CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207589Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	16 October 2015
From	Jill A. Lindstrom
Subject	Deputy Division Director Summary Review
NDA #	207589
Applicant	LEO Pharma A/S
Date of Submission	December 18, 2014
PDUFA Goal Date	October 18, 2014
Proprietary Name	Enstilar
Non-Proprietary Name	calcipotriene and betamethasone dipropionate
Dosage Form(s) / Strength(s)	Foam / 0.005%/0.064%
Applicant Proposed Indication(s)/Population(s)	Topical treatment of plaque psoriasis in adults 18 years of age and older
Action	*Approval*
Approved Indication	*Topical treatment of plaque psoriasis in patients 18 years of age and older*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Patricia Brown, MD
Statistical Review	Matthew Guerra, PhD
Pharmacology Toxicology Review	Norman See, PhD
OPQ Review	Debasis Ghosh, Ph.D., Sarah Ibrahim, Ph.D., Erin Kim, Ph.D., Erika Pfeiler, Ph.D., Juandria Williams, Ph.D.
Biopharmaceutics	Haritha Mandula, PhD
Clinical Pharmacology Review	Chinmay Shukla, PhD
OPDP	Tara Turner, PharmD, MPH
OSI	Roy Blay, PhD
CDTL Review	Gordana Diglisic, MD
Patient Labeling Team	Nathan Caulk, MS, BSN, RN
OSE/DMEPA	Carlos Mena-Grillasca, RPh
Administrative review and materials	Dawn Williams, BSN

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Introduction

Enstilar (calcipotriene and betamethasone dipropionate) foam, 0.005%/0.064%, is a topical [redacted] 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 psoriasis in adults. The applicant markets the same combination of calcipotriene and betamethasone dipropionate at the same strengths in ointment and suspension dosage forms. Both calcipotriene and betamethasone diproprionate are also marketed as single active ingredient products in a variety of topical dosage forms. The applicant cross-referenced their NDAs for their ointment and suspension products and owns the data on which they rely to support the safety and efficacy of their proposed foam product.

This memo summarizes the findings of the multidisciplinary review team and provides the rationale for my decision.

2. Background

Psoriasis is chronic inflammatory disease characterized by circumscribed erythematous, scaly plaques on the skin. Sites of predilection include scalp, sacrum, umbilical area, and extensor surfaces of the limbs. Involvement is typically symmetrical. As a result of the isomorphic response (Koebner's phenomenon), lesions may appear at sites of minor trauma, such as the elbows and knees. Associated comorbidities include psoriatic arthritis, other autoimmune inflammatory diseases, coronary artery disease, metabolic syndrome, obesity and depression. Topical treatment is used for patients with limited disease or for those with more widespread disease who do not want to undergo phototherapy or systemic therapy. Topical therapeutic options include corticosteroids, available in a range of potencies, strengths, and dosage forms, vitamin D analogs, tazarotene, and combination of calcipotriene and betamethasone dipropionate.

Calcipotriene is a synthetic vitamin D_3 analog and betamethasone dipropionate is a synthetic corticosteroid. Both moieties are marketed as single-active topical products in a variety of dosage forms. The applicant markets the combination, at identical strengths to the proposed product, in ointment and suspension dosage forms with the trade name Taclonex. Taclonex ointment [redacted] proposed foam product less the propellant excipients, and the [redacted] for the foam product.

The applicant participated in a preIND meeting on March 7, 2012, an EOP2 meeting (written responses), and a preNDA meeting on March 26, 2014. At both the PIND and EOP2 meetings the Agency indicated that a Phase 3 vehicle-controlled trial and a Phase 2 trial with the monads would be an acceptable approach for development of this product.

3. Product Quality

The combination product contains two drug substances: calcipotriene hydrate and betamethasone dipropionate. Their molecular formulas (and weights) are $C_{27}H_{40}O_3,H_2O$ (430.6) and $C_{28}H_{37}FO_7$ (504.6), respectively. Calcipotriene hydrate, a synthetic vitamin D_3 analogue, is a white to almost white crystalline (b) (4) Betamethasone dipropionate, a synthetic fluorinated corticosteroid, is a white to almost white crystalline powder.

