CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207589Orig1s000

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/BLA REVIEW AND EVALUATION

Application number:	207589
Supporting document/s:	DSN 1
Applicant's letter date:	18-DEC-2014
CDER stamp date:	18-DEC-2014
Product:	Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%
Indication:	Topical treatment of plaque psoriasis in adults 18 years of age or older.
Applicant:	LEO Pharma A/S
Review Division:	DDDP
Reviewer:	Norman A. See, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
Division Director:	Kendall Marcus, MD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Taclonex Ointment (calcipotriene 0.005% (as hydrate) and betamethasone dipropionate 0.064% in ointment base) was approved under NDA 21-852 on 09-JAN-2006 for the indication of topical treatment of psoriasis vulgaris in adults. Taclonex Topical Suspension, which also contains calcipotriene 0.005% and betamethasone dipropionate 0.064%, in a liquid formulation, was approved 09-MAY-2008 for the indication of topical treatment of psoriasis vulgaris of the scalp in adults. Under NDA 207589, clinical use of an aerosol product, LEO 90100 (proposed tradename "Enstilar® Foam"), that is similar to Taclonex ointment has been proposed. LEO 90100 contains calcipotriene 0.005% and betamethasone dipropionate 0.064%, (b) (4) (b) (4) into an aluminum can and administered as a spray. The indication, conditions of exposure, and patient population proposed under NDA 207589 are similar to those approved under NDA 21-852. NDA 207589 includes letters from LEO Pharma A/S that authorize reference to data associated with NDA 21-852 and IND 62,993 (Taclonex Ointment), and NDA 22-185 and IND 67,835 (Taclonex Topical Suspension). LEO Pharma A/S is the sponsor of NDA 21-852, NDA 22-185, IND 62,993, and IND 67,835. LEO Pharma A/S developed LEO 90100 under IND 114,063. I will refer to the CDER nonclinical reviews of NDA 21-852 and NDA 22-185, as well as IND 114,063, for summary and interpretation of the nonclinical data.

1.2 Brief Discussion of Nonclinical Findings

Summarizing information stated in Pharmacology/Toxicology reviews of NDA 21-852 and NDA 22-185:

The product contains both calcipotriene and betamethasone dipropionate.

Calcipotriene:

The primary sign of toxicity observed in studies that involved application of calcipotriene was perturbation of calcium homeostasis, including elevated concentrations of calcium in the serum and urine, microscopic evidence of stimulation of bone formation, and mineralization of the kidney. However, little transdermal absorption of calcipotriene occurs, and if treated animals are prevented from ingesting the applied material then little systemic exposure occurs and consequently little or no toxicity is observed. In a nine-month topical study in which minipigs were treated with Taclonex ointment six hours per day, under a dressing, and the residual material removed at the end of the treatment period to prevent ingestion, little toxicity was observed.

Calcipotriene was considered negative in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, and the mouse micronucleus test.

Calcipotriene was evaluated for activity as a cocarcinogen with UV light in a 12-month study with hairless mice. The median number of weeks on study at which the first tumor

(for a given animal) greater than or equal to 1.0 mm in diameter was observed was significantly reduced for males that received the greatest exposure to calcipotriene (30 µg/kg/day), while vehicle alone had no effect, suggesting that calcipotriene may enhance the carcinogenic effects of UV light. Calcipotriene was evaluated for activity as a carcinogen in a study in which mice were treated topically for 24 months at dosages of 3, 10 and 30 mcg/kg/day (corresponding to 9, 30 and 90 mcg/m^2/day). No biologically significant changes in tumor incidence were observed when compared to control. A 104-week oral carcinogenicity study was conducted with calcipotriene in male and female rats at doses of 1, 5 and 15 mcg/kg/day (corresponding to dosages of approximately 6, 30, and 90 mcg/m^2/day). Beginning week 71, the dosage for high-dose animals of both genders was reduced to 10 mcg/kg/day (corresponding to a dosage of approximately 60 mcg/m^2/day). A treatment-related increase in benign C-cell adenomas was observed in the thyroid of females that received 15 mcg/kg/day. A treatment-related increase in benign pheochromocytomas was observed in the adrenal glands of males that received 15 mcg/kg/day. No other statistically significant differences in tumor incidence were observed when compared to control.

Calcipotriene was evaluated for effects upon reproduction. Calcipotriene had no effects on fertility of male or female rats. Teratology studies conducted with calcipotriene in rats and rabbits indicated no effects on the incidence of major malformations, but found that at sufficient levels of systemic exposure calcipotriene can induce minor skeletal variations, including incomplete ossification of sternebrae, pubic bones, and fore limb phalanges. When assessed for effects on peri-natal or post-natal development, calcipotriene had no remarkable effects on any parameter, including survival, behavior, body weight, litter parameters, or the ability of female rats to nurse or rear pups.

