CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207589Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 16, 2015
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	207589
Applicant	LEO Pharma Inc.
Date of Submission	Letter date: December 18, 2014 CDER stamp date: December 18, 2014
PDUFA Goal Date	October 18, 2015
Proprietary Name / Established (USAN) names	Enstilar®/ calcipotriene and betamethasone dipropionate
Dosage forms / Strength	Foam, 0.005%/0.064%
Proposed Indication(s)	Topical treatment of plaque psoriasis in adults 18 years of age and older
Recommended:	*Approval*

1. Introduction

Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%, is a vitamin D analog and corticosteroid [redacted (b) (4)] topical drug product for which the applicant seeks approval under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act for the treatment of plaque psoriasis in patients 18 years of age and older. This application is for a new dosage form of calcipotriene and betamethasone dipropionate combination product. Enstilar® Foam is [redacted (b) (4)] of the approved ointment product (NDA 021852 Taclonex® Ointment). [redacted (b) (4)] In the United States the ointment formulation was approved January 2006 under the trade name Taclonex® Ointment.

The ointment and topical suspension formulation, containing the same active substances in the same concentration were developed prior to the foam formulation. Daivobet® Ointment, which includes the same active substances in the same concentration, was first approved in Denmark in March 2001 and is currently approved in 90 countries. In the United States (US), it was approved in January 9, 2006 under the trade name Taclonex® (calcipotriene and betamethasone dipropionate) Ointment, 0.005%/0.064%, for the treatment of plaque psoriasis in adults 18 years and older (NDA 21852) and on December 23, 2014 for the treatment plaque psoriasis in patients 12 years of age and older (S-15).

Taclonex® (calcipotriene and betamethasone dipropionate) Topical Suspension, 005%/0.064%, (known as Daivobet® Gel in Europe and Canada) was approved on May 9, 2008 for the treatment of moderate to severe plaque psoriasis of the scalp in adults 18 years and older (NDA 22185); on October 17, 2012 for the treatment plaque psoriasis of the scalp and body in the patients 18 years and older (S-010) and on August 29, 2014 for the treatment of the plaque psoriasis of the scalp in patents age 12 to 17 years (S-018).

Individual active substances in Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% are marketed as a single component drug product; calcipotriene is indicated for the treatment of plaque psoriasis and betamethasone dipropionate is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

This NDA 207589 includes letters from LEO Pharma A/S that authorize reference to data associated with NDA 21852 and IND 62,993 (Taclonex® Ointment), and NDA 22185 and IND 67,835 (Taclonex® Topical Suspension).

This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

The applicant developed Enstilar® Foam (LEO 90100 Foam) under IND 114063.
During their development program, the applicant interacted with the Agency at tree milestone meetings [PreIND Meeting (March 7, 2012), End-of-Phase 2 CMC Meeting (June 19, 2013) and PreNDA Meeting (March 26, 2014)].

An End of Phase 2 Meeting was scheduled for May 15, 2013. After review of the Premeeting Communication consisting of Agency responses to questions in the briefing package, the applicant determined that the responses were sufficient and the meeting was cancelled. Principal Agency comments include the following:

- The Agency agreed that an adequate and well-controlled Phase 2 trial demonstrating that the each drug makes a contribution to the claimed effects when combined and that the combination is safe and effective for the proposed population requiring such concurrent therapy, together with one Phase 3 trial comparing LEO 90100 to vehicle, would be acceptable to support an NDA.
- The proposed primary efficacy endpoint of the proportion of subjects who achieve ‘treatment success’ (‘clear’ or ‘almost clear’ for subjects with at least moderate disease at baseline, ‘clear’ for subjects with mild disease at baseline) according to the Investigator’s Global Assessment of Disease Severity (IGA) at Week 4 and the 5-point IGA are acceptable.
- A vasoconstrictor (VCA) trial is not required. However, to better characterize the new formulation the Agency recommended conducting a VCA trial. The Agency noted that

proposed comparators for the VCA trial would be inadequate to clearly identify the potency class of the proposed foam formulation. The Agency recommended that the applicant ensure adequate bracketing for the VCA trial.

At pre-NDA meeting (March 26, 2014), the applicant proposed a plan, for establishing a "bridge" for LEO 90100 to safety data for the two approved calcipotriene/BDP products which included:

- Safety data for LEO 90100 and Taclonex ® Ointment from Phase 2 trial LEO 90100-35
- Comparative vasoconstriction data (LP0053-69)
- Systemic exposure data from the Maximum Use Systemic Exposure trial (LEO 90100-30) compared with historical data from similar trials with Taclonex® Ointment and Taclonex® Topical Suspension
- Adverse event data from short term trials with LEO 90100, Taclonex® Ointment and Taclonex® Topical Suspension
- Comparative safety data from long-term clinical trials with Taclonex® Ointment and Taclonex® Topical Suspension

The Agency agreed that a long term safety study will not be required provided that the outcome of the proposed analyses supports the conclusion that the currently available long term safety data for Taclonex® Ointment and Taclonex® Topical Suspension can be extrapolated to provide sufficient information on the long term safety of LEO 90100.

In addition, the Agency stated that a multi-point vasoconstriction assessment will not be acceptable for providing any comparison between different dosage forms. The Agency recommended that the applicant include in the NDA single point visual assessment data at 2 hours following 16 hours of study medication application to clearly identify the potency class of LEO 90100. The applicant indicated that the vasoconstrictor trial was conducted with drug (b) (4)

The Agency also provided general comments regarding the Integrated Summary of Efficacy (ISE), Integrated Summary of Safety (ISS), and data submission.

3. CMC

Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%, is a vitamin D analog and corticosteroid (b) (4) topical drug product. It is a new dosage form, foam, based on Taclonex® Ointment. (b) (4)

(b) (4)

Enstilar® Foam is a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white foam after evaporation of the propellants (dimethyl ether and butane). Each gram of foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in a base of white petrolatum, polypropylene glycol stearyl ether, mineral oil, all-rac-alphatocopherol, and butylhydroxytoluene.