The drug product, Enstilar foam, is white to off-white in color and contains 0.005% (50 mcg/gm) of calcipotriene (equivalent to 52.2 mcg calcipotriene hydrate) and and 0.064% (0.643 mg/gm) of betamethasone dipropionate (equivalent to 0.5 mg betamethasone). The composition of the drug product is described in the following table:

Ingredient	Function	Quantity/gm in container	Quantity/gm after evaporation of propellants
Calcipotriol	Active ingredient	(b) (4)	50.0 mcg
Betamethasone dipropionate	Active ingredient		0.5 mg
Polyoxypropylene-11-stearyl ether	(b) (4)		
(b) (4)			
All-rac-α-tocopherol			
(b) (4)			
Dimethyl ether			
Butane			

The drug product, which contains no water, (b) (4) of the approved product Taclonex ointment. (b) (4) DME is (b) (4) in any approved drug products, but it is used in household products and cosmetics. The other excipients, including butane, are not novel.

The drug product is packaged into a pressurized aluminum can topped with a ball valve and an actuator with a cap. The can and ball valve are (b) (4) The container closure system is (b) (4). The marketed container size is 60 grams. Stability data support an expiry of 24 months shelf life and 6 months of use.

The facility review team from the Office of Process and Facilities completed facilities inspections and issued an overall "Acceptable" recommendation.

The CMC lead reviewer, Dr. Yichun Sun, concluded that the applicant provided sufficient information to assure the identity, strength, purity and quality of the drug product, and did not recommend any postmarketing commitments.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections

were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

The applicant submitted letters of authorization to reference data in NDAs 22185 and 21852. A battery of nonclinical studies submitted to those applications adequately qualifies calcipotriene and betamethasone dipropionate for topical use as proposed in this application. A 4 week local tolerance study in minipigs, conducted with the proposed formulation, supports the drug product.

The primary toxicity observed in nonclinical studies of topical calcipotriene was perturbation of calcium metabolism, including hypercalcemia, hypercalcuria, stimulation of bone formation and mineralization of the kidney. Additionally, calcipotriene was found to be a co-carcinogen with ultraviolet light. Toxicities of betamethasone, either alone or in combination with calcipotriene, included atrophy of the adrenal glands, spleen and thymus. Neither calcipotriene nor betamethasone appear to be mutagenic. Calcipotriene was fetotoxic in rabbits; betamethasone was teratogenic in mice and rabbits. These findings are addressed in labeling.

All non-propellant excipients are qualified. The pharmacology/toxicology reviewer, Dr. See, determined that both propellants were acceptable for use in the drug product.

The pharmacology/toxicology reviewer, Dr. Norman See, recommended *Approval* of this application from a pharmacology/toxicology perspective; he did not identify the need for any nonclinical postmarketing commitments or requirements.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology

Enstilar (calcipotriene and betamethasone dipropionate) foam, 0.005%/0.064%, is a (b) (4) product for the treatment of psoriasis that is intended to be applied topically to the affected areas once daily for up to four weeks.

The to-be-marketed formulation was used in all of the clinical trials, including the maximal use pharmacokinetic and hypothalamic pituitary adrenal (HPA) axis suppression study and the pivotal trial.

The applicant conducted study LEO90100-30, a prospective, multi-center, single-group, open-label study conducted under maximal use conditions in 35 adult subjects with at least moderate psoriasis, to evaluate the effect of Enstilar foam applied once daily on HPA axis suppression and calcium metabolism, and to assess the pharmacokinetic profile of the active ingredients and major metabolites. Study drug was applied once daily to affected areas for up to four weeks. Cosyntropin stimulation testing was conducted at baseline and at four weeks after

initiation of treatment; no subject had adrenal suppression, defined as a 30-minute post-stimulation cortisol level of ≤18 mcg/dL. Serum and urine calcium was assessed at baseline and four weeks; no subjects had elevated serum or urine calcium levels at week four. Plasma concentrations of calcipotriene, betamethasone dipropionate, and their major metabolites were assessed at baseline and at week four. Calcipotriene and its main metabolite were quantified in 1 and 3 subjects (of 35), respectively. Based on subjects with measurable concentrations of calcipotriene, the maximum plasma concentration (C_{max})was 55.9 pg/mL, and the area under the concentration curve until the last measured time point (AUClast) was 82.5pg-h/mL. Betamethasone dipropionate and its main metabolite were quantifiable in 5 and 27 (of 35) subjects, respectively. Based on subjects with measurable concentrations of betamethasone dipropionate, the mean (±standard deviation) value for C_{max} was 52.2 (±19.7) ng/mL, and for AUC_{last} was 36.5 (±27.4) ng-h/mL. Only the pharmacokinetic results will be incorporated into labeling; the negative results of the HPA axis suppression testing and the normal calcium data (from this study) will not be included, as the study was not of sufficient size to rule out these risks.