Betamethasone dipropionate:

In a nine-month topical study in which minipigs were treated with Taclonex ointment, little toxicity was observed. Treatment-related findings included slightly reduced mean adrenal weight, minimal to moderate adrenal atrophy, and thinning of the skin. All of those effects were probably secondary to exposure to betamethasone dipropionate. As a glucocorticoid, betamethasone dipropionate is capable of causing reversible adrenal atrophy through negative feedback of the HPA axis. Even with substantial oral doses of betamethasone dipropionate, however, serious toxicity was not observed in rats that were orally dosed for 13 weeks. In that oral rat study, in which rats received up to 0.2 mg/kg/day betamethasone dipropionate, there were no effects on survival, clinical signs, clinical chemistry, or urinalysis, and there was no clear effect on mean body weight, although a trend toward reduced mean body weight with increasing dosage seemed apparent. The mean WBC count decreased in proportion to dosage, as did the mean weights of the spleen and thymus. These are known effects of corticosteroids when systemically administered at sufficient levels. Treatment-related histopathological findings in the oral rat study were limited to the spleen (lymphoid depletion), thymus (cortical atrophy), and lymph nodes (lymphoid depletion or hyperplasia) of high-dose animals of both genders. In all, little toxicity was observed in rats that were orally dosed with betamethasone dipropionate for 13 weeks. Although all plasma samples that were

analyzed in that study were below the limit of quantitation for betamethasone dipropionate (75 pg/mL), substantial exposure to the metabolite, betamethasone 17-propionate, was documented.

Betamethasone dipropionate was negative in the Ames assay and in the mouse lymphoma TK locus assay with and without metabolic activation, and in an in vivo micronucleus assay.

Betamethasone dipropionate was evaluated for potential to induce carcinogenicity in studies in which male and female rats were orally dosed, and male and female mice were topically dosed, for up to 24 months. Under the conditions of those studies, betamethasone dipropionate did not significantly increase the incidence of tumors in either male or female rats or mice.

Betamethasone dipropionate was evaluated in a battery of reproductive toxicology studies. No effect on reproductive performance or fertility was observed when betamethasone dipropionate was orally administered to male rats at dosages up to 0.2 mg/kg/day, or in females orally dosed at up to 1.0 mg/kg/day. When administered subcutaneously to pregnant mice on days 7 through 13 of gestation, betamethasone dipropionate induced fetal toxicity, including fatality, reduced fetal body weight, increased incidence of cleft palate and crooked or short tail, and delayed ossification. A NOAEL was not observed in this study, as fetal toxicity was observed at the lowest exposure that was evaluated (0.156 mg/kg/day). When administered subcutaneously to pregnant rabbits on days 6 through 18 of gestation, betamethasone dipropionate induced fetal toxicity, including fatality, reduced fetal body weight, external malformations, and skeletal malformations. An exposure of 0.625 µg/kg/day was a NOAEL in this study; fetal toxicity was observed at 2.5 µg/kg/day and above. Betamethasone dipropionate was evaluated for effects when orally administered to pregnant rats from gestation day 6 through day 20 postpartum at dosages of 0, 0.1, 0.3, and 1.0 mg/kg/day. Mean maternal BW was significantly lower at 0.3 and 1.0 mg/kg/day on day 20 of gestation. The mean duration of gestation was slightly but statistically increased at 0.1, 0.3, and 1.0 mg/kg/day. The mean percentage of pups that survived to day 4 was reduced in F1 pups in relation to dosage, although the effects at 0.1 and 0.3 mg/kg/day were minimal. The percentage of pups with a righting-reflex on day 5 of lactation was significantly reduced at 1.0 mg/kg/day. No effects were observed on pup learning ability or reproduction of F1 animals.

Taclonex ointment was essentially non-irritating to the skin or eyes. LEO 90100 was assessed for potential to induce local irritation in a study in which LEO 90100, the vehicle of 90100, Taclonex Ointment, and the vehicle of Taclonex Ointment, were applied daily for four weeks to the skin of minipigs. The test materials were well tolerated.

1.3 Recommendations

1.3.1 Approvability

The product is approvable with respect to nonclinical concerns.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

It is recommended that section 8.1 (Pregnancy) and section 12.1 (Mechanism of Action) of the draft label be modified to the statements indicated below. Other portions of the draft label are acceptable in regard to nonclinical issues.

