval through May 14, 2010

The search retrieved eleven reports out of 457 total adverse event reports in AERS associated with calcipotriene. Of those eleven reports, we excluded seven reports because they did not meet the inclusion criteria of the case definition [tachycardia (4), miscoded cases* (2), syncope (1)]. We excluded one report for lack of a temporal relationship (sinus tachycardia occurring five months after discontinuation of Dovonex[®]). We describe the remaining three cases in Section 3.1 below.

* Two miscoded cases: The patients were not using calcipotriene products.

2.3 LITERATURE SEARCH

A PubMed literature search conducted on May 17, 2010 using the search terms and “calcipotriene” and “arrhythmia”.

3 RESULTS

3.1 AERS CASES

ISR 4378064, Foreign (2004), atrial fibrillation, ventricular fibrillation, CASE 1: A 55-year old female consumer reported that she was admitted to a hospital for observation as a result of developing atrioventricular fibrillation two weeks after two applications of calcipotriene ointment applied daily for the treatment of vitiligo. She noticed the symptoms of generalized anxiety immediately after initiating calcipotriene therapy. The calcipotriene was withdrawn and the events resolved. Concomitant medications were not reported.

ISR 4723920, Foreign (2005), supraventricular tachycardia, CASE 2: A health professional reported that a 50-year old male used less than one tube of calcipotriene cream (100g/tube) per week to treat psoriasis over four years. The patient did not feel well and complained to his physician of a sensation of “heart skipped a beat.” Based on his initial heart rate (72 beats/min), blood pressure (140/100 mmHg), and an EKG result reporting a diagnosis of supraventricular extrasystole, he was treated with bisoprolol 2.5mg daily for hypertension. The arrhythmia was considered non-serious and went untreated. Approximately one month later, the patient visited his dermatologist because he felt worse whenever calcipotriene was used and suspected that calcipotriene might have caused the events. Concomitant medications included iron, omeprazole, and calcipotriene + betamethasone. Medical history included anemia, gastritis, psoriatic arthritis,

and an iodine allergy. Calcipotriene was discontinued (on an unknown date in June 2005) and the events were resolving. The report also stated, “When calcipotriene was reintroduced, the events recurred.”

Table 1. Lab results of ISR 4723920					
	4/13/05	4/21/05	4/27/05	6/8/05	6/22/05
Heart rate	72 beats/min			64 beats/min	62 beats/min
Blood pressure	140/100mm Hg			150/80mm Hg	160/100mm Hg
EKG		Performed			
Diagnosis and Treatment			Supraventricular extrasystole. Start bisoprolol for hypertension	Still arrhythmic, continued bisoprolol	

ISR 5677204, US (2008), atrial fibrillation, CASE 3: A 53-year old male consumer reported that he initiated calcipotriene 0.005% + betamethasone 0.064% ointment once daily to treat psoriasis. Approximately three months after initiation of treatment, he experienced episodes of palpitations. Approximately one month later, during a routine check-up, an EKG confirmed atrial fibrillation. No treatment was prescribed. Calcipotriene + betamethasone treatment was ongoing, and the outcome of the atrial fibrillation was unknown. The medical history included hypertension and concomitant medications included nifedipine.

3.2 LITERATURE SEARCH

The search of the literature did not identify any additional reports of cardiac arrhythmia associated with calcipotriene use.

4 DISCUSSION

Calcipotriene is a synthetic analogue of vitamin D₃ with antipsoriatic activity, used for topical dermatological administration. The mechanism of action of calcipotriene is not fully understood, but *in vitro* evidence suggests that calcipotriene is roughly equipotent to the natural vitamin D₃ in its effects on proliferation and differentiation of a variety of cell types.⁶ Vitamin D maintains normal levels of calcium and phosphorus in the blood, and aids in the absorption of calcium, which is essential for the development of healthy teeth and bones. In excess doses, vitamin D can cause hypercalcemia (excess calcium in the blood). As an analogue of vitamin D, calcipotriene also has the ability to cause hypercalcemia. This adverse event is well documented in the currently approved calcipotriene product labels (see Appendix A).

Hypercalcemia can lead to arrhythmia by causing an imbalance in the ion exchange process. Ion channel exchange is a necessary component of the cardiac action potential and the heart’s ability to maintain a normal sinus rhythm. It is of interest whether serum calcium concentrations in a patient using calcipotriene could become sufficiently elevated to lead to hypercalcemia and a cardiac arrhythmia. Calcipotriene has been shown, in animal studies, to be 100-200 times less potent in its effects on calcium utilization than the natural hormone.⁶ Despite these findings, it is unclear whether serum concentrations of calcipotriene correlate directly with the formation of cardiac arrhythmias.

