

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-563**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 022563  
Supporting document/s: 001  
Applicant's letter date: December 18, 2009  
CDER stamp date: December 21, 2009  
Product: Sorilux™ (calcipotriene foam, 0.05%)  
Indication: Mild to moderate plaque psoriasis in patients aged 18 and older  
Applicant: Stiefel Laboratories, Inc.  
Review Division: Dermatology and Dental Products  
Reviewer: Carmen D Booker, PhD  
Supervisor/Team Leader: Barbara Hill, PhD  
Division Director: Susan Walker, MD  
Project Manager: Jeannine Helm

*Template Version: December 7, 2009*

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## **1 Executive Summary**

### **1.1 Recommendations**

#### **1.1.1 Approvability**

The product is approvable with respect to nonclinical concerns.

#### **1.1.2 Additional Non Clinical Recommendations**

None

#### **1.1.3 Labeling**

In the highlights section of the label, the sponsor states that the pharmacologic class is vitamin D analog. This designation of pharmacologic class is acceptable.

The following changes to labeling are recommended:

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Teratogenic Effects, Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. Therefore, SORILUX foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies of teratogenicity were done by the oral route where bioavailability is expected to be approximately 40-60% of the administered dose. Increased rabbit maternal and fetal toxicity was noted at 12 mcg/kg/day (132 mcg/m<sup>2</sup>/day). Rabbits administered 36 mcg/kg/day (396 mcg/m<sup>2</sup>/day) resulted in fetuses with a significant increase in the incidences of incomplete ossification of pubic bones and forelimb phalanges. In a rat study, doses of 54 mcg/kg/day (318 mcg/m<sup>2</sup>/day) resulted in a significantly higher incidence of skeletal abnormalities consisting primarily of enlarged fontanelles and extra ribs. The enlarged fontanelles are most likely due to calcipotriene's effect upon calcium metabolism. The maternal and fetal no-effect exposures in the rat (43.2 mcg/m<sup>2</sup>/day) and rabbit (17.6 mcg/m<sup>2</sup>/day) studies are approximately equal to the expected human systemic exposure level (18.5 mcg/m<sup>2</sup>/day) from dermal application.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Calcipotriene is a synthetic vitamin D<sub>3</sub> analog that has a similar receptor binding affinity as natural vitamin D<sub>3</sub>. However, the exact mechanism of action contributing to the clinical efficacy in the treatment of psoriasis is unknown.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Calcipotriene topically administered to mice for up to 24 months at dose levels of 3, 10, or 30 mcg/kg/day (corresponding to 9, 30, or 90 mcg/m<sup>2</sup>/day) showed no significant changes in tumor incidence when compared to controls. In a study in which albino hairless mice were exposed to both ultraviolet radiation (UVR) and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors. [see *Warnings and Precautions* (5.2)]

The genotoxic potential of calcipotriene was evaluated in an Ames assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration assay, and a mouse micronucleus assay. All assay results were negative.

Studies in rats at doses up to 54 mcg/kg/day (318 mcg/m<sup>2</sup>/day) of calcipotriene indicated no impairment of fertility or general reproductive performance.

### 1.2 Brief Discussion of Nonclinical Findings

Stiefel is relying on the Agency's previous findings of safety for the listed drug (LD), Dovonex<sup>®</sup> Ointment, NDA 20-273, and supporting literature. In addition, Stiefel conducted eight nonclinical studies to support this NDA. Since the sponsor is relying on the Agency's previous findings of safety for Dovonex<sup>®</sup> Ointment, this NDA is a 505(b)(2) regulatory submission.

Information from Dovonex<sup>®</sup> label: Calcipotriene has been tested in an Ames mutagenic assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration test and a mouse micronucleus test. All results were negative, indicating calcipotriene is not mutagenic.

Studies in rats at doses up to 54 µg/kg/day (318 µg/m<sup>2</sup>/day) indicated no impairment of fertility or general reproductive performance. Nonclinical studies in several species indicate that calcipotriene taken in high doses orally can cause skeletal and other abnormalities in the fetus and cause toxicity in the mother. The estimated no effect levels in the mother and fetus in rat and rabbit models are approximately equal to the expected exposure in humans with topical application.

Calcipotriene topically administered to mice for up to 24 months at dose levels of 3, 10, or 30 µg/kg/day (corresponding to 9, 30, or 90 µg/m<sup>2</sup>/day) showed no significant

changes in tumor incidence when compared to controls. In a study in which albino hairless mice were exposed to both UVR and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors.