1. Section 8.1:

"**8.1 Pregnancy**
Teratogenic Effects: Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. Pregnant women were excluded from the clinical studies conducted with Enstilar® Foam. Enstilar® Foam should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with Enstilar® Foam. Enstilar® Foam contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically.

Teratogenicity studies with calcipotriene were performed by the oral route in rats and rabbits. In rabbits, increased maternal and fetal toxicity were noted at a dosage of 12 mcg/kg/day (144 mcg/m^2/day); a dosage of 36 mcg/kg/day (432 mcg/m^2/day) resulted in a significant increase in the incidence of incomplete ossification of the pubic bones and forelimb phalanges of fetuses. In a rat study, a dosage of 54 mcg/kg/day (324 mcg/m^2/day) resulted in a significantly increased incidence of skeletal abnormalities (enlarged fontanelles and extra ribs). The enlarged fontanelles are most likely due to the effect of calcipotriene upon calcium metabolism. The estimated maternal and fetal no-adverse effect levels (NOAEL) in the rat (108 mcg/m^2/day) and rabbit (48 mcg/m^2/day) derived from oral studies are lower than the estimated maximum topical dose of calcipotriene in man (460 mcg/m^2/day).

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Betamethasone dipropionate has been shown to be teratogenic in mice and rabbits when given by the subcutaneous route at doses of 156 mcg/kg/day (468 mcg/m^2/day) and 2.5 mcg/kg/day (30 mcg/m^2/day), respectively. Those dose levels are lower than the estimated maximum topical dose in man (about 5,950 mcg/m^2/day). The abnormalities observed included umbilical hernia, exencephaly and cleft palate.

Two oral peri- and post-natal development studies were conducted with rats:

Pregnant Wistar rats were dosed daily with calcipotriene at exposures of 0, 6, 18, or 54 mcg/kg/day from gestation day 15 through day 20 postpartum. No remarkable effects

were observed on any parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.

Betamethasone dipropionate was evaluated for effects when orally administered to pregnant rats from gestation day 6 through day 20 postpartum at dosages of 0, 100, 300, and 1000 mcg/kg/day. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/kg/day. No effects on the ability of pups to learn were observed, and the ability the offspring of treated rats to reproduce was not affected."

2. Section 12.1:

"**12.1 Mechanism of Action**
Enstilar® Foam combines the pharmacological effects of calcipotriene hydrate as a synthetic vitamin D_3 analog and betamethasone dipropionate as a synthetic corticosteroid. However, while their pharmacologic and clinical effects are known, the exact mechanisms of their actions in plaque psoriasis are unknown."

2 Drug Information

2.1 Drug

CAS Registry Number(s)
Calcipotriene: 147657-22-5; Betamethasone: 5593-20-4

Generic Name(s)
Calcipotriene hydrate and betamethasone dipropionate (b) (4) (Note: calcipotriene is known as calcipotriol in Europe)

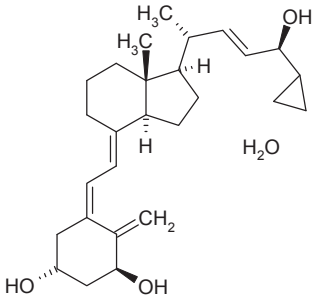
Code Name(s)
MC 903 (calcipotriene); 433/M (betamethasone); LEO 90100 (foam formulation)

Chemical Name(s)
Calcipotriene: (b) (4)

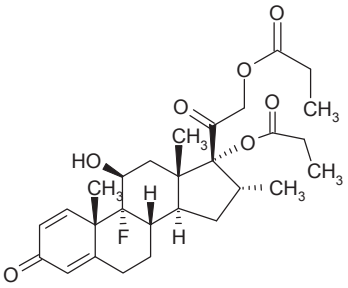
Betamethasone: (b) (4)

Molecular Formula/Molecular Weight
Calcipotriene hydrate: $C_{27}H_{40}O_3 \bullet H_2O/430.6$
Betamethasone dipropionate: $C_{28}H_{37}FO_7/504.59$

Structure or Biochemical Description



Calcipotriene Hydrate



Betamethasone Dipropionate

Pharmacologic Class(s)
Calcipotriene: Vitamin D analog
Betamethasone: Corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 21-852; NDA 22-185; IND 114,063; IND 62,993; IND 67,835

Note: NDA 207589 includes letters from LEO Pharma A/S that authorizes reference to data associated with NDA 21-852 and IND 62,993 (Taclonex Ointment), and NDA 22-185 and IND 67,835 (Taclonex Topical Suspension). LEO Pharma A/S is the sponsor of NDA 21-852, NDA 22-185, IND 62,993, and IND 67,835. LEO Pharma A/S developed LEO 90100 under IND 114,063. I will refer to the CDER nonclinical reviews of NDA 21-852 and NDA 22-185, as well as IND 114,063, for summary and interpretation of the nonclinical data.