The composition is described in the following Table 1:

Table 1: Composition of Enstilar® Foam

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

1 (b) (4)
2 Listed as betamethasone. 0.5 mg betamethasone is equivalent to 0.643 mg betamethasone dipropionate. (b) (4) (b) (4).
3 Polyoxypropylene-11-stearyl ether (b) (4) (b) (4) by the manufacturer.
4 Contains all-rac (b) (4) tocopherol (b) (4) by the manufacturer.
5 USP references: Mineral oil (b) (4) all-rac (b) (4) tocopherol) and white petrolatum (b) (4) (b) (4)

Source: review by Sarah Ibrahim Ph.D.

The expiration dating period of 24 months is recommended for the drug product when stored at 20 - 25°C based on the 12-month long-term and 6-month accelerated stability data obtained from 3 registration batches of the drug product.

The applicant has referenced drug substance information to DMF (b) (4) (for betamethasone dipropionate) and DMF 10514 (for calcipotriol (b) (4)). The proposed specifications for both active ingredients were provided in the NDA. Both DMFs are found to be adequate and support applroval (review by Debasis Ghosh, Ph.D.; Branch II, Division of New Drug API/ONDP; dated August 4, 2015)

The Quality Review Team concluded that the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product. The reader is referred to the comprehensive reviews by Yichun Sun, Ph.D and Sarah Ibrahim Ph.D.; Branch V/Division of New Drug Products II/ONDP; (dated September 1, 2015)

The Office of Process and Facilities (in OPQ) provided an overall acceptable recommendation for all facilities for the drug substance and drug product.

4. Nonclinical Pharmacology/Toxicology

A battery of nonclinical studies, which adequately qualifies topical use of calcipotriene and betamethasone dipropionate, has been reviewed in association with NDA 21852 and NDA 22185. 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. This NDA includes letters from LEO Pharma A/S that authorize reference to data associated with NDA 21852 and IND 62993 (Taclonex Ointment), and NDA 22185 and IND 67,835 (Taclonex Topical Suspension). The reader is referred to CDER nonclinical reviews of the NDA 21852 and NDA 22185 as well as IND 114063 for summary and interpretation of the nonclinical data.

In addition, the applicant conducted a study No. 72281("4-Week local tolerance study in minipigs, calcipotriene and betamethasone in spray and ointment formulation") to assess Enstilar® Foam (LEO 90100) for potential to induce dermal irritation when topically applied to the skin of minipigs. 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. Based on the results from this study it was concluded that Enstilar® Foam applied to minipig skin was well tolerated.

The formulation of the Enstilar® Foam is the (b) (4) for Taclonex® Ointment with additional two propellants; butane and dimethyl ether (DME). 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 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. DME is highly volatile, and is expected to rapidly dissipate in a typical home environment. Per Pharmacology/Toxicology reviewer:
"…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."
The other excipients of Enstilar® Foam, including polyoxyproylene-11-stearyl ether, α-tocopherol, mineral oil, and white petrolatum, have all been adequately qualified (see nonclinical reviews of NDA 21852 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 21852 and S-017 to NDA 22185).

Pharmacology/Toxicology Team Labeling Recommendations:

"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.

> **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/m2/day); a dosage of 36 mcg/kg/day (432 mcg/m2/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/m2/day) resulted in a significantly increased incidence of skeletal abnormalities (enlarged fontanelles and extra ribs). The enlarged fontanelles (b) (4) most likely due to the effect of calcipotriene upon calcium metabolism. The estimated maternal and fetal noadverse effect levels (NOAEL) in the rat (108 mcg/m2/day) and rabbit (48 mcg/m2/day) derived from oral studies are lower than the estimated maximum topical dose of calcipotriene in man (460 mcg/m2/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/m2/day) and 2.5 mcg/kg/day (30 mcg/m2/day), respectively. Those dose levels are lower than the estimated maximum topical dose in man (about 5,950 mcg/m2/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."

12.1 Mechanism of Action

Enstilar® Foam combines the pharmacological effects of calcipotriene hydrate as a synthetic vitamin D3 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."

The Pharmacology/Toxicology reviewer, Norman A See, Ph.D., recommended *Approval* of this application pending agreements on the recommended labeling changes (Review dated July07, 2015).

5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted one clinical pharmacology trial; a maximal use pharmacokinetic (PK) trial to assessed PK of LEO 90100 Foam, and effect of LEO 90100 Foam on calcium metabolism and hypothalamic- pituitary- adrenal (HPA) axis (LEO90100-30). In addition, the applicant conducted a vasoconstriction trial (LP0053-69).

Maximal use PK trial (LEO90100-30)

This trial was a multi-center, open, single-group, 4-week trial in 37 adult subjects with moderate to severe plaque psoriasis on the trunk, limbs and scalp. The subjects applied the study drug to all affected areas once daily (excluding skin folds, face and genitals) for 28 days with a maximum weekly application of 120g.

In this study, the mean % body surface area (BSA) involvement was 17.5% and median was 16% (range 12-28%); the mean scalp involvement was 50.2% and the median was 40% (range 30-100%). The mean total BSA treated was 20.9% and range was 16 - 30%.

The PK of parent calcipotriol (LLOQ 50 pg/mL) and betamethasone dipropionate (LLOQ 30 pg/mL) and their main metabolites [MC1080 (LLOQ 20 pg/mL) and betamethasone 17-propionate (LLOQ 30 pg/mL), respectively] was assessed. Plasma samples were obtained at baseline (before treatment), pre-dose at Day 14 and Day 28, and post-dose serial samples were obtained on Day 28 at 1, 2, 3, 5 and 7 hours. PK samples from 2 subjects that were discontinued (Subject 1023 and Subject 1028) were only collected at baseline and at Day 14. Therefore, these 2 subjects were excluded from PK analysis and 35 subjects were eligible for PK evaluation.

The results indicated that plasma concentrations were below LLOQ for betamethasone dipropionate, calcipotriol and MC1080 in most subjects and PK parameters C_{max} and AUC_{last} could be reliably determined only in few subjects. For calcipotriol only 1 subject had quantifiable plasma levels and no PK parameters could be reliably determined. For metabolite betamethasone 17-propionate PK parameters were quantifiable in 27 out of 35 subjects and the mean ± SD C_{trough} concentrations on Day 14 (n = 16) and Day 28 (n = 14) were 36.95 ± 50.29

pg/mL (Range BLQ - 204 pg/mL) and 28.01 ± 44.65 pg/mL (Range BLQ - 190 pg/mL), respectively indicating steady state was achieved.