A thorough QT/QT_c study was not performed. Neither calcipotriene nor betamethasone dipropionate is a new molecular entity; both active ingredients are approved in other topical products at the same concentrations used in Enstilar foam. Topical administration of the drug product results in low systemic exposure to both active moieties. Nonclinical studies and postmarketing data do not suggest a signal for prolongation of repolarization. For these reasons, a TQT study is not needed.

A multipoint vasoconstrictor assay was conducted, but was not suitable for the purpose of assessing potency classification.

The Clinical Pharmacology reviewer, Dr. Chinmay Shukla, found that the applicant met the requirements for approval from a clinical pharmacology perspective, and recommended a post-marketing requirement to assess the pharmacokinetics, HPA axis suppression potential and effect on calcium metabolism of Enstilar foam in adolescent subjects with moderate to severe psoriasis, and a post-marketing commitment to conduct a single-point vasonconstriction assay with adequate bracketing to determine the potency classification for Enstilar foam.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted data from a Phase 3 trial, LP0053-1001, which compared Enstilar foam to its vehicle, and a Phase 2 trial, LEO 90100-7, which compared Enstilar foam to each monad in vehicle foam, to establish the effectiveness of their product in the treatment of psoriasis vulgaris. Both trials were multi-center, parallel group, randomized, and double-

blind. Enrolled subjects for both trials were 18 years or older with psoriasis vulgaris with a score of at least "Mild" on the Investigator Global Assessment (IGA) scale and approximately 2-30% body surface area (BSA) involvement. The primary timepoint was at 4 weeks, and the primary efficacy endpoint was "treatment success," defined as an IGA score of 0 (clear) or 1 (almost clear) *and* a 2-grade improvement from baseline.

The results for the primary efficacy endpoint (ITT, LOCF) are presented in the following table:

	Enstilar Foam	Betamethasone dipropionate in vehicle foam	Calcipotriene in vehicle foam	Vehicle foam
LP0053-1001 Treatment success rate p-value	(N=323) 172.1 (53.3%)			(N=103) 4.9 (4.8%) <0.001
LEO 90100-7 Treatment success rate p-value	(N=100) 45 (45.0%)	(N=101) 31(30.7%) 0.047	(N=101_ 15 (14.9%) <0.001	

Source: Adapted from Statistical Review and Evaluation, NDA 207589, Matthew Guerra, PhD, archived 9/2/15, p.3.

The reader is referred to the biostatistical and clinical reviews by Matthew Guerra, PhD, and Patricia Brown, MD, respectively, for detailed review of the pivotal trials and additional analyses, including post hoc explorations of the data and sensitivity analyses.

I concur with Drs. Guerra and Brown that the clinical trial data support a determination of efficacy.

8. Safety

Five hundred and sixty-four subjects with psoriasis were exposed to Enstilar foam (at the conditions of proposed labeling, hereafter the safety population) during the development program, including 323 subjects in the pivotal trial. For these subjects, the mean duration of exposure was 4.0 weeks, and the mean weekly medication use was 30.92 grams.

No deaths were reported during the development program. Three subjects in the safety population experienced serious adverse events (SAE): substance abuse psychotic disorder, bipolar disorder, and hypersensitivity. The first two SAEs were considered to be unrelated to study drug by the investigator and the applicant. The third, hypersensitivity, was considered as possibly related; in this case the subject experienced urticaria on day 13 of study drug administration. The subject took aspirin, and the following day noted eyelid and lip edema, shortness of breath, dysphagia and tongue swelling. The subject was treated for anaphylaxis and discontinued study drug administration.

Adverse events occurred more frequently in the safety population treated with Enstilar foam (14%) than in those subjects treated with vehicle foam (9%). However, no adverse reactions

occurred at a rate greater than 1% in the safety population treated with Enstilar foam. Adverse reactions that occurred in ≤1% of subjects treated with Enstilar foam included application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, urticaria and exacerbation of psoriasis.

Disturbance of calcium homeostasis is a safety concern with calcipotriene. Elevations of serum and urine calcium were identified in three subjects treated with Enstilar foam in the safety population. No subjects in the maximum use trial developed hypercalcemia or hypercalcuria. The risk for (b) (4) is addressed in the Warnings and Precautions section of labeling.

Suppression of the HPA axis, a safety concern with betamethasone dipropionate, is discussed in section 5 of this review, and addressed in labeling.

The reader is referred to the clinical review by Dr. Patricia Brown for a full discussion of the safety database.