2.3 Drug Formulation

Name of components	Quantity per g in the container	Quantity per g after evaporation of propellants	Function	Reference to quality standard(s)
Drug substance(s):	(b) (4)			
Calcipotriol[1] (b) (4)		50.0 mcg	Drug substance	Ph. Eur./LEO
Betamethasone[2] (as dipropionate)		0.5 mg	Drug substance	Ph. Eur./USP
Excipients. (b) (4) (b) (4)		(b) (4)		
PPG-11 stearyl ether[3] (b) (4)[4+5]				LEO
all-*rac*-α-tocopherol[5] (b) (4)[4+5]				Ph. Eur./USP Ph. Eur./USP Ph.Eur./USP
Excipients, propellants:				
Dimethyl ether		N/A	(b) (4) propellant	LEO
Butane		N/A	propellant	NF/LEO

1 (b) (4)

2 Listed as betamethasone. 0.5 mg betamethasone is equivalent to 0.643 mg betamethasone dipropionate. (b) (4)

3 Polyoxypropylene-11-stearyl ether contains approximately (b) (4) (b) (4) by the manufacturer.

4 Contains all-*rac*-α-tocopherol (b) (4) by the manufacturer.

5 USP references: Mineral oil (b) (4) (all-rac-α-tocopherol) and white petrolatum (b) (4)

Note: The formulation of the applied product, following propellant (b) (4) of Taclonex Ointment (NDA 21-852).

2.4 Comments on Novel Excipients

The product essentially consists of (b) (4) (b) (4) butane and dimethyl ether (DME). The inactive components (excipients) within the (b) (4) of the product, including polyoxyproylene-11-stearyl ether, α-tocopherol, mineral oil, and white petrolatum, have all been adequately qualified (see nonclinical reviews of NDA 21-852 for detailed information). Polyoxypropylene-11-stearyl ether was previously referred to as "polyoxypropylene-15-stearyl ether", but has been redesignated "polyoxypropylene-11-stearyl ether" (this matter was addressed under the CMC review of S-014 to NDA 21-852 and S-017 to NDA 22-185). Only the nomenclature has been changed; polyoxypropylene-11-stearyl ether is the same compound that was previously known as polyoxypropylene-15-stearyl ether. According to NDA 207589, the sponsor tested several potential propellants for their (b) (4)

(b) (4) Of the propellants tested, DME was stated to be the only propellant in which (b) (4) DME has not been a component of a product previously approved by CDER. However, DME is used as a propellant in a number of currently marketed household products and cosmetics.

The following information was obtained from the US EPA "Robust Summaries" database in association with the "High Production Volume (HPV) Challenge" program:

(b) (4)

The key citation (study report) discussed in the EPA document appears to be a two-year inhalation study with rats. This reference is listed as being "unpublished", but the source (the US EPA) is regarded as being reliable. The citation for the two-year rat study is "(b) (4) Unpublished Data, (b) (4) According to the EPA "robust summary for dimethyl ether", in this study Crl:CD (SD)BR

rats (100/sex/group) were exposed (within chambers) to DME 6 hours per day, 5 days per week (excluding holidays) at levels of 0, 2000, 10,000, and 25,000 ppm, for up to two years. The no-observable-effect-level (NOEL) was 2000 ppm DME based on an increase in body weight and a decrease in survival in male rats exposed to 10,000 or 25,000 ppm DME vapors and on hemolytic effects noted in male rats exposed to 25,000 ppm DME vapors for 6 months. No DME-related histological lesion was consistently observed throughout the study. No neoplastic lesions were observed that could be attributable to DME exposure. DME was not carcinogenic.

A maximum daily dose of LEO 90100 (100 g/week, divided by 7 days/week, equates to (b) (4) which corresponds to approximately (b) (4) % of a 60 g container) is associated with approximately (b) (4) of DME. If (b) (4) of DME was released into a room of 8 m^3, the theoretical concentration of DME in the room would be approximately (b) (4) mg/m^3 (approximately (b) (4) ppm under standard conditions) at the time of release. This value is well below the concentration that was regarded as a NOEL in rats when exposed 6 hours per day, for a lifetime (2000 ppm).