Effect on Hypothalamic-Pituitary-Adrenal (HPA) axis:
In the maximal use PK trial, approximately 3 to 7 days before Visit 1 (Day 0), baseline Adrenocorticotrophic Hormone (ACTH)-challenge test and the albumin-corrected serum calcium tests were conducted. The subjects were advised to maintain the intake of calcium-rich nutrients (number of servings). Post treatment ACTH-challenge test was performed at Day 28.

On Day 28 (last day of treatment), the CORTROSYN injection was administered after the pre-dose trough PK sample. The last dose of LEO 90100 Foam was applied at the clinic following the 30 and 60 minute blood samples for ACTH challenge test. The primary response criterion for evaluation of HPA axis function was percentage of subjects with serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test. None of the 35 subjects who completed 28 days of treatment as per protocol had a serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test at Day 28. The applicant also evaluated the effect on serum cortisol concentrations at 30 minutes after ACTH-challenge at Day 28 versus average weekly use of study drug. Per clinical pharmacology reviewer, there appears to be a trend of decreasing cortisol levels 30 minutes post ACTH stimulation with increasing amount of the drug applied.

Effect on calcium metabolism
The effect of LEO 90100 on calcium metabolism was evaluated based on change from baseline to Day 28 in the following parameters:

- Albumin-corrected serum calcium, 24-hour urinary calcium excretion and urinary calcium:creatinine ratio, serum phosphate, serum ALP, plasma PTH, 24-hour urinary phosphate excretion and urinary phosphate:creatinine

The mean and median values for albumin-corrected serum calcium were within the normal range (2.15 to 2.55 mmol/L) and the mean change in albumin corrected serum calcium from baseline to Day 28 was 0.014 mmol/L, which is not considered to be a clinically relevant increase. None of the subjects had elevated albumin-corrected serum calcium values above the normal range at any visit.

The mean and median values for 24-hour urinary calcium were within the normal range (2.5 to 7.5 mmol/24 h).The mean decrease from baseline to Day 28 was 0.5 mmol/24 h; this decrease was not considered to be of clinical significance.

Vasoconstriction trial (trial LP0053-69)

The Applicant conducted a multipoint VCA assessment in 35 healthy subjects with 6 hour application under non-occluded conditions. This trial evaluated relative vasoconstriction

comparing LEO90100 Foam (TEST) with reference products of different dosage forms (i.e., Dermovate Cream, Daivobet Ointment, and Synalar Ointment).

The multipoint VCA is currently an acceptable method for establishing bioequivalence (BE) for topical corticosteroids; however, this method is not acceptable when comparing different dosage forms. (b) (4) At the Pre-NDA meeting, the applicant was advised that the multipoint VCA will not be acceptable and the applicant was advised to provide results of single point VCA evaluated by visual assessment at 2 hours following 16 hours of study medication application under non-occluded conditions. (b) (4)

Therefore, the Clinical Pharmacology Team recommended Post-Marketing Commitments:

- Conduct a single point vasoconstriction assay with adequate bracketing using visual assessment to determine the topical corticosteroid potency classification for Enstilar® Foam

Clinical Pharmacology Team Labeling Recommendations:

The following changes are recommended in Sponsor's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

5.3 (b) (4)

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

(b) (4) **that** (b) (4) **HPA axis suppression** (b) (4) (b) (4)

(b) (4)

(b) (4) systemic absorption, (b) (4) of topical corticosteroids (b) (4) (b) (4) HPA axis suppression. Factors that predispose a patient (b) (4) topical corticosteroid to HPA axis suppression include the use of more potent steroids, (b) (4) large surface areas, (b) (4) prolonged (b) (4) use (b) (4) (b) (4) altered skin barrier, (b) (4) liver failure.

(b) (4) ACTH stimulation (b) (4)

If HPA axis suppression is documented, (b) (4) withdraw the drug, reduce the frequency of application, or substitute with a less potent (b) (4) (b) (4) systemic corticosteroids. (b) (4)

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. [*See Use in Specific Populations (8.3)*]

8.4 Pediatric Use

Safety and effectiveness of the use of Enstilar® Foam in pediatric patients have not been studied. Because of a higher ratio of skin surface area to body mass, children ~~under the age of 12 years~~ are at particular risk of systemic adverse effects when they are treated with topical corticosteroids. [*See Warnings and Precautions (5.3, 5.4)*]

12 CLINICAL PHARMACOLOGY

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.**

(b) (4)

(b) (4)

12.2 Pharmacodynamics

(b) (4)

(b) (4)

(b) (4)

(b) (4), effects of once daily application of Enstilar® Foam for 4 weeks on calcium metabolism in adult subjects (N=564) with plaque psoriasis were examined in three randomized, multicenter, prospective vehicle- and/or active-controlled clinical trials (b) (4) (b) (4) Following once daily application of Enstilar® Foam, elevated serum calcium levels outside the normal range were observed in 3 subjects. Elevated urinary calcium levels outside the normal range were observed in 17 subjects.

12.3 Pharmacokinetics
Absorption

The **pharmacokinetics (PK)** (b) (4) of Enstilar® Foam (b) (4) was investigated in (b) (4) **Plasma concentrations** (b) (4) of calcipotriene and betamethasone dipropionate and their main metabolites were measured after 4 weeks of once daily application of Enstilar® Foam (b) (4) (b) (4) Calcipotriene was quantifiable in 1 of 35 (2.9%) subjects and its main metabolite, MC1080, in 3 of 35 (8.6%) subjects. **For subjects with measurable concentrations, t**~~T~~he maximal plasma concentrations (C_{max}) **and area under the concentration curve until the last measured time point (AUC_{last})** (b) (4) **for** calcipotriene **were** (b) (4) 55.9 pg/mL **and 82.5 pg*h/mL, respectively;** and **the mean ± SD C_{max} and AUC_{last} for MC1080 was** (b) (4) **24.4 ± 1.9** pg/mL **and 59.3 ± 5.4 pg*h/mL**, respectively. Betamethasone dipropionate was quantifiable in 5 of 35 (14.3%) subjects and its main metabolite, betamethasone 17-propionate (B17P), was quantifiable in 27 of 35 (77.1%) subjects. The **mean ± SD C_{max} and AUC_{last} for** (b) (4) betamethasone dipropionate **were 52.2 ± 19.7 pg/mL and 36.5 ± 27.4 pg*h/mL, respectively** and **for** B17P were **147.9 ± 224.0** (b) (4) pg/mL and **683.6 ± 910.6 pg*h/mL** (b) (4) respectively. The clinical significance of these findings is unknown.