We identified three cases of adverse events related to arrhythmia in AERS associated with calcipotriene; atrial fibrillation + ventricular fibrillation (1), supraventricular tachycardia (1), and atrial fibrillation (1). All three cases were reported as expedited 15-day reports, with outcomes of hospitalization (1) and other serious outcomes (2). Two cases reported the use of an EKG to diagnose the arrhythmia.

Contributing factors included concomitant medications in two cases (omeprazole-1, calcipotriene + betamethasone-1, nifedipine-1) and comorbidities in two cases (hypertension-2). The omeprazole label lists tachycardia, bradycardia, and palpitations as possible adverse events. The nifedipine label lists ventricular arrhythmia as a possible adverse event. Therefore, the presence of omeprazole or nifedipine may have contributed to the cardiovascular complications in the second and third cases. The use of calcipotriene + betamethasone allows for additional calcipotriene application, potentially leading to excessive administration beyond the recommended dosing of twice daily application of plain calcipotriene cream in the second case.⁷ The excess calcipotriene could potentially lead to increased absorption of the product, thereby increasing the possibility of adverse events. In addition, two patients had a diagnosis of hypertension in the second and third cases. Underlying conditions such as hypertension or myocardial infarction, which damage the heart's electrical system can cause arrhythmias.⁵

Although two cases reported a positive dechallenge (i.e. the events resolved when calcipotriene was withdrawn), one of those cases provided minimal information, and the other case was confounded by multiple factors. Additionally, one case reported a positive rechallenge (i.e. the events recurred when calcipotriene was reintroduced); however, the case was confounded by multiple factors. Despite these results, the cases do not provide sufficient information or clarity to support an association between cardiac arrhythmias and calcipotriene.

5 CONCLUSIONS

Based on the lack of post-marketing cases in both the AERS database and the literature, the data do not suggest a compelling safety signal for cardiac arrhythmias with the use of calcipotriene formulations. We are mindful of the fact that the absence of reporting does not necessarily mean the absence of a signal and that the AERS database is subject to substantial under-reporting. However, considering these factors and the information provided in three cases, which was either limited in scope or confounded by other factors, an association between cardiac arrhythmia and calcipotriene cannot be concluded.

6 RECOMMENDATIONS

Since this review did not identify any new post-marketing safety signals associated with calcipotriene and cardiac arrhythmias, DPV I has no recommendations for labeling enhancements. Based solely on the data we reviewed, we feel that further assessment of cardiac repolarization is not indicated at this time; however, DPV will continue to monitor the AERS database for reports of cardiac arrhythmias associated with calcipotriene use to determine the need for any regulatory action in the future.

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8 APPENDICES

8.1 APPENDIX A. LABELING INFORMATION FOR HYPERCALCEMIA AND CALCIPOTRIENE

The present labels for approved calcipotriene products contain the following:

- **CONTRAINDICATIONS:**
 - Dovonex[®] is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation. It should not be used by patients with demonstrated hypercalcemia or evidence of vitamin D toxicity. Dovonex[®] should not be used on the face.
 - Taclonex[®] Ointment is contraindicated in patients with known or suspected disorders of calcium metabolism.
- **PRECAUTIONS:**
 - Dovonex[®]: Reversible elevation of serum calcium has occurred with use of topical calcipotriene. If elevation in serum calcium outside the normal range should occur, discontinue treatment until normal calcium levels are restored.
 - Taclonex[®] Ointment: Hypercalcemia has been observed with use of Taclonex[®] Ointment. If elevation of serum calcium outside the normal range occurs, discontinue treatment until normal calcium levels are restored. In the trials that included assessment of the effects of Taclonex[®] Ointment on calcium metabolism, such testing was done after 4 weeks of treatment. The effects of Taclonex[®] Ointment on calcium metabolism following treatment durations of longer than 4 weeks are not known.
- **WARNINGS AND PRECAUTIONS:**
 - Taclonex[®] Scalp Topical Suspension: Hypercalcemia and hypercalciuria have been observed with use of Taclonex[®] Scalp Topical Suspension. If hypercalcemia or hypercalciuria develop, treatment should be discontinued until parameters of calcium metabolism have normalized. The effects of Taclonex[®] Scalp Topical Suspension on calcium metabolism following treatment durations of more than 8 weeks have not been evaluated.
- **OVERDOSAGE:**
 - Dovonex[®]: Topically applied calcipotriene can be absorbed in sufficient amounts to produce systemic effects. Elevated serum calcium has been observed with excessive use of topical calcipotriene. If elevation in serum calcium should occur, discontinue treatment until normal calcium levels are restored. (See **PRECAUTIONS**.)
 - Taclonex[®] Ointment: Topically applied Taclonex[®] Ointment can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS**.)
- **PATIENT INFORMATION**
 - Who should not use Taclonex[®] Ointment?
 - Do not use Taclonex[®] Ointment if you:
 - have a calcium metabolism disorder
 - Taclonex[®] Ointment may cause serious side effects if you use too much or use it for too long. Taclonex[®] Ointment can pass through your skin. Serious side effects may include:
 - too much calcium in your blood
 - adrenal gland problems

