

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-563

CHEMISTRY REVIEW(S)

NDA 22-563

Sorilux
(Calcipotriene) Foam

0.005%

Stiefel Laboratories, Inc

Rajiv Agarwal

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

**CMC REVIEW OF NDA 22-563
For the Division of Dermal and Dental Products (HFD-540)**

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Executive Summary Section

CMC Review Data Sheet

1. NDA 22-563
2. REVIEW #: 1
3. REVIEW DATE: 30-AUG-2010
4. REVIEWER: Rajiv Agarwal, Ph.D; Ph.D
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	18-DEC-2009
Amendment	07-MAY-2010
Amendment	28-JUN-2010
Amendment	06-AUG-2010
Amendment	23-AUG-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Stiefel, a GSK company
Address: 20 T.W Alexander Drive
Research Triangle Park, NC 27709
Representative: Salisa Hauptmann
Telephone: 919-990-6133

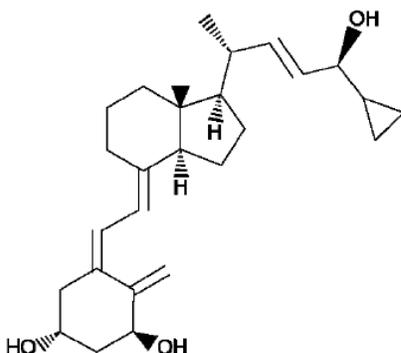
8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Sorilux
b) Non-Proprietary Name (USAN):	Calcipotriene
c) Code Name/# (ONDQA only):	N/A
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	4
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

Executive Summary Section

10. PHARMACOL. CATEGORY: Treatment of plaque psoriasis in patients (b) (4)
11. DOSAGE FORM: Foam
12. STRENGTH/POTENCY: 0.005%
13. ROUTE OF ADMINISTRATION: Topical
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed0y
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Calcipotriene:

USAN:	Calcipotriene
Chemical name:	(1 <i>R</i> ,3 <i>S</i>)-5-[2-[(1 <i>R</i> ,3 <i>aR</i> ,7 <i>aS</i>)-1-[(2 <i>S</i>)-5-cyclopropyl-5-hydroxy-pent-3-en-2-yl]-7 <i>a</i> -methyl-2,3,3 <i>a</i> ,5,6,7-hexahydro-1 <i>H</i> -inden-4-ylidene]ethylidene]-4-methylidene-cyclohexane-1,3-diol
Alternate Chemical Name:	(5 <i>Z</i> , 7 <i>E</i> , 22 <i>E</i> , 24 <i>S</i>)-24-cyclopropyl-9, 10-secochola-5, 7, 10(19), 22-tetraene-1 <i>α</i> , 3 <i>β</i> ,24-triol
Molecular formula:	C ₂₇ H ₄₀ O ₃
Molecular weight:	412.6

Executive Summary Section

RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	2-JUL-2009	Dr. Liang-Lii Huang for ANDA 77-029
	III			3	Adequate	30-OCT-2002	Ernest Pappas for NDA 20-934

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	71,198	
NDA s	21-142 21-978	Olux-E Verdeso

Executive Summary Section

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	24-MAR-2010	OC
Pharmacology/ Toxicology	Approval	25-AUG-2010	Carmen Booker
Microbiology	Approval	27-AUG-2010	Robert Mello
Methods Validation	N/A, according to the current ONDQA policy		Rajiv Agarwal
EA	Categorical Exclusion granted	30-AUG-2010	Rajiv Agarwal

Executive Summary Section

The CMC Review for NDA 22-563

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The final "Acceptable" recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations has been made.

The amended labels and labeling are now Acceptable.

Therefore, this NDA is recommended for Approval from a CMC standpoint.

However, the following statement should be conveyed to the sponsor through the action letter:

(b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The Chemistry, Manufacturing, and Control information on the **Calcipotriene** drug substance is provided in the cross referenced DMF (b) (4) from (b) (4). A letter authorizing an access to the DMF is provided in the submission. DMF (b) (4) for calcipotriene is deemed adequate per the DMF review dated 2-JUL-2009.

Executive Summary Section

(2) Drug Product

Sorilux, 0.005% is a topical, aqueous-based emulsion (b) (4) foam containing the active ingredient calcipotriene, a well-known synthetic Vitamin D3 analog, that is prescribed for the treatment of plaque-type psoriasis.

In solution, precalcipotriene and calcipotriene are in equilibrium. This is a common phenomenon of Vitamin D type systems and the conversion of the previtamin to the vitamin is part of the normal metabolic pathway for these compounds. The previtamin-to-vitamin conversion is exothermic, a first-order reaction, and has been proven to be an intramolecular rearrangement. Hence, there is an equilibrium established in solution between the previtamin and vitamin isomers, the ratio of which is dependent upon temperature. Therefore, the following acceptance criterion for the drug substance is developed: Calcipotriene 78.5 – 105.1% of label, Precalcipotriene 4.9 – 11.5% label, Total Calcipotriene 90.0 – 110.0% label claim deemed adequate.