Metabolism

Calcipotriene:
Calcipotriene metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriene are less potent than the parent compound.

Calcipotriene is metabolized to MC1046 (the α,ß-unsaturated ketone analog of calcipotriene),which is metabolized further to MC1080 (a saturated ketone analog). MC1080 is the main metabolite in plasma. MC1080 is slowly metabolized to calcitroic acid.

Betamethasone dipropionate:

Betamethasone dipropionate is metabolized to betamethasone 17-propionate (B17P) and betamethasone, including the 6ß-hydroxy derivatives of those compounds by hydrolysis. B17P is the (b) (4) **primary** metabolite.

The reader is referred to the comprehensive review by, Chinmay Shukla Ph.D. for a full discussion of the clinical pharmacology data (Review dated August 24, 2015).

The clinical pharmacology reviewer, Chinmay Shukla, PhD., recommended *Approval* of this application pending agreements on the recommended labeling changes.

Post-Marketing Commitments:

- Conduct a single point vasoconstriction assay with adequate bracketing using visual assessment to determine the topical corticosteroid potency classification for Enstilar® Foam

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from single Phase 3 trial (LP0053 -1001) and two Phase 2 trials (LEO 90100-7 and LEO 90100-35) to establish the safety and effectiveness of their product applied once daily for up to 4 weeks in the treatment of plaque psoriasis in patients 18 years of age and older. The applicant designated trials LP0053 -1001 and LEO 90100-7 as pivotal/confirmatory trials and LEO 90100-35 as a supportive trial. Trial LEO 90100-7 compared Enstilar® Foam to the two monads (no vehicle arm) and trial LP0053 -1001 compared Enstilar® Foam to Vehicle Foam (no monad arms). Trial LEO 90100-35 compared Enstilar® Foam to Taclonex® Ointment, Vehicle Foam and Vehicle Ointment. The inclusion and exclusion criteria were similar among the trials [subjects must have had an IGA score of at least mild, with 2-30% body surface area (BSA) involvement at baseline]. However, it should be noted that although there was a requirement for 2-30% BSA (trunk and limbs) in trials LP0053 -1001, LEO 90100-35, and LEO 90100-7, for trial LEO 90100-7 there was also a requirement for at least 10% scalp involvement.

Trial LP0053 -1001 (Study 1001) was multicenter (27 sites in the U.S.) randomized, double-blind, 2-arm, vehicle-controlled, parallel-group Phase 3 trial. The population enrolled was subjects 18 years of age and older with plaque psoriasis of the body (trunk and/or limbs; excluding face, axillae and groin), a sore of at least mild (2) on the Investigator's Global Assessment (IGA) scale, a modified Psoriasis Area and Severity Index (m-PASI) sore ≥ 2 and

2-30% total BSA involvement. Eligible subjects were randomized in a 3:1 ratio to either Enstilar® Foam or Vehicle Foam. The randomization was stratified by center. Subjects applied study product once daily for 4 weeks. Subjects were evaluated at baseline and Weeks 1, 2, and 4.

Trial LEO 90100-7 (Study 7) was a multicenter (28 sites in U.S.), double-blind, randomized, parallel-group, active-controlled, Phase 2 trial. The population enrolled was subjects 18 years of age and older with plaque psoriasis on the body (trunk and/or limbs) with 2-30% BSA involvement, plaque psoriasis on the scalp with at least 10% of the total scalp area involvement, a m-PASI score ≥ 2 and an IGA score of at least mild for both scalp and body. Eligible subjects were randomized in a 1:1:1 ratio to one of the following treatment arms: Enstilar® Foam, Betamethasone Dipropionate (BDP) in vehicle foam, and Calcipotriene in vehicle foam. The randomization was stratified by baseline disease severity (IGA=2 or IGA≥3). Subjects applied study product once daily for 4 weeks. Subjects were evaluated at baseline and Weeks 1, 2, and 4.

Study 1001 enrolled and randomized a total of 426 subjects (323 to Enstilar® Foam and 103 to Vehicle Foam) and Study 7 enrolled and randomized a total of 302 subjects (100 to Enstilar® Foam, 101 to BDP monad, and 101 to Calcipotriene monad). For Study 1001, the mean age was 51 years in the Enstilar® arm and 46 years in the Vehicle arm. For Study 7, the mean age was 47 years in the Enstilar® arm, 49 years in the BDP arm and 51 years in the Calcipotriene arm. The majority of the subjects were White (> 82%) in both studies. For Study 1001, there were a higher proportion of male subjects in the Enstilar® arm compared to the Vehicle arm (i.e., 63% vs. 48%). The majority of the subjects enrolled in the Study 1001 and Study 7 were classified as having an IGA score of 3 (Moderate) with mean percent BSA involvement from 6.7 to 8%.

The protocol-specified primary efficacy endpoint in both studies was the proportion of subjects with "treatment success" on the trunk and limbs at Week 4. Treatment success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

In Study 1001, Enstilar® Foam was statistically superior to Vehicle Foam ($p < 0.001$). The response rate for Enstilar® Foam was lower in Study 7 compared to Study 1001 (i.e., 45% vs. 53%). In Study 7, Enstilar® Foam was statistically superior to both the BDP monad ($p = 0.047$) and the Calcipotriene monad ($p < 0.001$). Table 2 presents results for the primary efficacy endpoint at Week 4 for both studies in the intent-to-treat (ITT) population.