Your doctor may do special blood and urine tests to check your calcium levels and adrenal gland function while you are using Taclonex[®] Ointment.

8.2 APPENDIX B. ALL PREFERRED TERMS INCLUDED IN THE AERS SEARCH STRATEGY FOR CARDIAC ARRHYTHMIAS AND CALCIPOTRIENE

Accelerated idioventricular rhythm	PT	Brugada syndrome	PT	Electrocardiogram QT interval abnormal	PT	Pacemaker generated arrhythmia	PT	Trifascicular block	PT
Accessory cardiac pathway	PT	Bundle branch block	PT	Electrocardiogram QT prolonged	PT	Pacemaker syndrome	PT	Ventricular arrhythmia	PT
Adams-Stokes syndrome	PT	Bundle branch block bilateral	PT	Electrocardiogram repolarisation abnormality	PT	Palpitations	PT	Ventricular asystole	PT
Agonal rhythm	PT	Bundle branch block left	PT	Electrocardiogram RR interval prolonged	PT	Parasystole	PT	Ventricular extrasystoles	PT
Anomalous atrioventricular excitation	PT	Bundle branch block right	PT	Electrocardiogram U-wave abnormality	PT	Paroxysmal arrhythmia	PT	Ventricular fibrillation	PT
Arrhythmia	PT	Cardiac arrest	PT	Electrocardiogram U-wave biphasic	PT	Rebound tachycardia	PT	Ventricular flutter	PT
Arrhythmia neonatal	PT	Cardiac arrest neonatal	PT	Electromechanical dissociation	PT	Reperfusion arrhythmia	PT	Ventricular pre-excitation	PT
Arrhythmia supraventricular	PT	Cardiac death	PT	Extrasystoles	PT	Rhythm idioventricular	PT	Ventricular tachyarrhythmia	PT
Arrhythmogenic right ventricular dysplasia	PT	Cardiac fibrillation	PT	Foetal arrhythmia	PT	Sick sinus syndrome	PT	Ventricular tachycardia	PT
Atrial conduction time prolongation	PT	Cardiac flutter	PT	Foetal heart rate deceleration	PT	Sinoatrial block	PT	Wandering pacemaker	PT
Atrial fibrillation	PT	Cardiac telemetry abnormal	PT	Foetal heart rate disorder	PT	Sinus arrest	PT	Withdrawal arrhythmia	PT
Atrial flutter	PT	Cardio-respiratory arrest	PT	Gallop rhythm present	PT	Sinus arrhythmia	PT	Wolff-Parkinson-White syndrome	PT
Atrial tachycardia	PT	Cardio-respiratory arrest neonatal	PT	Heart alternation	PT	Sinus bradycardia	PT	Wolff-Parkinson-White syndrome congenital	PT
Atrioventricular block	PT	Chronotropic incompetence	PT	Heart block congenital	PT	Sinus tachycardia	PT		
Atrioventricular block complete	PT	Conduction disorder	PT	Heart rate abnormal	PT	Sudden cardiac death	PT		
Atrioventricular block first degree	PT	ECG P wave inverted	PT	Heart rate decreased	PT	Sudden death	PT		
Atrioventricular block second degree	PT	Electrocardiogram abnormal	PT	Heart rate increased	PT	Supraventricular extrasystoles	PT		
Atrioventricular conduction time shortened	PT	Electrocardiogram ambulatory abnormal	PT	Heart rate irregular	PT	Supraventricular tachyarrhythmia	PT		
Atrioventricular dissociation	PT	Electrocardiogram change	PT	Long QT syndrome	PT	Supraventricular tachycardia	PT		
Atrioventricular extrasystoles	PT	Electrocardiogram delta waves abnormal	PT	Long QT syndrome congenital	PT	Syncope	PT		
Bifascicular block	PT	Electrocardiogram P wave abnormal	PT	Loss of consciousness	PT	Tachyarrhythmia	PT		
Bradyarrhythmia	PT	Electrocardiogram PQ interval prolonged	PT	Lown-Ganong-Levine syndrome	PT	Tachycardia	PT		
Bradycardia	PT	Electrocardiogram PR prolongation	PT	Neonatal tachycardia	PT	Tachycardia foetal	PT		
Bradycardia foetal	PT	Electrocardiogram PR shortened	PT	Nodal arrhythmia	PT	Tachycardia paroxysmal	PT		
Bradycardia neonatal	PT	Electrocardiogram QRS complex prolonged	PT	Nodal rhythm	PT	Torsade de pointes	PT		