9. Advisory Committee Meeting

No advisory committee meeting was held, as the application did not present novel issues which merited advisory committee input. The two active ingredients in this product, calcipotriene and betamethasone diproprionate, are marketed at the same concentrations in ointment and topical suspension dosage forms.

10. Pediatrics

The applicant submitted safety and efficacy data obtained from adult subjects.

The applicant requested partial pediatric waiver for children aged 0 to 11 years because use of the product would be unsafe in this age group (b) (4) . The applicant requested a deferral of pediatric studies in adolescents aged 12 to (b) (4) years because adult studies are completed and ready for approval. The applicant proposed a single open-label safety study in 100 adolescents with plaque psoriasis of the body and scalp to assess the safety of Enstilar foam and the effect on HPA axis suppression and calcium metabolism. The application was presented to the Pediatric Review Committee (PeRC) on 2 September 2015; PeRC agreed with the applicant's request for waiver of studies in children 0 to 11 years of age and deferral of study in adolescents.

To establish the safety of Enstilar foam in adolescents, the applicant needs to conduct an additional study under maximal use conditions in subjects 12 to (b) (4) years of age with plaque psoriasis of the body and scalp to assess the pharmacokinetics of each active and the impact of the product on the HPA axis and calcium metabolism. The efficacy of Enstilar foam, however, can be extrapolated from adult data. Plaque psoriasis occurs in both children and adults, and although the disease prevalence varies with age, the pathophysiology is understood to be the

same. Additionally, there are not age-related factors that would make the disease either more or less responsive to treatment in pediatric patients. Therefore it is scientifically appropriate to extrapolate efficacy from the adult population to the adolescent population, but the safety of the product will need to be established for the pediatric age group 12 to (b) (4) years of age.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations conducted inspections at two sites. At one of the site, (US15, Dr. Janet Lee), the investigator did not properly assess the extent of body surface area involvement, which was used in calculation of the mPASI, a secondary endpoint. However it appeared that the investigator correctly used the Investigator Global Assessment scale, which was the measure for the primary endpoint. The biostatistical reviewer performed a sensitivity analysis in which the site was excluded and trial outcome was not affected.

12. Labeling

All components of labeling were reviewed.

Enstilar is indicated for the topical treatment of plaque psoriasis in patients 18 years and older, as the applicant has not yet conducted studies in a younger population.

The applicant proposed to include warnings about the risk for disturbances of calcium metabolism and HPA axis suppression. The totality of the data support inclusion of this risk information in labeling. However I disagree with inclusion of the negative laboratory results for (b) (4) and the negative results of (b) (4) from Study LEO 90100-30, an open-label study with 35 evaluable subjects, as I think it would present a conflicting message to health care providers. Though the study was conducted under maximum use conditions, it was not of sufficient size to allow one to draw conclusions from the fact that hypercalcemia, hypercalciuria, and HPA axis suppression were not identified. In addition, general Agency guidance and specific advice from the Labeling Development Team recommend against inclusion of negative outcome data regarding an adverse reaction unless it is sufficiently persuasive to resolve concern for the adverse reaction.

Patient labeling (Patient Information and Instructions for Use) was proposed and is appropriate for this product to convey information adverse reactions, risk mitigation, and product use.

13. Postmarketing

Regulatory Action: Approval

I concur with the recommendations of the multi-disciplinary review team regarding approval of NDA 207589 Enstilar (calcipotriene and betamethasone dipropionate) foam, 0.005%/0.064% for the topical treatment of plaque psoriasis in patients 18 years of age and older.

Risk-benefit assessment: The applicant established the safety and efficacy of their product for the proposed use and provided sufficient information to inform product labeling. The efficacy of the product justifies the risks, which include HPA axis suppression and disturbance of calcium metabolism.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

Postmarketing requirements (PMR) and commitments (PMC):

1) Conduct an open-label study to assess the effect of Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% on calcium metabolism in 100 evaluable pediatric subjects aged 12 years to 16 years and 11 months with plaque psoriasis of the scalp and body. Assess the pharmacokinetics (PK) of Enstilar® Foam and hypothalamic-pituitary axis (HPA) suppression in a sub-set of 30 subjects with at least moderate plaque psoriasis under maximal use conditions. The applicant is required to conduct this study under the Pediatric Research Equity Act.

2) Conduct a single point vasoconstriction assay (VCA) trial in healthy subjects with adequate bracketing using visual assessment to determine the topical corticosteroid potency classification for Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%. The applicant agreed to this voluntary PMC.

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/s/

JILL A LINDSTROM
10/16/2015