DME is highly volatile, and is expected to rapidly dissipate in a typical home environment. Therefore, the time-weighted average concentration of DME (e.g., the average concentration over a period of time) in the vicinity of a patient who used the product would likely be substantially less than the (b) (4) mg/m^3 mentioned above. Exposure to DME from use of LEO 90100 will presumably resemble exposure from other products that utilize DME as a propellant, such as certain hairspray products. In a published account, exposure to DME as a result of use of hairspray that contained DME was estimated[1]. DME concentration was measured in the 'breathing zone' of a manikin following a 10 second use of hairspray that contained 50% DME. A mean 10 minute time-weighted average value for an adult user in a closed room (volume 21 m^3) was estimated at (b) (4) ppm ((b) (4) mg/m^3). Thus, the exposures to DME that may result from proper use of LEO 90100 are unlikely to approach or exceed the level that was found to be without apparent toxicity in rats. The available data suggest that DME is not genotoxic, teratogenic, or carcinogenic. In view of the clinical benefit to be derived from use of the product, the exposure to DME that has been proposed under NDA 207589 is considered to be acceptable.

Butane was added to the product to help achieve the desired (b) (4). Butane has been used as a propellant in a number of approved drug products, and is GRAS as a direct human food ingredient (as a propellant, 21 CFR 184.1165). The proposed use of butane is acceptable.

DME and butane are both highly flammable. Section 5.1 of the draft label states:

[1] Hartop, PJ, Cook, TL, and Adams, MG. Simulated consumer exposure to dimethyl ether and propane/butane in hairsprays. International Journal of Cosmetic Science 13:161-167 (1991).

"The propellants in Enstilar® Foam are flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application."

2.5 Comments on Impurities/Degradants of Concern

2.5.1 Impurities Associated with Drug Substances (APIs)
The APIs (calcipotriene hydrate and betamethasone dipropionate) proposed for use under NDA 207589 (b) (4) (including specifications for impurities) to those that are associated with the related LEO products "Taclonex Ointment" (NDA 21-852) and "Taclonex Topical Suspension" (NDA 22-185). The maximum daily exposures to the APIs in association with NDA 207589 (b) (4) to those in association with NDA 21-852. The related exposures to impurities that are associated with the APIs are considered to be qualified, in part though clinical experience and marketing history of Taclonex Ointment.

2.5.2 Impurities that are Degradation Products in the Drug Product
The specifications for organic impurities of the drug product are summarized below:

Specification

Strength	50 mcg/g calcipotriol (as calcipotriol hydrate 52.2 mcg/g) after evaporation of propellants. 0.5 mg/g betamethasone (as betamethasone dipropionate 0.643 mg/g) after evaporation of propellants.	
Primary packaging material	Pressurised aluminium spray can with a continuous valve and actuator.	
Description	The sprayed foam is white to off-white	
Tests	**Limits**	**Test methods***
Appearance (after spraying)	Conforms to description	visual examination
Identification (RT, UV spectrum):		
calcipotriol	Positive	00398402
betamethasone dipropionate	Positive	00398402
Assay:		
calcipotriol (anhydrous)	90.0 – 110.0 %	00398402
betamethasone dipropionate	90.0 – 110.0 %	00398402
Organic impurities, calcipotriol:		00398402
(b) (4)	≤ (b) (4)%	
	≤ %	
	≤ %	
any unspecified impurity	≤ %	
total	≤ %	
Organic impurities, betamethasone dipropionate:		00398402
any unspecified impurity	≤ (b) (4)%	
total	≤ %	
all-*rac*-α-Tocopherol	(b) (4)**	00399926
Delivered amount	(b) (4)**	USP <603>
Leak rate	USP <604>**	USP <604>

* All pharmacopoeia references are to current editions of pharmacopoeias.
All references to LEO methods are to current revisions of analytical procedures.
** Release limit only.
RT Retention time.

Under ICH Q3B, the qualification threshold for degradation products that are associated with calcipotriene under NDA 207589 is 1.0%. The degradation products of calcipotriene that exceed the qualification threshold include (b) (4) (b) (4), and (b) (4). (b) (4) and (b) (4) are by-products formed during the (b) (4) of calcipotriene, as well as potential degradation

products. (b) (4) is a degradation product that has been identified as (b) (4) . These compounds are all close structural relatives of calcipotriene:

Compound	Structure
(b) (4)	

(b) (4) do not exhibit any structural alerts regarding genotoxicity that are not associated with calcipotriene.