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/

TRACY M SALAAM
06/01/2010

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

Date: May 20, 2010

From: Elizabeth L. Durmowicz, MD, Medical Officer

Through: Hari Cheryl Sachs, MD, Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Melinda McCord, MD, Clinical Reviewer
Jill Lindstrom, MD, Clinical Team Leader
Division of Dental and Dermatology Products (DDDP)

Re: pediatric development plan

Sponsor: Stiefel Laboratories, Inc.

Drug: Sorilux™ (calcipotriene)

NDA: 22-563

Supporting Doc: original NDA

Indication (proposed): treatment of plaque psoriasis in patients (b) (4)

Dosage form/ strength: topical foam (0.005%)

Consult Question: DDDP is interested in PMHS comment on the ability of the available data to support safety and effectiveness in pediatric patients 12-<18 years (b) (4)
(b) (4) Specific comments on the need for systemic exposure data in adolescent patients and the lower age limit for the study of psoriasis products in pediatric patients is requested.

Materials Reviewed:

- PMHS Consult Request Document (April 22, 2010)
- PMHS Dovobet® (calcipotriene and betamethasone) Consult (IND 62,993) December 2005
- PMHS Silkis® (later named Vectical™)/ calcitriol Consult (IND 62,151) August 2008
- Approval letter and pediatric postmarketing requirements (PMRs) for Vectical™ (calcitriol) NDA 22-087. January 23, 2009.
- Draft Written Request and Pediatric Review Committee documents for calcitriol to be issued to NDA 22-087 (Draft for PeRC Review May 5, 2010)
- Written Request for calcipotriene and the combination of calcipotriene and betamethasone (February 20, 2007)

Regulatory Background:

The current submission for this product, Sorilux™, a calcipotriene foam for use in the treatment of plaque psoriasis in patients (b) (4) is the original NDA and a 505(b)(2) submission, with Dovonex® ointment (0.005%) as the listed drug. Dovonex® ointment is no longer marketed in the US or Europe secondary to business reasons; however, a generic formulation of calcipotriene ointment was approved for use in adults with plaque psoriasis in March 2010. Dovonex® ointment was approved prior to the enactment of PREA and is not approved in pediatric patients. (b) (4)

(b) (4)

Reviewer Comment:

(b) (4)

Pediatric Psoriasis:

The epidemiology of pediatric psoriasis has been extensively reviewed in previous PMHS consults. Briefly, although a variety of clinical psoriasis types are seen in childhood, including plaque, guttate, erythrodermic, napkin (diaper) and nail-based disease², the most common form of psoriasis in children is plaque psoriasis or psoriasis vulgaris. In patients less than 2 years, plaque psoriasis is relatively uncommon (< 2% of cases) and can be difficult to diagnose. However, psoriasis occurs in patients less than 10 years in approximately 10% of patients and the prevalence of psoriasis in patients 2-11 years appears to be comparable to that in adolescents. The Division has concluded based on epidemiologic and US census data that the prevalence of psoriasis in patients ≤ 9 years

is approximately 55 per 10,000, and therefore has estimated that 220,000 US pediatric patients ≤ 9 years have psoriasis.

Most pediatric patients respond to topical therapies, including emollients, antihistamines and topical steroids. Most low to mid-potency topical steroids are approved for use in children of all ages; however, other therapeutic alternatives such as tazarotene (approved in adolescent patients) and calcipotriene cream (approved in adults) are not approved for use in children less than 12 years.

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.