Table 2: Primary Efficacy Results at Week 4 (ITT, LOCF [1], MI [2]

	Enstilar® Foam	Betamethasone dipropionate in Vehicle Foam	Calcipotriene in Vehicle Foam	Vehicle Foam
Study 7	(N=100)	(N=101)	(N=101)	-
Treatment Success[3] Rate	45 (45.0%)	31 (30.7%)	15 (14.9%)	-
P-value[4]	-	0.047	<0.001	-
Study 1001	(N=323)	-	-	(N=103)
Treatment Success[3] Rate[5]	172.1 (53.3%)	-	-	4.9 (4.8%)
P-value[4]	-	-	-	<0.001

(1) Missing data for Study 7 was imputed using last observation arr
(2) Missing data for Study 1001 was imputed using multiple imputat
(3) Treatment success is defined as an IGA score of 0 or 1 with at le
(4) P-value based on a CMH test stratified by pooled centers.
(5) Rates displayed are the averages over the 1000 imputed datasets.
Source: Statistical Review by Matthew Guerra, Ph.D. (Table 7, page 11)

In both trials, the response rate for the Enstilar® Foam was generally consistent across the age, gender and race subgroups. In addition, the response rate for the Enstilar® Foam arm was consistently higher than the other treatment arms across these subgroups in both trials. For Study 7, the response rate for the Enstilar® Foam arm was lower than the BDP arm in subjects with a baseline IGA score of 4 (severe); however, a small proportion of subjects (10%) had a baseline IGA score of 4.

Primary Efficacy Results at Week 4 by Age, Gender, Race and Baseline Disease Severity for Study 1001 (ITT, MI[1]) and Study 7 are provided in the Tables (3&4) below:

Table 3: Primary Efficacy Results at Week 4 by Age, Gender, Race and Baseline Disease Severity for Study 1001 (ITT, MI[1])

Subgroup (N_E, N_V)	Enstilar® Foam (N=323)	Vehicle Foam (N=103)
Age		
< 65 (260, 93)	52.5%	5.3%
≥ 65 (63, 10)	56.5%	0%
Gender		
Male (204, 49)	56.8%	5.9%
Female (119, 54)	47.3%	3.7%
Race		
White (276, 90)	53.8%	4.3%
Non-White (47, 13)	50.0%	7.7%
IGA		
2 – Mild (50, 15)	30.2%	0.2%
3 – Moderate (244, 75)	59.8%	5.2%
4 – Severe (29, 13)	37.9%	7.7%

(1) Missing data for Study 1001 was imputed using multiple imputation (MI).

(2) Rates displayed are the averages over the 1000 imputed datasets.
Source: Statistical Review by Matthew Guerra, Ph.D. (Table 16, page 15)

Table 4: Primary Efficacy Results at Week 4 by Age, Gender, Race and Baseline Disease Severity for Study 7 (ITT, LOCF[1])

Subgroup (NE, NBDP, NC)	Enstilar® Foam (N=100)	BDP in Vehicle (N=101)	Calcipotriene in Vehicle (N=101)
Age			
< 65 (88, 88, 81)	44.3%	28.4%	13.6%
≥ 65 (12, 13, 20)	50.0%	46.2%	20.0%
Gender			
Male (53, 56, 61)	43.4%	28.6%	18.0%
Female (47, 45, 40)	46.8%	33.3%	10.0%
Race			
White (93, 83, 92)	45.2%	30.1%	14.1%
Non-White (7, 18, 9)	42.9%	33.3%	22.2%
IGA			
2 – Mild (11, 16, 14)	45.5%	18.8%	0%
3 – Moderate (77, 75, 78)	49.4%	32.0%	19.2%
4 – Severe (12, 10, 9)	16.7%	40.0%	0%

(1) Missing data for Study 7 was imputed using last observation carried forward (LOCF).
Source: Statistical Review by Matthew Guerra, Ph.D. (Table 15, page 15)

The protocol-specified secondary efficacy endpoints were different between the two studies. The protocol for Study 7 specified one secondary endpoint, i.e., the proportion of subject with treatment success on the trunk and limbs at Week 1. For Study 1001, the protocol specified two secondary endpoints: m-PASI at Week 1 and m-PASI at Week 4. Since the secondary endpoints were different and the applicant is not seeking labeling claims for any of the secondary endpoints, this review will not present the results of the secondary endpoints.

Phase 2 trial, LEO 90100-35 (Study 35), was a supportive trial. It was a randomized, multicenter (35 centers in the U.S.), investigator-blind, parallel-group, active and vehicle controlled, 4-week trial in subjects with mild to severe plaque psoriasis. Eligible subjects were randomized to one of the following treatment arms in a 3:3:1:1 ratio: Enstilar® Foam, Taclonex® Ointment, Vehicle Foam, and Vehicle Ointment. A total of 376 subjects were enrolled and randomized (141 to Enstilar® Foam, 135 to Taclonex® Ointment, 49 to Vehicle Foam, and 51 to Vehicle Ointment). The randomization was stratified by baseline disease severity (IGA=2 or IGA≥3). Subjects were evaluated at baseline (Week 0) and Weeks 1, 2, and 4. The results for the primary efficacy endpoint at Week 4 are presented in Table 5 below. Enstilar® Foam was statistically superior (p = 0.025) to Taclonex® Ointment. It should be noted that the comparison between Enstilar® Foam and Vehicle Foam was not pre-specified in the

protocol and therefore is a post-hoc analysis. The results for Study 35 are supportive of those observed in Studies 1001 and 7.

Table 5: Primary Efficacy Results at Week 4 for Study 35 (ITT, LOCF(1))

	Enstilar® Foam (N=141)	Taclonex® Ointment (N=135)	Vehicle Foam (N=49)	Vehicle Ointment (N=51)
Treatment Success(2) Rate P-value(3)	77 (54.6%) -	58 (43.0%) 0.025	3 (6.1%) <0.001	4 (7.8%) -

(1) Missing data was imputed using last observation carried forward (LOCF).
(2) Treatment success is defined as an IGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(3) P-value based on a CMH test stratified by pooled centers.
Source: Statistical Review by Matthew Guerra, Ph.D. (Table A1, page 19)

In summary, based on the data from two trials (Study 1001 and Study 7) the applicant has established the efficacy of their product in the treatment of plaque psoriasis of the body in the subjects 18 years of age and older.

The reader is referred to the comprehensive statistical review and evaluation by Matthew Guerra, Ph.D. (Division of Biostatistics III) for a more complete discussion of the efficacy results (dated September 2, 2015).