The levels of (b) (4), unspecified impurities, and total impurities in representative lots of LEO 90100 that have been reported under NDA 207589 are within the limits that are currently approved under NDA 21-852 (b) (4) However, those analyses are from release testing, and may not reflect the maximum levels that would be present at expiry (24 months post-production). The sponsor has projected that the levels of (b) (4) at expiry may approach (b) (4) % of the API, respectively. (b) (4) is a newly detected degradation product that is not a specified impurity under NDA 21-852. The sponsor has proposed under NDA 207589 specifications for organic impurities related to calcipotriene (b) (4)

(b) (4)%, any unspecified impurity (b) (4) % and total (b) (4) %. Even if present in LEO 90100 at the maximum permissible levels, the theoretical daily exposures to (b) (4) in association with LEO 90100 would be low (on the order of (b) (4) per day or less), and exposure would occur via topical application to the skin, with resulting low systemic absorption. Given that these compounds have no apparent pharmacodynamic actions (other than being less potent forms of calcipotriene), exhibit no structural alerts for genotoxicity, and were present in various amounts in lots of calcipotriene that were evaluated in nonclinical and clinical safety studies, the proposed specification for organic impurities related to calcipotriene are considered to be qualified. It is noted that the proposed specifications for organic impurities related to calcipotriene are apparently necessary to permit marketing of the product under reasonable circumstances (e.g., to achieve a reasonable shelf-life), and are therefore necessary to permit potential benefits to be derived by patients who will use the product.

2.5.3 Evaluation of Extractables and Leachables
Studies were conducted to investigate the potential for toxic compounds to be extracted from components of the container-closure system proposed for use under NDA 207589. Extraction studies were performed on the primary components of the container-closure system, in which the components were subjected to reflux extraction using a mixture of 64% hexane and 36% methyl tert-butyl ether (MTBE) as extraction medium. The extracts were then analyzed for organic compounds. The hexane:MTBE extraction medium was selected because it exhibited polarity similar to that of the pressurized drug product formulation, and hence was expected to provide an extractable profile similar to that of the drug product. The overall conclusion from the extraction studies is that no extractables (unidentified or identified) appear to be of potential safety concern.

2.6 Proposed Clinical Population and Dosing Regimen

The product is proposed for the topical treatment of plaque psoriasis in adults 18 years of age and older. The proposed labeling states:

- Apply Enstilar® Foam to affected area(s) once daily for up to 4 weeks.
- (b) (4)
- Enstilar Foam is not for oral, ophthalmic, or intravaginal use. Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

2.7 Regulatory Background

Under NDA 207589, clinical use of an aerosol product, LEO 90100 (proposed tradename "Enstilar® Foam"), has been proposed. LEO 90100 contains calcipotriene 0.005% and betamethasone dipropionate 0.064% (b) (4) (b) (4) into an aluminum can, and administered as a spray. The (b) (4), indication, conditions of exposure, and patient population proposed under NDA 207589 are similar to those approved under NDA 21-852 (Taclonex Ointment, approved on 09-JAN-2006 for the indication of topical treatment of psoriasis vulgaris in adults). LEO Pharma A/S

developed LEO 90100 under IND 114,063. Taclonex Topical Suspension, which also contains calcipotriene 0.005% and betamethasone dipropionate 0.064%, in a liquid formulation, was approved 09-MAY-2008 for the indication of topical treatment of psoriasis vulgaris of the scalp in adults. NDA 207589 includes letters from LEO Pharma A/S that authorizes reference to data associated with NDA 21-852 and IND 62,993 (Taclonex Ointment), and NDA 22-185 and IND 67,835 (Taclonex Topical Suspension), all of which are owned by LEO Pharma A/S.

3 Studies Submitted

3.1 Studies Reviewed

A battery of nonclinical studies, which adequately qualifies topical use of calcipotriene and betamethasone dipropionate within the context of NDA 207589, has been reviewed in association with NDA 21-852 and NDA 22-185. Those studies include assessment of calcipotriene and betamethasone dipropionate as individual compounds (involving both oral and topical dermal administration), as well as studies that involved topical administration of various formulations that contained both APIs. The studies include assessment of both calcipotriene and betamethasone dipropionate in regard to pharmacology, pharmacokinetics, pharmacodynamics, safety pharmacology, single and repeated-dose general toxicity, genetic toxicology, reproductive toxicology (assessment of potential to impact fertility/reproductive success of male and female rodents, developmental toxicity of rats and rabbits, and prenatal and postnatal development, including maternal function, of rodents), carcinogenicity, and special toxicology issues. See reviews of NDA 21-852 and NDA 22-185 for details concerning these studies. Data obtained in these studies are summarized in section 1.2 of this review. In addition, the following study was conducted to assess LEO 90100 (the clinical formulation under NDA 207598) for potential to induce dermal irritation when topically applied to the skin of minipigs:

1. 4-Week local tolerance study in minipigs, calcipotriene and betamethasone in spray and ointment formulation, study No. 72281.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

NDA 21-852 - Nonclinical reviews

NDA 22-185 - Nonclinical reviews

4 Pharmacology

4.1 Primary Pharmacology

See nonclinical reviews of NDA 21-852 and NDA 22-185.