Vitamin D Analogs:

Calcipotriene Products

Currently marketed calcipotriene products include calcipotriene cream and ointment (approved in adults for the treatment of plaque psoriasis) and calcipotriene scalp solution (approved in adults for the treatment of chronic, moderately severe psoriasis of the scalp). The combination of calcipotriene and betamethasone dipropionate is approved in adults as Taclonex® ointment and Taclonex Scalp® for the treatment of topical psoriasis vulgaris and the treatment of moderate to severe psoriasis of the scalp, respectively. PREA studies for the Taclonex® products were waived in patients <12 years secondary to safety, specifically secondary to the risk of hypothalamic-pituitary-adrenal (HPA) axis suppression, and studies were deferred in patients 12-17 years as the products were ready for approval in adults. (b) (4)



Calcitriol Products

Vectical™ (NDA 22-087), a topical calcitriol ointment, was approved in January 2009 for the treatment of mild to moderate plaque psoriasis in adults. The PREA study requirement was waived in patients <2 years because too few patients are available to study and deferred in patients 2-17 years as the product was ready for approval in adults (See Appendix I: Vectical™ PREA Requirements). The Division is in the process of finalizing a WR for the studies outlined in the PREA requirement, i.e. studies of calcitriol ointment in patients 2-16 years with mild to moderate plaque psoriasis.

Reviewer Comment:

Because topical calcitriol is only approved in adults for mild to moderate plaque psoriasis and as an ointment, the Division has concluded that without supportive adult

data, studies of calcitriol for additional indications and/or as a different topical formulation are not feasible due to the limited number of pediatric patients.

In addition, because plaque psoriasis is uncommon in patients <2 years and can be difficult to diagnose in this age group, the Division has determined that studies in patients <2 years are not feasible even under BPCA, which allows for studies of uncommon conditions.

Oral forms and injectable forms of calcitriol are approved for use in predialysis chronic renal failure patients (including pediatric patients 1 year and older) for the management of secondary hyperparathyroidism and bone disease, and the management of hypocalcemia in pediatric patients 6 years and older with hypoparathyroidism or pseudohypothyroidism and in adult dialysis patients. Of note, studies of an injectable formulation of calcitriol, Calcijex NDA 18-874, in pediatric patients with end stage renal disease receiving dialysis were performed under a pediatric WR and exclusivity was granted to the sponsor in February 2001.

Sorilux™ Clinical Development Program

Per the Division, the integrated summary of safety and efficacy consists of data from a multicenter, randomized, double-blind safety and efficacy study comparing calcipotriene foam versus vehicle foam, calcipotriene ointment and vehicle ointment in 101 patients with mild to moderate plaque psoriasis (CAL 201) and two phase 3 multicenter, randomized, double-blind, safety and efficacy studies of calcipotriene foam versus vehicle foam in 659 patients with plaque psoriasis (U0267-301, n=301, and U0267-302, n=323). Of note, because Dovonex® ointment was withdrawn from the market and the generic calcipotriene ointment had not been approved, the Phase 3 trials do not include a comparator ointment arm and the clinical bridge to the findings of safety for Dovonex® ointment are from study CAL 201. Although one patient <18 years was enrolled in the pharmacokinetic (PK) study (CAL 203), no patients <18 years were enrolled in CAL 201. Nine subjects less than age 18 were enrolled in the Phase 3 trials (U0267-301, U0267-302), and 6 of these patients were exposed to drug. Safety endpoints assessed in the clinical trials included albumin-adjusted serum calcium levels, but no additional serological tests or assessments to evaluate the effects of calcipotriene on calcium metabolism were performed.

Reviewer comment:

As discussed, the listed drug for this 505(b)(2) application, Dovonex® ointment, is not approved in pediatric patients, and the data provided by the Sponsor do not appear adequate to determine safety and effectiveness in pediatric patients 12-16 years, as only one patient was enrolled in the PK study and only six patients <18 years were exposed to calcipotriene foam and enrolled in the trials included in the integrated summary of safety and efficacy.

Because the pathophysiology and disease progression of plaque psoriasis are considered similar in adults and children, extrapolation of efficacy from adult data may be acceptable; however, dosing and safety must be demonstrated. Although

pharmacokinetic (PK) and pharmacodynamic (PD) parameters are important measures to evaluate systemic absorption and potential effect on calcium metabolism, PK/PD parameters are unable to confirm dosing.

Furthermore, even if adequate adolescent PK/PD data were available AND an adequate number of adolescent patients were enrolled in the Phase 3 Sorilux™ trials, the safety monitoring appears to be inadequate to assess effects on calcium metabolism. Required safety monitoring in both the calcipotriene WR and proposed calcitriol WR includes not only general serological testing and assessment of albumin-corrected calcium levels, but also additional assessments, specifically the assessment of serum parathyroid hormone and alkaline phosphatase (total and bone-specific), as well as the assessment of urine creatinine, calcium, calcium/creatinine-ratio, phosphate, phosphate/creatinine ratio, hydroxyproline and hydroxyproline/creatinine ratio.