Studies conducted by Stiefel: Sprague Dawley rats were treated dermally with calcipotriene foam (0.005, 0.015, 0.025 %), Dovonex® ointment, 0.005% or vehicle foam daily for 91 days. These concentrations of calcipotriene foam correspond to doses of 15, 45 and 75 µg/kg/day, respectively. Increases in dermal irritation and calcium were observed at all doses; therefore, a NOAEL could not be determined. Gottingen minipigs were treated dermally with calcipotriene foam (4, 12, 20 µg/kg or 0.005, 0.015, 0.025 %), Dovonex® ointment (4 µg/kg or 0.005%) or vehicle foam daily for 90 days. Dermal irritation, severe testicular hypospermatogenesis and minimal to moderate renal nephropathy were observed; however, these effects were partially to completely reversible. No NOAEL could be determined for this study.

Sorilux™ appears to be a dermal irritant in rabbits, but was not an eye irritant in rabbits or dermal sensitizer in guinea pigs.

## **2 Drug Information**

### **2.1 Drug**

#### **2.1.1 CAS Registry Number**

112965-21-6

#### **2.1.2 Generic Name**

Calcipotriene, 0.005%

#### **2.1.3 Code Name**

None

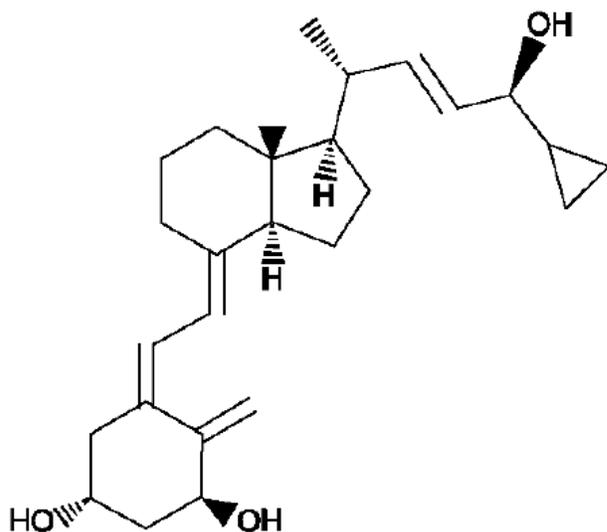
#### **2.1.4 Chemical Name**

(1*R*,3*S*)-5-[2-[(1*R*,3*aR*,7*aS*)-1-[(2*S*)-5-cyclopropyl-5-hydroxy-pent-3-en-2-yl]-7*a*-methyl-2,3,3*a*,5,6,7-hexahydro-1*H*-inden-4-ylidene]ethylidene]-4-methylidene-cyclohexane-1,3-diol

#### **2.1.5 Molecular Formula/Molecular Weight**

C<sub>27</sub>H<sub>40</sub>O<sub>3</sub> / 412.6

## 2.1.6 Structure



## 2.1.7 Pharmacologic class

Vitamin D analog

## 2.2 Relevant IND/s, NDA/s, and DMF/s

IND 71,198, DMF (b) (4), DMF (b) (4), NDA 20-273

## 2.3 Clinical Formulation

### 2.3.1 Drug Formulation

The propellant used in Sorilux foam is a propane/butane propellant (b) (4). The sponsor states that this is the same propellant used in previously approved products including OLUX and OLUX-E foam.

Table copied from sponsor's electronic submission:

**Table 1 Quantitative Composition of Calcipotriene Foam, 0.005%**

Ingredient	Function	Reference to Quality Standard <sup>a</sup>	Target Quantity (% w/w)
Calcipotriene	Active Ingredient	In-house	0.005
Purified Water	(b) (4)		
Propylene Glycol			
Light Mineral Oil			
Polyoxyl 20 Cetostearyl Ether			
Cetyl Alcohol			
Stearyl Alcohol			
White Petrolatum			
Isopropyl Myristate			
Dibasic Sodium Phosphate, Anhydrous			
Edetate Disodium			
dl- $\alpha$ -Tocopherol <sup>b</sup>			
Total			

<sup>a</sup> USP/NF: United States Pharmacopeia/National Formulary, current edition

<sup>b</sup> Vitamin E, USP

### 2.3.2 Comments on Novel Excipients

None

### 2.3.3 Comments on Impurities/Degradants of Concern



## 2.4 Proposed Clinical Population and Dosing Regimen

Patients with mild to moderate plaque psoriasis, aged 18 and older, will be advised to dose twice daily. An eight week treatment duration was evaluated in Phase 3 clinical studies.