4.2 Secondary Pharmacology

See nonclinical reviews of NDA 21-852 and NDA 22-185.

4.3 Safety Pharmacology

See nonclinical reviews of NDA 21-852 and NDA 22-185.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

See nonclinical reviews of NDA 21-852 and NDA 22-185.

5.2 Toxicokinetics

See nonclinical reviews of NDA 21-852 and NDA 22-185.

6 General Toxicology

6.1 Single-Dose Toxicity

See nonclinical reviews of NDA 21-852 and NDA 22-185.

6.2 Repeat-Dose Toxicity

See nonclinical reviews of NDA 21-852 and NDA 22-185.

7 Genetic Toxicology

See nonclinical reviews of NDA 21-852 and NDA 22-185. Quoting the approved label for NDA 22-185, the available genetic toxicology database associated with calcipotriene and betamethasone dipropionate may be summarized as follows:

"Calcipotriene did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test."

8 Carcinogenicity

See nonclinical reviews of NDA 21-852 and NDA 22-185. Quoting the approved label for NDA 22-185, the available carcinogenesis database associated with calcipotriene and betamethasone dipropionate may be summarized as follows:

"When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10, and 30 mcg/kg/day (corresponding to 9, 30, and 90 mcg/m^2/day), no significant changes in tumor incidence were observed when compared to control.

In a study in which albino hairless mice were exposed to both ultra-violet 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.

A 104-week oral carcinogenicity study was conducted with calcipotriene in male and female rats at doses of 1, 5 and 15 mcg/kg/day (corresponding to dosages of approximately 6, 30, and 90 mcg/m^2/day). Beginning week 71, the dosage for high-dose animals of both genders was reduced to 10 mcg/kg/day (corresponding to a dosage of approximately 60 mcg/m^2/day). A treatment-related increase in benign C-cell adenomas was observed in the thyroid of females that received 15 mcg/kg/day. A treatment-related increase in benign pheochromocytomas was observed in the adrenal glands of males that received 15 mcg/kg/day. No other statistically significant differences in tumor incidence were observed when compared to control. The relevance of these findings to patients is unknown.

When betamethasone dipropionate was applied topically to CD-1 mice for up to 24 months at dosages approximating 1.3, 4.2, and 8.5 mcg/kg/day in females, and 1.3, 4.2, and 12.9 mcg/kg/day in males (corresponding to dosages of up to approximately 26 mcg/m^2/day and 39 mcg/m^2/day, in females and males, respectively), no significant changes in tumor incidence were observed when compared to control.

When betamethasone dipropionate was administered via oral gavage to male and female Sprague Dawley rats for up to 24 months at dosages of 20, 60, and 200 mcg/kg/day (corresponding to dosages of approximately 120, 360, and 1200 mcg/m^2/day), no significant changes in tumor incidence were observed when compared to control."

9 Reproductive and Developmental Toxicology

See nonclinical reviews of NDA 21-852 and NDA 22-185. Quoting portions of the approved label for NDA 22-185, the available reproductive toxicology database associated with calcipotriene and betamethasone dipropionate may be summarized as follows:

"Studies in rats with oral doses of up to 54 mcg/kg/day (324 mcg/m^2/day) of calcipotriene indicated no impairment of fertility or general reproductive performance.

Studies in male rats at oral doses of up to 200 mcg/kg/day (1200 mcg/m^2/day), and in female rats at oral doses of up to 1000 mcg/kg/day (6000 mcg/m^2/day), of betamethasone dipropionate indicated no impairment of fertility.

Teratogenicity studies with calcipotriene were performed by the oral route in rats and rabbits. In rabbits, increased maternal and fetal toxicity were noted at a dosage of 12 mcg/kg/day (144 mcg/m^2/day); a dosage of 36 mcg/kg/day (432 mcg/m^2/day) resulted in a significant increase in the incidence of incomplete ossification of the pubic bones and

forelimb phalanges of fetuses. In a rat study, a dosage of 54 mcg/kg/day (324 mcg/m^2/day) resulted in a significantly increased incidence of skeletal abnormalities (enlarged fontanelles and extra ribs). The enlarged fontanelles are most likely due to the effect of calcipotriene upon calcium metabolism. The estimated maternal and fetal no-adverse effect levels (NOAEL) in the rat (108 mcg/m^2/day) and rabbit (48 mcg/m^2/day) derived from oral studies are lower than the estimated maximum topical dose of calcipotriene in man (460 mcg/m^2/day).