The PREA PMR for Vectical™, calcitriol ointment, includes PK/PD studies in 25 patients 2-12 years and 25 patients 12 to 17 years, a vehicle-controlled safety and efficacy study in 100 patients 2-12 years, and a long-term safety study in 100 patients 2 to 17 years. If the Sorilux™ sponsor provides adequate data to support safety and effectiveness in patients 2-<12 years, the Division could consider requiring a small PK/PD study in adolescent patients and extrapolating efficacy and safety from the younger patients up to the adolescent population, as outlined in the pediatric development program for Vectical™.

Comments on the Division's Consult Questions:

1. During Phase 2 and 3 studies only 7 subjects less than age 18 were exposed to calcipotriene foam and 3 exposed to vehicle foam. A single subject under the age of 18 was assessed for systemic exposure to calcipotriene foam.

a. Does PMHS agree with the sponsor that the data collected in the Phase 2 and Phase 3 studies for NDA 22563 allow a determination of the safety and efficacy of calcipotriene foam in children ages 12 to 18?

PMHS Response:

No, we do not agree with the Sponsor. Although the pathophysiology and disease progression of plaque psoriasis are considered similar in adults and children, and, therefore, extrapolation of efficacy may be acceptable, the Sponsor has not provided adequate PK/PD or safety data to support a determination of safety and effectiveness in patients 12-16 years. Additional pediatric studies should be required under PREA (See below).

b. Should the Division request systemic exposure data in subjects age 12 to 18?

PMHS Response:

Although PMHS defers to the Division, requiring systemic exposure data appears necessary to evaluate for potential systemic absorption and the potential effect of calcipotriene ointment on calcium metabolism. Per the July 2008 PMHS calcitriol

review, systemic absorption (approximately 10%) was observed in radio-labeled studies in adults and was a concern in the PK/PD and safety study based on interim summary data on 5 of 11 pediatric patients 12-17 years that demonstrated decreased intact parathyroid hormone (iPTH) levels. (b) (4)

2. (b) (4)

The Division is considering a partial pediatric waiver below 2 years of age and a deferral for ages 2 to 12. Does PMHS agree with the DDDP plan to request that the sponsor study pediatric subjects age 2 years and above? Please recommend a lower age limit for study of psoriasis products in pediatric subjects.

PMHS Response:

DDDP's approach to the PREA requirements for patients <12 years appears appropriate and consistent with the PREA requirement for Vectical™, calcitriol ointment. Based on the prevalence data provided, pediatric studies in patients < 2 years do not appear to be feasible based on too few patients to study and could not be required under PREA. In addition, because of difficulties in diagnosis and the low prevalence of plaque psoriasis in patients <2 years, this product may not offer a meaningful health benefit and may not be used in a substantial number of patients in this age cohort.

Studies in patients ≥ 2 years should be required under PREA, as a waiver is not justified based on the prevalence data and limited number of approved topical products for psoriasis. If the Division concurs that the available data are inadequate to support safety and effectiveness in pediatric patients 12-16 years, not only should studies be required in patients 2-<12 years, but also in patients 12-16 years. Of note, as discussed, if the Sponsor provides adequate data to support safety and effectiveness in patients 2-<12 years, the Division could consider requiring a small PK/PD study in adolescent patients and extrapolating efficacy and safety from the younger patients up to the adolescent population, as outlined in the pediatric development program for Vectical™, calcitriol ointment; however, this would not change the PREA requirement to provide a pediatric assessment in pediatric patients ≥ 2 years. If Sorilux™ is ready for approval in adults and the safety data in adults are adequate to support initiation of studies in pediatric patients, deferring PREA studies based on the criteria that the product is ready for approval in adults would be appropriate.

(b) (4)
the Sponsor will need to submit a request for a partial waiver (in patients <2 years) and a deferral request (in patients in which PREA studies

are to be required). The deferral request must include a pediatric plan which is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetic/pharmacodynamic, safety, efficacy) sufficient to demonstrate safety and efficacy. If extrapolation of efficacy (and/or safety from younger patients) is acceptable, the Sponsor must include the data to support the extrapolation, as well as the plans for the supportive studies to demonstrate dosing and, if appropriate, safety. The pediatric plan must contain a timeline for the completion of pediatric studies, i.e. the dates of (1) protocol submission, (2) study completion and (3) submission of study reports. In addition, the Sponsor must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