8. Safety

The applicant submitted data from the clinical trials presented in Table 6 below:

Table 6: Source of Clinical Data: Clinical trials

Protocol #	Type of trial	Trial Design	Subject Population / # of sites	Test products/dosage regimen	Subjects in group: randomized/completed	Diagnosis/ treatment duration
LP0053-1001	Safety and efficacy	Phase 3 multi-center, double-blinded, vehicle controlled, 2-arm, randomized, parallel group	Age 18 and older 27 US	1. Enstilar® foam 2. Foam vehicle Once daily	323/313 103/99 Total: 426/412	Psoriasis vulgaris on body Up to 4 weeks

Protocol #	Type of trial	Trial Design	Subject Population / # of sites	Test products/dosage regimen	Subjects in group: randomized/completed	Diagnosis/ treatment duration
LEO 90100-35	Safety and efficacy	Phase 2, multi-center, investigator blinded, active and vehicle controlled, 4-arm, randomized, parallel group	Age 18 and older 35 US	1. Enstilar® foam 2. Taclonex ointment 3. Foam vehicle 4. Ointment vehicle Once daily	141/136 135/127 49/47 51/48 Total: 376/358	Psoriasis vulgaris on body Up to 4 weeks
LEO 90100-7	Safety and efficacy	Phase 2, multi-center, double-blinded, 3- arm, active controlled randomized, parallel group	Age 18 and older 28 US	1. Enstilar® 2. Betamethasone 3. Calcipotriol * Once daily	100/94 101/94 101/93 Total:302/281	Psoriasis vulgaris on body and scalp Up to 4 weeks
LEO 901100-30	MUSE	Open label, non-controlled HPA axis test, Ca++ metabolism, PK	Age 18 and older 8 Canada	Enstilar Once daily	37 exposed 35 completed	Extensive psoriasis vulgaris, trunk, limbs, scalp Up to 4 weeks
LP0053-69	Vasoconstriction	Randomized, investigator-blinded, single-dose, intra-individual comparison	Age 18 to 50 1 France	1. Enstilar 2.Dermoval/Dermovate cream 3. Taclonex ointment 4. Synalar ointment 5. BDP in Enstilar vehicle 6. Enstilar foam vehicle	35/35	Healthy subjects Single dose
LP0053-66	Dermal safety trial	Randomized, double-blind, intra-individual comparison	Age 18 to 65 1 France	1. Enstilar 2. Enstilar Foam vehicle 3. white petrolatum	218/214	Healthy subjects 16 applications
LEO 90100-01	Psoriasis plaque test	Randomized, Investigator blinded, Active & Vehicle controlled, repeat dose, intra-individual comparison	Age 18 or above 1 France	1. Enstilar 2. Taclonex ointment 3. BDP 4.Enstial foam vehicle	24/24	Psoriasis vulgaris on body 4 weeks

*It is noted that calcipotriol is identical to calcipotriene. Calcipotriol is the International Non-proprietary Name and calcipotriene is the US Adopted Name (USAN).

Source: Applicant's NDA, from Module 5, 5.2, adapted from Tabular Listing of All Clinical Studies

The safety database is adequate. The trials in the pooled safety database (LP0053-1001, LEO 90100-7 and LEO 90100-35) were randomized, multicenter, prospective vehicle and/or active controlled clinical trials in subjects with plaque psoriasis on the body (and scalp also for trial LEO 90100-7). Subjects were to have applied study product to the affected areas (trunk and/or limbs; excluding face, axillae and groin) once daily for up to 4 weeks. Safety was assessed by Vital signs, laboratory evaluation and local safety and tolerability assessment. Subjects were evaluated at Baseline, Week, 1, 2 and 4.

The pooled safety database includes 1,099 subjects exposed to study drugs; Enstilar® Foam (564), BPD Foam (99), Calcipotriene Foam (99), Vehicle Foam (152), Taclonex® Ointment (134), and Ointment Vehicle (51). The distribution of age groups was similar for the treatment groups. Subject ages ranged from 18 to 88 years and the mean age for those exposed to Enstilar® Foam was 50.5 years. All treatment groups had a mildly higher proportion of male subjects (range 52 to 65%) as compared with female subjects. The majority of the subjects were White in all treatment groups (range 81.8% to 91.9%). The subjects were instructed not to use more than 90 grams of the study product per week. For subject treated with Enstilar® Foam, the median weekly dose was 24.8 grams.

There were no deaths reported during the development program. In the pooled safety studies, a total of 6 non-fatal serious adverse events (SAEs) were reported in 5 subjects; Enstilar® Foam (3 SAEs/3 subjects 0.5%) and Taclonex® Ointment (3 SAEs/2 subjects 1.5%). In the Enstilar® Foam group SAEs were hypersensitivity/urticaria, bipolar disorder, and substance-induced psychotic disorder. Hypersensitivity/urticaria was considered possibly related to treatment with Enstilar® Foam and led to subject withdrawal from the trial. The other 2 SAEs were considered not related to treatment with Enstilar® Foam. One of them (substance induced psychotic disorder) led to discontinuation of treatment with study drug. In the Taclonex® Ointment group the SAEs were bronchitis, hypertension, and bile duct stone. Two of them (bronchitis and hypertension) were experienced by the same subject. All three SAE are unlikely to be related to study product.

In the Enstilar® Foam group, 3 of 564 subjects (0.5%) had AEs that were reported as a reason for permanent discontinuation of treatment with study product. The events were hypersensitivity/urticaria, substance-induced psychotic disorder, and irregular menstruation. Each event was reported for one (0.2%) subject. Only hypersensitivity/urticaria was assessed as possibly related to study product. In the Calcipotriene group, 3 of 99 subjects (3%) had AEs that were recorded as a reason for permanent discontinuation of treatment with study product. The events were medication residue (e.g. greasy hair) (2 AEs) and contact dermatitis (1 AE). These AE were assessed as probably related to study product. In the Taclonex® Ointment group, 1 of 134 subjects (0.7%) had AEs that were recorded as a reason for permanent discontinuation of treatment with study product. The events, reported by one subject, were dizziness, dyspnea, increased heart rate, and swelling of face. The events were assessed as not related to study product.