Calcipotriene foam (b) (4) is packaged in an aluminum container (b) (4). It is supplied in a 60 g trade size canister (can). (b) (4)

All of the calcipotriene foam, 0.005% excipients are USP/NF grade ingredients that meet the current compendial monograph. Nitrogen is utilized in the manufacture of calcipotriene foam, 0.005%, and is controlled in accordance with the current version of the USP-NF compendial monograph. Propane/butane propellant is added to calcipotriene foam to ensure sufficient can pressure to deliver the product.

(b) (4)

(b) (4)

Calcipotriene foam, 0.005% is supplied in 60 g containers. The commercial product is packaged in a seamless, one-piece aluminum container (b) (4)

Executive Summary Section

(b) (4)

This container closure system fully protects the product from environmental ingress and is structurally durable to withstand handling during transportation, storage, and use. Stiefel has evaluated can/valve assembly for Stiefel foam products, which is currently marketed in the United States with Olux-E, and Verdeso. During the course of this evaluation, (b) (4) extraction residues were analyzed using Fourier Transform Infrared Spectroscopy (FTIR), High Performance Liquid Chromatography (HPLC), Gas Chromatography/Mass Spectrometry (GC/MS), Optical Microscopy (OM) and Electron Microprobe (EM) analysis. A list of extractables observed for the can/valve system is provided in the submission and they were deemed acceptable per Pharmacology/Toxicology reviewer (see the Review dated 25-AUG-2010)..

The physical stability of the pressurized emulsion was evaluated. Total calcipotriene was assayed following 3 months storage at 40°C, then equilibration at 25°C for 1 week. The cans were analyzed for calcipotriene assay after no shaking and after various levels of shaking intensity. The results confirmed that the pressurized emulsion is easily re-dispersed with (b) (4) of the can. The product is now labeled with instructions to “shake well before use.”

The formulation does not contain any preservative, but it is deemed acceptable per Quality Microbiologist’s review (see the Review dated 27-AUG-2010).

(b) (4)

The packaging of calcipotriene foam is not featured for child resistant because it is not an oral product and therefore not subject to 16 CFR 1700.14(a)(10).

An 24-month of expiration dating period is requested when stored at a controlled room temperature of 68–77°F (20–25°C) and it is granted based on the submitted stability data.

B. Description of How the Drug Product is Intended to be Used

1. Shake the can before use. Remove the cap. Before applying for the first time, break the tiny plastic piece at the base of the can's rim by gently pushing back (away from the piece) on the nozzle.
2. Turn the can upside down and press the nozzle. Dispense a small amount of SORILUX into the palm of your hand or the cap.

Executive Summary Section

3. Gently massage foam into affected area(s) until it disappears. Use enough SORILUX to cover the affected area(s) with a thin layer. Avoid contact with the eyes; if contact occurs, rinse thoroughly with water.
4. SORILUX should not be used in the eyes, mouth, or vagina. Wash hands after applying SORILUX (excluding affected areas of the hands).

C. Basis for Approvability or Not-Approval Recommendation

The raw material controls for the production of Sorilux, and the manufacturing process and controls are adequate. The specifications for the drug substance, calcipotriene, and the drug product, Sorilux, are adequate for controlling and assuring consistent quality of the commercial production. The proposed container closure system is adequate for protecting the drug product during the expiration dating period, 24 months, which is determined from the submitted stability data.

An overall “Acceptable” recommendation for the facilities involved in this application is made by the Office of Compliance.

The CMC information submitted for the label and labeling is adequate.

Therefore, from the CMC perspective, this application is recommended for approval.

III. Administrative**A. Reviewer’s Signature:**

(See appended electronic signature page)

Rajiv Agarwal, Ph.D; Ph.D

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D, Branch Chief, Branch III, ONDQA

C. CC Block: entered electronically in DARRTS

54 Page(s) has 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%

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

/s/

RAJIV AGARWAL
09/07/2010

MOO JHONG RHEE
09/07/2010
Chief, Branch IV

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Dermatology and Dental Products
NDA: 22-563
Applicant: Stiefel, a GSK company
Stamp Date: Dec. 21, 2009
PDUFA Date: Oct 21, 2010
Trademark: Sorilux™
Established Name: Calcipotriene
Dosage Form: Foam
Route of Administration: Topical
Indication: Plaque psoriasis in patients (b) (4)

PAL: Shulin Ding

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

Stiefel is submitting a 505(b) (2) New Drug Application (NDA) for the prescription use of Sorilux (calcipotriene) foam 0.005%. The product is intended for treatment of plaque psoriasis in patients (b) (4). The referenced drug is Dovonex (calcipotriene) ointment, 0.005% (NDA 20-273, Leo Pharma).