Of note, if the Division decides to issue a WR to this calcipotriene sponsor, additional pediatric studies of calcipotriene can be requested. Unlike PREA, under BPCA a WR can request studies in pediatric populations in which a condition is rare or uncommon. Given the low incidence of all types of psoriasis in patients < 2 years and that supportive adult data is only available for the treatment of plaque psoriasis, studies do not appear to be feasible in patients < 2 years. In addition, BPCA applies to the drug moiety, and therefore a WR can include studies for additional indications and formulations. Calcipotriene scalp solution is approved in adults for the treatment of moderate to severe plaque psoriasis and pediatric studies of this formulation for this indication may be feasible and provide a health benefit. However, although the literature suggests that Vitamin D analogs may play a role in the treatment of many autoimmune conditions, including dermatologic conditions other than psoriasis, calcipotriene is only approved in formulations for topical use and does not appear to be routinely used to treat other conditions¹. Therefore, although PMHS defers to the Division, if a WR is issued, it appears that the WR should include a request for studies of the calcipotriene topical solution in pediatric patients ≥ 2 years with moderate to severe plaque psoriasis of the scalp; however, studies of additional indications or other formulations do not appear to be needed.

APPENDIX I:

Vectical™ Ointment (NDA 22-087) PREA Postmarketing Requirements (excerpts from the Approval Letter)

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required studies are listed below.

1. Conduct PK/PD study of Vectical Ointment under maximum use conditions in 25 evaluable pediatric subjects with psoriasis aged 12 to 17 years. The study protocol has been submitted and initiated.

Study Start: June 2006
Final Report Submission: March 2010

2. Conduct a PK/PD study of Vectical Ointment under maximum use conditions in pediatric subjects with psoriasis aged 2 to 12 years; the number of subjects enrolled should be sufficient to detect a 10% change in serum ionized calcium from baseline with 90% confidence or a minimum of 25 evaluable subjects, whichever is larger.

Protocol Submission: April 2009
Study Start: July 2009
Final Report Submission: March 2012

3. Conduct a vehicle-controlled study of the safety and efficacy of Vectical Ointment in pediatric subjects with psoriasis 2 to 12 years of age with a minimum of 100 evaluable subjects exposed to active.

Protocol Submission: April 2009
Study Start: July 2009
Final Report Submission: July 2011

4. Conduct a long-term safety study of Vectical Ointment in 100 evaluable pediatric patients 2 to 17 years of age.

Protocol Submission: April 2009
Study Start: October 2009
Final Report Submission: January 2012

Appendix II:

Studies included in the Integrated Summary of Safety and Efficacy:

Study Location of full report	CAL.201 Module 5, section 5.3.5.1	U0267-301 and U0267-302 Module 5, section 5.3.5.1
Title	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	A Multicenter, Randomized, Double-Blind, Phase 3 Study of the Safety and Efficacy of Emulsion Formulation Calcipotriene Foam, 0.005%, versus Vehicle Foam in Subjects with Plaque-type Psoriasis
Study design	Multicenter, randomized, double-blind, vehicle controlled	Multicenter, randomized, double-blind, vehicle controlled
Number of study centers	8 centers	U0267-301, 13 centers; U0267-302, 12 centers
Population	Male and female subjects at least 12 years of age in good general health with mild-to-moderate plaque-type psoriasis involving 2% to 10% of BSA (excluding face and scalp)	Male and female subjects at least 12 years of age in good general health with mild-to-moderate plaque-type psoriasis involving 2% to 20% of BSA (excluding face and scalp)
Investigational product	Calcipotriene foam 0.005%	Calcipotriene foam 0.005%
Comparator	Dovonex Ointment (calcipotriene 0.005%), vehicle ointment, vehicle foam	Vehicle foam
Duration of treatment	8 weeks	8 weeks
Treatment groups	Subjects were randomized in a 4:4:2:1 ratio to the calcipotriene foam, vehicle foam, Dovonex Ointment, and vehicle ointment groups	Subjects were randomized 2:1 to the calcipotriene foam and vehicle foam groups

REFERENCES

1. Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev.* 2005 Aug;26(5):662-87.
2. Silverberg NB. Pediatric psoriasis: an update. *Ther Clin Risk Manag.* 2009;5:849-56.

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/s/

ELIZABETH L DURMOWICZ
05/20/2010

HARI C SACHS
05/21/2010
I agree with the recommendations in this consult

LISA L MATHIS
05/27/2010

**REGULATORY PROJECT MANAGER LABELING REVIEW
(PHYSICIAN LABELING RULE)**

Division of Dermatology and Dental Products

Application Number: NDA 022563

Name of Drug: Sorilux™ (calcipotriene) Foam, 0.005%

Applicant: Stiefel, a GSK Company

Material Reviewed:

Submission Date: December 18, 2009

Receipt Date: December 21, 2009

Submission Date of Structure Product Labeling (SPL): December 18, 2009

Type of Labeling Reviewed: WORD

Background and Summary

The sponsor submitted draft labeling on December 18, 2009 and received on December 21, 2009 as part of a new NDA submission. This NDA is in eCTD format and includes labeling in Word and SPL formats.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling:

In the Highlights section:

1. For the Initial U.S. Approval, delete '2010' and replace with the four-digit year in which FDA initially approved the new molecular entity, new biological product, or new combination of active ingredients.