## 2.5 Regulatory Background

A preIND meeting was held March 7, 2005. IND 71,198 was submitted on June 21, 2006. An End-of-Phase 2 meeting was conducted on October 24, 2007. A preNDA

meeting was conducted on October 21, 2009. Pharm/tox comments on all of these occasions simply reminded that the sponsor that the adequacy of their clinical bridge would determine whether additional nonclinical studies were necessary.

### **3 Studies Submitted**

#### **3.1 Studies Reviewed**

A 28-Day Toxicity Study of EF Calcipotriene Foam Administered Dermally to Rats. Study Number NPB00029. March 2007.

A 28-Day Dermal Toxicity Study of EF Calcipotriene Foam Administered Daily to Gottingen Minipigs. Study Number CB06-5080-P-TX. April 2007.

#### **3.2 Studies Not Reviewed**

The following studies were previously reviewed under IND 71,198:

14-Day Toxicity Study of Calcipotriene Foam, 0.005% and Dovonex® Ointment, 0.005% Administered by the Dermal Route to Rats. Study Number NPB00023A. March 2006.

Primary Skin Irritation Study in Rabbits with Calcipotriene Foam, 0.005%. Study Number NPB00021A. March 2006.

Primary Eye Irritation Study in Rabbits with Calcipotriene Foam, 0.005%. Study Number NPB00020A. March 2006.

Dermal Sensitization Study in Guinea Pigs with Calcipotriene Foam, 0.005%. Study Number NPB00022A. March 2006.

A 91-Day Toxicity Study of EF Calcipotriene Foam Administered Dermally to Rats with a 1-Month Recovery Period. Study Number NPB00034. January 2008.

Calcipotriene: A 90-Day Dermal Toxicity Study in Gottingen Minipigs with a 1-Month Recovery. Study Number 1236-002. June 2008.

#### **3.3 Previous Reviews Referenced**

Reviews for IND 71,198 written by Carmen D Booker, PhD and placed in DARRTS on July 25, 2006; January 17, 2007 and July 29, 2008.

### **4 Pharmacology**

#### **4.1 Primary Pharmacology**

Calcipotriene is a synthetic analog of Vitamin D<sub>3</sub> derived from naturally occurring Vitamin D. Calcipotriene inhibits the proliferation of epidermal cells of the skin and

induces cell differentiation. However, unlike calcitriol, the active form of the vitamin, calcipotriene does not affect calcium metabolism. Its antiproliferative effects are thought to involve the induction of sphingomyelin hydrolysis in keratinocytes. Calcipotriene has immunomodulatory effects including inhibition of T-cell proliferation, increasing IL-10, and reducing other cytokine levels (IL-1, IL-2, IL-6, and IL-8). Calcipotriene's efficacy is derived from its ability to induce keratinocyte differentiation and its inhibitory effect on proliferation of epidermal cells in the skin.

#### **4.2 Secondary Pharmacology**

No new data or information on the secondary pharmacodynamics of calcipotriene was submitted.

#### **4.3 Safety Pharmacology**

No new safety pharmacology studies were submitted with this NDA. The literature and previous clinical experience with Dovonex<sup>®</sup> suggest that there is no safety pharmacology concerns associated with calcipotriene.

### **5 Pharmacokinetics/ADME/Toxicokinetics**

#### **5.1 PK/ADME**

Calcipotriene is a synthetic analog of Vitamin D<sub>3</sub> derived from naturally occurring Vitamin D. Bound to plasma proteins, vitamin D and its metabolites are transported in the blood. Calcitriol, the active form of the vitamin, is recycled via the liver and excreted in the bile. Calcipotriene metabolism is rapid and occurs via a similar pathway as Vitamin D hormone. Its primary metabolites are less potent than the parent compound. Clinical studies with radiolabelled calcipotriene ointment indicate that approximately 6% of topically applied calcipotriene is absorbed systemically when applied to psoriasis plaques. When applied to normal skin, 5% is absorbed systemically. In clinical studies with radiolabelled calcipotriene ointment, maximal mean serum levels were reached at 6 hours and were no longer detectable by 36 hours. Clinical studies with radiolabelled calcipotriene ointment also demonstrated that much of the absorbed active is converted to inactive metabolites within 24 hours of application. Calcipotriene is excreted in bile.