The applicant references DMF (b) (4) for the CMC information of the proposed drug substance, calcipotriene. DMF (b) (4) was most recently reviewed for calcipotriene topical solution, 0.005% (ANDA 77-029), and deemed adequate to support the ANDA.

The proposed drug product is an emulsion packaged in an aluminum aerosol can under pressure at a fill size of 60 g. In addition to the active ingredient and a propellant, the formulation also contains the following excipients: propylene glycol, USP; white petrolatum, USP; light mineral oil, NF; isopropyl myristate, NF; polyoxyl 20 cetostearyl ether, NF; cetyl alcohol, NF; stearyl alcohol, NF; purified water, USP; dibasic sodium phosphate anhydrous, USP; edetate disodium, USP; and dl- α -tocopherol, USP. The components of the propellant (propane, n-butane and isobutene) are the only non-compendial excipients. There are no novel excipients in the formulation.

The aluminum aerosol container is lined with (b) (4). The container, the subject of DMF (b) (4), has been reviewed previously and found adequate. The components of the can/valve assembly are currently used in approved foam products such as Olux-E® and Verdeso®.

The proposed product is manufactured by (b) (4)

The to-be-marketed formulation is the same formulation used in all clinical trials and registration stability batches. Stability data provided in the initial submission to support an expiration dating period of 24 months at a controlled room temperature of 68-77°F (20-25°C) include long term (25°C/60% RH) data of 12-36 months, intermediate temperature (30°C/65% RH) data of 12 months and accelerated temperature (40°C/75% RH) data of 6 months from four full scale batches (b) (4). Both upright and inverted orientations were studied.

B. Critical issues for review

Function of Excipients

- (b) (4)

Drug Product Microbiological Attributes

- The applicant states in the NDA that the proposed product failed to meet USP<51> Antimicrobial Effectiveness Test. As a result, the applicant proposes the exclusion of USP<51> from the drug product specification with a justification addressing three areas: micro-organisms' ingress possibility, formulation's self preservation, and cGMP manufacturing. USP requires that a non-sterile product packaged in multiple dose container/closure system be adequately preserved and should meet USP<51>. A consult should be sent to Quality Microbiology for this issue.

Comparability Protocol

- (b) (4)

Extractables in Drug Product

- Two extractables (b) (4) were detected in the long term stability samples of drug product at a trace level. The applicant proposes no control over them in the NDA with a justification which involves "no observed effect level (NOEL)." A critical review on the proposal needs to be performed with a consultation to Pharm/tox reviewer.

Manufacturing Process and In-Process Controls

- The manufacturing process and in-process controls need to be closely evaluated. (b) (4)

(b) (4)

- There are no in-process tests to confirm the formation of a (b) (4) emulsion and the quality of the emulsion. Usually, a check in microscopic appearance is highly desirable in the emulsification step.

- (b) (4)

Emulsion stability

- (b) (4)

Drug Product Specification

- The concern with precipitation and emulsion stability can be addressed by the addition of a microscopic examination to drug product specification on the collapsed foam. Under an optical microscope, the collapsed foam should show presence of oil globules and absence of solid particles.
- The proposed limits for related substances appear high. A portion of the justification provided by the applicant to support the proposed limits is based on toxicity assessment. A consultation with Pharm/tox reviewer is necessary before agreeing with the proposed limits.

C. Comments for 74-Day Letter:

Request the applicant to provide a copy of Master Batch Record for review, and a representative sample for dosage form evaluation.

D. Comments/Recommendation:

The application is fileable from the CMC perspective. The major CMC review issues with this NDA are microbiological attribute, limits for related substances in drug product, in-process control, homogeneity, emulsion stability, extractables, and comparability protocol. A consult should be sent to Quality Microbiology.

The drug substance manufacturing site is located in Israel, and drug product manufacturing sites are located in U.S. GMP inspection requests have been submitted.

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead

Moo-Jhong Rhee, Ph.D.
Chief, Branch III

NDA Number: 22-563

Supplement Number and Type:

Established/Proper Name:
Calcipotriene

Applicant: Stiefel, a
GSK company

Letter Date: 12/18/09

Stamp Date: 12/21/09

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			n/a

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Applicant claims categorical exclusion.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		x	Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?		x	Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?	x		Also referenced to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?		x	Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		Executed batch record is provided for one exhibit batch. Master batch record is not provided.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	n/a
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	8/31/09	Drug Substance
	III			8/26/08	The DMF covers the entire to-be-marketed container/closure system

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			n/a
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		See pp. 2-3 of this review document.

{See appended electronic signature page}

Shulin Ding, Ph.D.
 Pharmaceutical Assessment Lead
 Division of Pre-Marketing Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Branch Chief
 Division of Pre-Marketing Assessment II
 Office of New Drug Quality Assessment

Date

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/

SHULIN DING
02/16/2010

MOO JHONG RHEE
02/16/2010
Chief, Branch III