In the pooled safety trials a total of 8 severe AEs were reported. These included 6 AE in 6 subjects (6/78 or 8% of subjects having adverse events) in the Enstilar® Foam group and 2 AEs in one subject (1/14 or 7% of subjects having adverse events) in the Taclonex ® Ointment group. The severe AEs for the Enstilar® Foam group include the following: cellulitis (in arm) possibly related to venipuncture, substance-induced psychotic disorder, bipolar disorder, peripheral edema (right hand swelling), psoriasis 'flare', and hypersensitivity/urticaria. Of the 6 AEs, the latter two are considered to be possibly related to study medication and are included in proposed labeling as 'worsening psoriasis' and 'urticaria.' The severe events reported for Taclonex® Ointment included hypertension and bronchitis, not considered to be related to study drug.

In the pooled safety studies, at least one AE was reported by 78 (13.8%) of subjects in the Enstilar® Foam group, 13 (13.1%) in the BDP group, 10 (10.1%) in the Calcipotriene group, 14 (10.4%), in the Taclonex® Ointment group, 13 (8.6%) in the Vehicle Foam group, and 2 (3.9%) in the Vehicle Ointment group. For the pooled safety trials, in those exposed to Enstilar® Foam, the most common adverse event was nasopharyngitis, reported for 6 (1.1%) subjects.

Adverse drug reactions were not seen in 1% or greater of subjects for any investigational drug product; Enstilar® Foam, BDP foam, Calcipotriene Foam, Vehicle Foam, Taclonex Ointment, or Vehicle Ointment. In the pool of controlled trials, for Enstilar® Foam, adverse drug reactions occurring at a rate greater than in Vehicle Foam included; application site pruritus (0.4%), application site irritation (0.2%), skin irritation (0.2%), folliculitis (0.2%), application site discoloration (0.2%), hypercalcemia (0.2%), urticaria (0.2%), and exacerbation of psoriasis (0.2%).

The results of an additional analysis of pooled safety data from the two vehicle controlled trials (LP0053-1001 and LEO 90100-35) were supportive of findings from the pool of 3 trials (LP0053-1001, LEO 90100-35 and LEO 90100-7). In the pooled vehicle controlled trials, 464 subjects were exposed to Enstilar® Foam and 152 to Vehicle Foam. For Enstilar® Foam, adverse drug reactions occurring at a rate greater than in Vehicle Foam included; application site pruritus (0.4), application site irritation (0.2%), skin irritation (0.2%), folliculitis (0.2), application site discoloration (0.2%), hypercalcemia (0.2%), and application site reaction (0.2%).

Of subjects exposed to Enstilar® Foam 97 were aged 65 and older and 21 were aged 75 and older. Clinically significant differences in safety of Enstilar® Foam between subjects in these age ranges versus younger subjects were not seen.

Special safety concern

HPA axis suppression and effects on calcium metabolism are special safety concerns with this combination drug product.

In the trial LEO 901100-30, the maximal use PK trial, the applicant assessed hypothalamic pituitary axis (HPA) suppression and effect on calcium metabolism in adult subjects with moderate to severe plaque psoriasis (with a mean body surface area involvement of 17.5% and mean scalp involvement of 50.2%) following once daily Enstilar® Foam application for 28 days. The mean ± SD weekly amount of formulation used was 61.8 ± 27.7 grams. The primary response criterion for evaluation of HPA axis function was percentage of subjects with serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test at Day 28. None of the 35 subjects who completed 28 days of treatment as per protocol had a serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test at Day 28.

There was no significant mean change from baseline to Day 28 in albumin-corrected serum calcium, 24-hour urinary calcium excretion or the urinary calcium:creatinine ratio. No subjects developed elevated serum or urinary calcium levels above the normal range following treatment with Enstilar® Foam. There was no clinically relevant mean change in the other serum and urinary parameters assessed in the study for the evaluation of calcium metabolism including serum phosphate, serum ALP, plasma PTH, 24-hour urinary phosphate excretion and urinary phosphate:creatinine ratio.

No SAEs, discontinuation of investigational product due to AEs or other significant AEs were reported in this trial.

The reader is referred to the Section 5 (Clinical Pharmacology) of this review and to the reviews by Chinmay Shukla, Ph.D. and Patricia C Brown, MD, for full discussion.

Dermal Safety Study:

A dermal safety study was performed in support of this application, evaluating the potential of Enstilar® Foam and the Vehicle Foam for skin irritation and sensitization in healthy subjects. Under the conditions of the study, Enstilar® Foam showed no potential for sensitization and repeated applications revealed limited potential for irritancy. The applicant received a waiver from conduct of phototoxicity and photoallergy studies on the basis that, apart from propellants, no new excipients have been added to Enstilar® Foam as compared to Taclonex® Ointment and the UV/VIS spectra obtained for Taclonex® Ointment and Enstilar® Foam before and after evaporation of the propellants are very similar. The phototoxic and photoallergenic potential of Taclonex® Ointment, which absorbs light in the 290-700 nm range, has been evaluated in healthy volunteers (trial MCB 0101 FR and trial MCB 0204 FR, respectively). No phototoxic or photoallergic reactions were observed. One SAE (rectal hemorrhage) was reported after application of Enstilar® Foam. The event was assessed by the investigator as not related to treatment, and led to withdrawal from the trial.

Long Term Safety Assessment:

The applicant did not conduct any long term studies with Enstilar® Foam for the proposed indication, treatment of plaque psoriasis in patients 18 years of age and older. Instead, the applicant provided data from the following studies to establish the "clinical bridge" for the

long term safety of the two approved products, Taclonex® Ointment and Taclonex® Topical Suspension:

- Direct comparison of safety data for LEO 90100 and Taclonex ® Ointment from Phase 2 trial LEO 90100-35
- Comparative vasoconstriction data (LP0053-69)
- Systemic exposure data from the Maximum Use Systemic Exposure trial (LEO 90100-30) compared with historical data from similar trials with Taclonex® Ointment (MCB 0201 FR and MBL 0404 FR) and Taclonex® Topical Suspension (LEO 80185-G24).
- Adverse event data from short term trials with LEO 90100 (LP0053-1001, LEO 90100-7, and LEO 90100-35), Taclonex® Ointment (MCB 0003 INT, MCB 0002 INT, MCB 0001 INT, MCB 0201 FR, and MCB 9905 INT) and Taclonex® Topical Suspension (LEO 80185-G23, MBL 0202 INT, and LEO 80185-G21)
- Comparative safety data from long-term clinical trials with Taclonex® Ointment (MCB 0102 INT) and Taclonex® Topical Suspension (MBL 0502 US and MBL 0407 INT)

Based on data provided, clinical reviewer, Dr. Patricia C. Brown, conclude that that a long term study with Enstilar® Foam is unlikely to yield any new safety information.