#### **5.2 Toxicokinetics**

See toxicology summaries.

### **6 General Toxicology**

#### **6.1 Single-Dose Toxicity**

No single-dose toxicity studies were submitted to support this NDA.

## 6.2 Repeat-Dose Toxicity

In this NDA, the sponsor submitted final reports for two 28-day repeat dose dermal toxicity studies in rats and minipigs with calcipotriene foam at concentrations up to 0.025%. In both studies, a dose related increase in dermal irritation was observed. No other significant toxicities were observed in the 28-day rat and minipig studies.

Studies reviewed under IND 71,198: Sprague Dawley rats were treated dermally with calcipotriene foam, 0.005%, Dovonex® ointment, 0.005% or vehicle foam daily for 14 days. Mild dermal irritation, including desquamation, was observed in the vehicle foam, calcipotriene foam, 0.005% and Dovonex® ointment, 0.005% groups. Grade 1 and Grade 2 erythema was observed in both the calcipotriene foam, 0.005% and Dovonex® ointment, 0.005% groups. Foam vehicle males had increased calcium and decreased sodium. Calcipotriene foam, 0.005% males had increased calcium, decreased sodium and decreased chloride. Dovonex® ointment, 0.005% males had increased calcium and decreased chloride. Discoloration of peritesticular fat was observed in half of the males from the calcipotriene foam, 0.005% and Dovonex® ointment, 0.005% groups. Acanthosis and hyperkeratosis of the epidermis and mononuclear cell infiltration of the dermis were noted in all groups except the sham controls.

Sprague Dawley rats were treated dermally with calcipotriene foam (0.005, 0.015, 0.025 %), Dovonex® ointment, 0.005% or vehicle foam daily for 91 days. These concentrations of calcipotriene foam correspond to doses of 15, 45 and 75 µg/kg/day, respectively. Increases in dermal irritation and calcium were observed at all doses; therefore, a NOAEL could not be determined. Gottingen minipigs were treated dermally with calcipotriene foam (4, 12, 20 µg/kg or 0.005, 0.015, 0.025 %), Dovonex® ointment (4 µg/kg or 0.005%) or vehicle foam daily for 90 days. Dermal irritation, severe testicular hypospermatogenesis and minimal to moderate renal nephropathy were observed; however, these effects were partially to completely reversible. No NOAEL could be determined for this study.

## 7 Genetic Toxicology

Information from Dovonex® label: Calcipotriene has been tested in an Ames mutagenic assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration test and a mouse micronucleus test. All results were negative, indicating calcipotriene is not mutagenic.

## 8 Carcinogenicity

No carcinogenicity data was submitted with this NDA.

Information from Dovonex® label: Calcipotriene topically administered to mice for up to 24 months at dose levels of 3, 10, or 30 µg/kg/day (corresponding to 9, 30, or 90 µg/m<sup>2</sup>/day) showed no significant changes in tumor incidence when compared to controls. In a study in which albino hairless mice were exposed to both UVR and topically applied calcipotriene, a reduction in the time required for UVR to induce the

formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors.

## 9 Reproductive and Developmental Toxicology

Information from Dovonex<sup>®</sup> label: Studies in rats at doses up to 54 µg/kg/day (318 µg/m<sup>2</sup>/day) indicated no impairment of fertility or general reproductive performance. Nonclinical studies in several species indicate that calcipotriene taken in high doses orally can cause skeletal and other abnormalities in the fetus and cause toxicity in the mother. The estimated no effect levels in the mother and fetus in rat and rabbit models are approximately equal to the expected exposure in humans with topical application.

## 10 Special Toxicology Studies

Studies reviewed under IND 71,198: Six New Zealand White rabbits each received two 0.5 mL doses of the test material as single dermal applications to one intact and one abraded test site. The foam was occluded for 24 hours. Test sites were examined and scored for dermal irritation for up to 21 days. On intact skin, well-defined erythema was seen on all test sites and very slight edema on 4 of 6 test sites at one hour. By 48 hours, the irritation had resolved on one site, on three sites by day 7, on one site by day 10 and on the remaining site by day 14. Superficial lightening was noted on one intact skin test site. On abraded skin, well-defined erythema was noted on all test sites and very slight edema was observed on four test sites at one hour. The irritation resolved completely on one site by 48 hours, on three sites by day 7, on one site by day 10 and on one site by day 21. Superficial lightening was noted on one abraded test site. The calculated mean Primary Irritation Index for calcipotriene foam, 0.005% was 2.29. These results indicate that calcipotriene foam, 0.005% is a minimal dermal irritant.