Betamethasone dipropionate has been shown to be teratogenic in mice and rabbits when given by the subcutaneous route at doses of 156 mcg/kg/day (468 mcg/m^2/day) and 2.5 mcg/kg/day (30 mcg/m^2/day), respectively. Those dose levels are lower than the estimated maximum topical dose in man (about 5,950 mcg/m^2/day). The abnormalities observed included umbilical hernia, exencephaly and cleft palate.

Two oral peri- and post-natal development studies were conducted with rats. Pregnant Wistar rats were dosed daily with calcipotriene at exposures of 0, 6, 18, or 54 mcg/kg/day from gestation day 15 through day 20 postpartum. No remarkable effects were observed on any parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.

Betamethasone dipropionate was evaluated for effects when orally administered to pregnant rats from gestation day 6 through day 20 postpartum at dosages of 0, 100, 300, and 1000 mcg/kg/day. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/kg/day. No effects on the ability of pups to learn were observed, and the ability the offspring of treated rats to reproduce was not affected."

10 Special Toxicology Studies

10.1. 4-Week local tolerance study in minipigs, calcipotriene and betamethasone in spray and ointment formulation, study No. 72281.

Methods. Gottingen minipigs (4 females) received for 4 weeks daily topical applications of LEO 90100, the vehicle of 90100, Taclonex Ointment, and the vehicle of Taclonex Ointment, to skin on the back. Each material was applied to a separate application site of approximately 2.8 cm^2. The application sites were observed daily for signs of irritation, and were graded on a scale of 0-4 for erythema and edema. Body weight and food consumption were monitored. At the end of the treatment period a gross necropsy was performed and skin samples from all treatment sites, plus untreated skin samples, were histologically examined.

Results. The test materials were well tolerated. No adverse systemic clinical signs were observed and all animals gained body weight throughout the treatment period.

Two out of four animals had very slight erythema at the application site that received LEO 90100 spray on several occasions during the study. Microscopically, treatment with LEO 90100 correlated with minimal epidermal atrophy.

Conclusion. LEO 90100, applied to minipig skin under the conditions of this study, was well tolerated.

11 Integrated Summary and Safety Evaluation

LEO 90100 (proposed tradename "Enstilar® Foam") consists of calcipotriene 0.005% and betamethasone dipropionate 0.064%, (b) (4) propellants and administered as a spray. The propellant (a mixture of dimethyl ether and butane) quickly evaporates following application. The product that remains on the skin post-evaporation is essentially indistinguishable from Taclonex Ointment, which was approved under NDA 21-852 on 09-JAN-2006. The conditions of exposure (including concentrations of APIs, route of exposure, quantity applied per day, percent of the body surface area and portions of the skin exposed, duration of exposure, indication, and patient population) proposed under NDA 207589 are essentially identical to those that are associated with NDA 21-852. NDA 207589 includes letters from LEO Pharma A/S that authorize reference to data associated with NDA 21-852 and IND 62,993 (Taclonex Ointment), and NDA 22-185 and IND 67,835 (Taclonex Topical Suspension). The proposed exposures to the APIs (calcipotriene and betamethasone dipropionate) and excipients that remain post-evaporation of the propellants have been fully qualified under NDA 21-852 and NDA 22-185. As discussed under section 2.4 of this review, the proposed exposures to the propellants are considered to be qualified.

Recommended changes to the proposed label are presented under section 1.3.3 of this review. NDA 207589 is approvable with respect to nonclinical issues.

12 Appendix/Attachments

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/s/

NORMAN A SEE
07/07/2015

BARBARA A HILL
07/07/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207589 **Applicant:** LEO Pharma AS **Stamp Date: 18**-DEC-2014

Drug Name: Enstilar (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% **NDA/BLA Type:** 505(b)(1) NDA

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

	Content Parameter	Yes	No	Comment
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		Some pivotal nonclinical studies involved oral dosing, or use of different topical formulations. Suitable data have been submitted which concern local tolerance of the proposed new formulation.
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 submitted a rationale to justify the alternative route?	X		As appropriate, some nonclinical studies involved oral exposure.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?		X	The pivotal nonclinical studies have been examined and found to have been conducted in compliance with Good Laboratory Practice regulations, as appropriate.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 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?			There are no known abuse issues.
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.

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

None.

Norman See, PhD	04-FEB-2015
Reviewing Pharmacologist	Date
Barbara Hill, PhD	see sign-off
Team Leader/Supervisor	Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

NORMAN A SEE
02/04/2015

BARBARA A HILL
02/04/2015