2. Remove 'and FDA-Approved Patient Labeling' from the following sentence: 'See 17 for PATIENT COUNSELING INFORMATION' and FDA-Approved Patient Labeling. FDA-Approved Patient Labeling is not part of Section 17 but can be included at the end of the Full Prescribing Information started on a separate page. Place the FDA-Approved Patient Labeling on a separate page after the Full Prescribing Information.
3. Delete the revision date, '12/2009' at the end of the Highlights. For a new NDA, the revision date should be left blank at the time of submission and be edited to the month/year of application approval.

Between the Highlights and Table of Contents Sections:

4. Add a horizontal line between the Highlights and Table of Contents sections. A horizontal line must be located between these sections.

In the Contents (Table of Contents) section:

5. Delete subsection, 17.1 Patient Package Insert. FDA-Approved Patient Labeling is not part of Section 17 but can be included at the end of the Full Prescribing Information started on a separate page.

In the Full Prescribing Information:

6. Add the statement, '*See FDA-Approved Patient Labeling.*' to section 17 PATIENT COUNSELING INFORMATION.
7. Delete '17.1 Patient Package Insert' and '-See below-'.

Recommendations

Convey the identified deficiencies/issues and issue advice letter to applicant to request that they re-submit labeling by May 7, 2010. This updated version of labeling will be used for future labeling discussions.

Jeannine M. Helm
Regulatory Project Manager
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Supervisory Comment/Concurrence:

Margo Owens
Team Leader, Project Management Staff

Drafted: JHelm: 2.13.2010

Revised/Initialed: MOWens: 3.22.2010

Finalized: 3.22.2010

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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/

JEANNINE M HELM
03/23/2010

MARGO L OWENS
03/23/2010

DSI CONSULT: Request for Clinical Inspections

Date: Date submitted March 23, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Roy Blay, M.D., Regulatory Director, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Melinda McCord, M.D., M.O., DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP

From: Jeannine M. Helm, RPM, DDDP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-22563
Applicant/ Applicant contact information (to include phone/email):

Stiefel, a GSK Company
20 T. W. Alexander Drive
Research Triangle Park, NC 27709
919.990.6000

Drug Proprietary Name: Sorilux
NME or Original BLA (Yes/No): No.
Review Priority (Standard or Priority): Standard.

Study Population includes < 17 years of age (Yes/No): Yes.
Is this for Pediatric Exclusivity (Yes/No): No.

Proposed New Indication: Topical treatment of plaque psoriasis in patients

(b) (4)

PDUFA: October 21, 2010
Action Goal Date: October 1, 2010
Inspection Summary Goal Date: July 15, 2010

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
011: James A Solomon, Advanced Dermatology & Cosmetic Surgery 725 W Granada Blvd, # 44 Ormond Beach, FL 32174, (386) 898-0547, FAX: (386) 898-0551, drjsolomon@leavittmgt.com	Protocol Number: U0267-302	25	Mild to moderate plaque-type psoriasis vulgaris in individuals (b) (4)
005: Kimberly Grande. The Skin Wellness Center, PC 10215 Kingston Pike #200 Knoxville, TN 37922, (865) 584-8580, FAX: (865) 694-1949	Protocol Number: U0267-302	36	Mild to moderate plaque-type psoriasis vulgaris in individuals (b) (4)
002: Sunil Dhawan, East Bay Dermatology Medical Group, Inc. 2557 Mowry Ave., Suite 34 Fremont, CA 94538, (510) 797-4111 or (408) 957-7676	Protocol Number: U0267-302	18	Mild to moderate plaque-type psoriasis vulgaris in individuals (b) (4)

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for DSI’s thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify): All the sites were chosen based on the magnitude of the treatment effect.
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Jeannine Helm at 301-796-0637 or Melinda McCord at 301-796-2223.

Concurrence: (as needed)

<u>Jill Lindstrom: 3.24.2010</u>	Medical Team Leader
<u>Melinda McCord: 3.23.2010</u>	Medical Reviewer
<u>N/A</u>	Division Director (for foreign inspection requests or requests for 5 or more sites only)

*****Things to consider in decision to submit request for DSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/

JEANNINE M HELM

03/25/2010