Three New Zealand White Rabbits received 0.1 mL dose of calcipotriene foam 0.005% in the conjunctival sac of the right eye. The left eye remained untreated and served as a control. Conjunctivitis was seen in 2 out of 3 test eyes at the 1-hour scoring interval; however, the irritation resolved within 24 hours. No corneal opacity or iritis was noted during the study. These results indicate that calcipotriene foam, 0.005% is non-irritating to the eyes.

Ten male and ten female guinea pigs were topically treated with calcipotriene foam, 0.005% once per week for 3 consecutive weeks. Dermal scores of 0 were noted in all test animals and in all challenge control animals at 24 and 48 hours. Based on the results of this study, calcipotriene foam, 0.005% is not considered to be a contact sensitizer in guinea pigs.

## 11 Integrated Summary and Safety Evaluation

There are no nonclinical safety issues relevant to the clinical use of Sorilux<sup>™</sup>. This is a 505 (b) 2 application in which the sponsor is relying on the Agency's previous findings of nonclinical safety for the LD, Dovonex<sup>®</sup> ointment. The sponsor conducted a clinical

bridging study, a pharmacokinetic study comparing the bioavailability of Sorilux™ Foam to that of Dovonex® ointment.

Calcipotriene has been tested in an Ames mutagenic assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration test and a mouse micronucleus test. All results were negative, indicating calcipotriene is not mutagenic.

Sprague Dawley rats were treated dermally with calcipotriene foam (0.005, 0.015, 0.025 %), Dovonex® ointment, 0.005% or vehicle foam daily for 91 days. These concentrations of calcipotriene foam correspond to doses of 15, 45 and 75 µg/kg/day, respectively. Increases in dermal irritation and calcium were observed at all doses; therefore, a NOAEL could not be determined. Gottingen minipigs were treated dermally with calcipotriene foam (4, 12, 20 µg/kg or 0.005, 0.015, 0.025 %), Dovonex® ointment (4 µg/kg or 0.005%) or vehicle foam daily for 90 days. Dermal irritation, severe testicular hypospermatogenesis and minimal to moderate renal nephropathy were observed; however, these effects were partially to completely reversible. No NOAEL could be determined for this study.

Sorilux™ appears to be a dermal irritant in rabbits, but was not an eye irritant in rabbits or dermal sensitizer in guinea pigs.

Studies in rats at doses up to 54 µg/kg/day (318 µg/m<sup>2</sup>/day) indicated no impairment of fertility or general reproductive performance. Nonclinical studies in several species indicate that calcipotriene taken in high doses orally can cause skeletal and other abnormalities in the fetus and cause toxicity in the mother. The estimated no effect levels in the mother and fetus in rat and rabbit models are approximately equal to the expected exposure in humans with topical application.

Calcipotriene topically administered to mice for up to 24 months at dose levels of 3, 10, or 30 µg/kg/day (corresponding to 9, 30, or 90 µg/m<sup>2</sup>/day) showed no significant changes in tumor incidence when compared to controls. In a study in which albino hairless mice were exposed to both UVR and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors.

In the highlights section of the label, the sponsor states that the pharmacologic class is vitamin D analog. This designation of pharmacologic class is acceptable.

Labeling proposed by sponsor:

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

*Teratogenic Effects, Pregnancy Category C:*

Studies of teratogenicity were done by the oral route where bioavailability is expected to be approximately 40-60% of the administered dose. Increased rabbit maternal and fetal toxicity was noted at 12 µg/kg/day (132 µg/m<sup>2</sup>/day). Rabbits administered 36 µg/kg/day (396 µg/m<sup>2</sup>/day) resulted in fetuses with a significant increase in the incidences of incomplete ossification of pubic bones and forelimb phalanges. In a rat study, doses of 54 µg/kg/day (318 µg/m<sup>2</sup>/day) resulted in a significantly higher incidence of skeletal abnormalities consisting primarily of enlarged fontanelles and extra ribs. The enlarged fontanelles are most likely due to calcipotriene's effect upon calcium metabolism.