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

The reader is referred to the clinical review by Dr. Patricia C. Brown, MD for discussion of the safety database (dated September 16, 2015).

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

9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary or held.

10. Pediatrics

In the support of current submission, the applicant conducted a Phase 3 and two Phase 2 clinical trials in subjects 18 years of age and older with plaque psoriasis. The applicant submitted an initial Pediatric Study Plan (iPSP) on June 26, 2013. Agreement to the initial Agreed iPSP was achieved on December 3, 2013. The applicant requested a partial pediatric waiver for children 0 to 11years 11 months because the product would be unsafe in this age group (b) (4) The applicant requested a deferral for pediatric patients aged 12 to (b) (4) years.

Establishment of the safety of Enstilar® Foam, for the treatment of pediatric subjects 12-(b) (4) years with plaque psoriasis of the body would require an understanding of the systemic exposure and systemic safety of that exposure. Safety evaluation would include evaluation of the effect of Enstilar® Foam on calcium metabolism in all subjects in the trial, and the hypothalamic-pituitary axis and pharmacokinetics of the two drug components, calcipotriene and betamethasone, in a subset subjects treated with Enstilar® Foam under maximal use conditions.

The application was presented to the Pediatric Review Committee (PeRC) on September 2, 2015. The PeRC agreed with the planned partial waiver and deferral for patients aged 12 to (b) (4) years.

11. Other Relevant Regulatory Issues

Department of Scientific Investigations (DSI) inspections were requested for a two sites (Trial LP0053-1001) with the following rationales:

- Site US15: Jane Lee MD, in Edison, New Jersey
  The applicant admitted that an efficacy assessment (m-PASI) was not conducted according to the protocol. The site also had a fairly high number of subjects, 26.
- Site US26: Stephen Tyring MD, in Houston, Texas
  The site had many protocol deviations with all of them for subjects treated with Enstilar® Foam. In addition, the response rate to Enstilar® Foam was, on average, the lowest of all the clinical sites.

Inspection results: (DSI Clinical Inspection Summary, dated August 28, 2015)

Site US15: Jane Lee, MD

> "The final classification of Dr. Lee's inspection was Voluntary Action Indicated (VAI). Because of Dr. Lee's failure to properly conduct assessments of psoriatic area involvement according to protocol specifications for use in calculation of subject's' m-PASI scores, the review division should consider excluding this site's m-PASI study data from the efficacy analysis. Notwithstanding an isolated failure to obtain a safety laboratory assessment for a single subject, the clinical investigator's assessment of safety appeared to be otherwise adequate and safety data as reported appears to be reliable."

Site US26: Stephen Tyring, MD

> "The final classification of Dr. Tyring's inspection was Voluntary Action Indicated (VAI) resulting from two instances of inadequate records and one protocol deviation. Other than these isolated observations, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication."

Per statistical review:

> "The Agency conducted an inspection of this center to verify the above protocol violations and to determine whether other assessments (e.g., IGA) were done according to the protocol. The Agency determined that the investigator at this center did not properly assess the extent of psoriatic involvement of the arms, trunk, and legs for the calculation of m-PASI. While the Agency was able to confirm that the IGA assessments were done according to protocol, this reviewer conducted a sensitivity analysis where all subjects from this center were removed. Table 2 presents the primary efficacy results at Week 4 with and without center #15. The treatment success rates are very similar with and without center #15, and the center did not affect the overall conclusion."

The reader is referred to the comprehensive statistical review by Matthew Guerra, Ph.D. (dated September 02, 2015).

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding their content are ongoing at the time of close of this review.

Significant changes incorporated into revised draft labeling, following labeling review, include:

2	DOSAGE AND ADMINISTRATION
5	WARNINGS AND PRECAUTIONS
6	ADVERSE REACTIONS
12	CLINICAL PHARMACOLOGY
14	CLINICAL STUDIES

The non-proprietary name for the proposed drug product is calcipotriene and betamethasone dipropionate foam, 0.005%/0.064%. By letter dated May 29, 2015 the applicant requested a review of a proprietary name, Enstilar (calcipotriene and betamethasone dipropionate) Foam, 005%/0.064%. On August 12, 2015 the Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk, completed their review of the proposed proprietary name and concluded that it is conditionally acceptable pending approval of this NDA.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Approval*

- I concur with the recommendations of the multi-disciplinary review team for approval of NDA 207589, Enstilar® (calcipotriene and betamethasone

dipropionate) Foam, 0.005%/0.064% pending agreement of the applicant with the recommended labeling revisions.

Risk Benefit Assessment

- The risk-benefit assessment supports approval of this product for the treatment of plaque psoriasis

Recommendation for Postmarketing Risk Evaluation and Management Strategies

- Postmarketing risk management beyond professional labeling, prescription status and routine pharmacovigilance is not needed.

Recommendation for other Postmarketing Requirements and Commitments

- To fulfill the requirements of PREA, the applicant will need to:

  An open-label trial to assess the effect on calcium metabolism of Enstilar® Foam in 100 evaluable pediatric subjects aged 12 years to 16 years and 11 months with plaque psoriasis of the scalp and body. Pharmacokinetics (PK) of Enstilar® Foam and assessment of hypothalamic-pituitary axis (HPA) suppression will be conducted in a sub-set of 30 subjects with at least moderate plaque psoriasis under maximal use conditions.

- Postmarketing Commitment:

  Conduct vasoconstriction assay (VCA) with adequate bracketing using visual assessment to determine the topical corticosteroid potency classification for Enstilar® Foam.

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

/s/

GORDANA DIGLISIC
09/16/2015