(b) (4)

There are no adequate and well-controlled studies in pregnant women. Therefore, SORILUX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

(b) (4)

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Calcipotriene topically administered to mice for up to 24 months at dose levels of 3, 10, or 30 µg/kg/day (corresponding to 9, 30, or 90 µg/m<sup>2</sup>/day) showed no significant changes in tumor incidence when compared to controls. In a study in which albino hairless mice were exposed to both UVR and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors.

(b) (4)

The genotoxic potential of calcipotriene was evaluated in an Ames assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration assay, and a mouse micronucleus assay. All assay results were negative.

Studies in rats at doses up to 54 µg/kg/day (318 µg/m<sup>2</sup>/day) of calcipotriene indicated no impairment of fertility or general reproductive performance.

Proposed labeling:

*Reviewer comments:* Section 8.1 of the label has been modified to incorporate reference to human clinical studies, or lack thereof, at the beginning of this section followed by reference to animal studies. The wording concerning lack of clinical studies in pregnant women has been modified to the standard wording recommended by SEALD. A statement comparing species exposures to the expected human exposure has been added in. A similar statement was previously in the Dovonex label. The abbreviation for microgram has been modified to incorporate the abbreviation recommended by SEALD. The recommended wording for this section of the label is provided below.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Teratogenic Effects, Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women [REDACTED] (b) (4) [REDACTED] SORILUX foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies of teratogenicity were done by the oral route where bioavailability is expected to be approximately 40-60% of the administered dose. Increased rabbit maternal and fetal toxicity was noted at 12 mcg/kg/day (132 mcg/m<sup>2</sup>/day). Rabbits administered 36 mcg/kg/day (396 mcg/m<sup>2</sup>/day) resulted in fetuses with a significant increase in the incidences of incomplete ossification of pubic bones and forelimb phalanges. In a rat study, doses of 54 mcg/kg/day (318 mcg/m<sup>2</sup>/day) resulted in a significantly higher incidence of skeletal abnormalities consisting primarily of enlarged fontanelles and extra ribs. The enlarged fontanelles are most likely due to calcipotriene's effect upon calcium metabolism. The maternal and fetal no-effect exposures in the rat (43.2 mcg/m<sup>2</sup>/day) and rabbit (17.6 mcg/m<sup>2</sup>/day) studies are approximately equal to the expected human systemic exposure level (18.5 mcg/m<sup>2</sup>/day) from dermal application.

*Reviewer comments:* Section 12.1 was modified to state that the mechanism of action is unknown.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Calcipotriene is a synthetic vitamin D<sub>3</sub> analog that has a similar receptor binding affinity as natural vitamin D<sub>3</sub>. However, the exact mechanism of the action contributing to the clinical efficacy in the treatment of psoriasis is unknown.

*Reviewer comments:* Section 13.1 was modified to delete clinical statements already appearing in Section 5.2, to include the word ultraviolet radiation to define “UVR” and to include the abbreviation recommended by SEALD.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Calcipotriene topically administered to mice for up to 24 months at dose levels of 3, 10, or 30 mcg/kg/day (corresponding to 9, 30, or 90 mcg/m<sup>2</sup>/day) showed no significant changes in tumor incidence when compared to controls. In a study in which albino hairless mice were exposed to both ultraviolet radiation (UVR) and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors. [see *Warnings and Precautions (5.2)*]

The genotoxic potential of calcipotriene was evaluated in an Ames assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration assay, and a mouse micronucleus assay. All assay results were negative.

Studies in rats at doses up to 54 mcg/kg/day (318 mcg/m<sup>2</sup>/day) of calcipotriene indicated no impairment of fertility or general reproductive performance.

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/

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CARMEN D BOOKER  
08/24/2010

BARBARA A HILL  
08/25/2010  
I concur

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

**NDA/BLA Number: 22-563**

**Applicant: Stiefel**

**Stamp Date: 12/21/2009**

**Drug Name: Sorilux;**

**NDA/BLA Type: 505(b)(2)**

**Calcipotriene foam, 0.005%**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

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	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_\_\_\_**

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

N/A

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

None

Carmen D Booker, PhD  
Reviewing Pharmacologist

5 February 2010  
Date

\_\_\_\_\_  
Team Leader/Supervisor

\_\_\_\_\_  
Date

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

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/s/

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CARMEN D BOOKER  
02/17/2010

BARBARA A HILL  
02/17/2010