DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207589

WRITTEN REQUEST

LEO Pharma A/S
Attention: Jordanis Joy, PharmD
Senior Manager, US Regulatory Affairs
7 Giralda Farms; 2nd Floor
Madison, New Jersey 07940

Dear Dr. Joy:

Reference is made to your September 27, 2018 Proposed Pediatric Study Request for Enstilar® (calcipotriene and betamethasone dipropionate) foam, 0.005%/0.064%.

BACKGROUND:

This study investigates the potential use of calcipotriene 0.005% and betamethasone dipropionate 0.064% for the topical treatment of pediatric patients with plaque psoriasis. Calcipotriene is a vitamin D analog and betamethasone dipropionate is a high potency corticosteroid.

Psoriasis is a chronic, inflammatory skin disease which occurs in the pediatric population ages 12 to 17 years. In the United States, the annual incidence of psoriasis in patients aged younger than 18 years was estimated to be 40.8 per 100,000.[1] Extrapolation of efficacy from adults to pediatric patients ages 12 to less than 18 years of age for plaque psoriasis is reasonable as disease progression and response to intervention are similar and consistent with other topical products to treat plaque psoriasis. Assessments in pediatric patients 11 years of age and younger with plaque psoriasis including neonates are not required as part of this Written Request because of a) safety considerations (e.g., the greater risk of HPA axis suppression with high potency corticosteroids), and b) the small number of pediatric patients with psoriasis where high potency topical corticosteroids are a medically appropriate therapy.

The FDA has not determined that further studies in conditions such as vitiligo or morphea will produce health benefits in children. Therefore, the sponsor will not be required to evaluate their drug product in the pediatric population with other diseases.

To obtain needed pediatric information on calcipotriene 0.005% and betamethasone dipropionate 0.064%, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the study described below.

- *Nonclinical study(ies)*:

[1] Tollefson MM, Crowson CS, McEvoy MT, et al. Incidence of psoriasis in children: a population based study. J. Amer. Acad. Dermatol. 2010; 62: 979-987.

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical study(ies)*:

  An open-label study to assess the effect of calcipotriene 0.005% and betamethasone dipropionate 0.064% foam on calcium metabolism in 100 evaluable pediatric patients aged 12 years to 16 years and 11 months with plaque psoriasis of the scalp and body. Pharmacokinetics of calcipotriene 0.005% and betamethasone dipropionate 0.064% foam and assessment of hypothalamic-pituitary axis (HPA) suppression will be conducted in a subset of 30 patients with at least moderate plaque psoriasis under maximal use conditions.

  Efficacy in pediatric patients from age 12 years to 16 years and 11 months will be supported by extrapolation of efficacy from adequate and well controlled studies in the adult population age 18 years and above.

  A formal protocol and statistical analysis plan for this study must be agreed upon with the Agency before initiation of the study

- *Objective of the study:*
  - To evaluate the safety and effect of calcipotriene 0.005% and betamethasone dipropionate 0.064% foam on calcium metabolism in pediatric patients from age 12 years to 16 years and 11 months with mild to moderate plaque psoriasis.
  - To evaluate the pharmacokinetics (PK) of calcipotriene 0.005% and betamethasone dipropionate 0.064% foam and assess hypothalamic-pituitary axis (HPA) suppression in a subset of 30 patients with at least moderate plaque psoriasis under maximal use conditions.

- *Patients to be Studied:*
  - *Age group in which study(ies) will be performed*: age 12 years to 16 years and 11 months
  - *Number of patients to be studied:* at least 100 evaluable patients with at least 30 patients under maximal use conditions.

  Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  Pharmacokinetic/Pharmacodynamic Endpoints
  The pharmacodynamic endpoints must include the albumin-corrected serum calcium concentration and calcium:creatinine ratios. In the subset of patients who are treated under maximal use conditions, the pharmacodynamic endpoints must include the proportion of patients with serum cortisol concentration of ≤18 mcg/dl at 30 minutes after ACTH challenge at Week 4.

  The pharmacokinetic endpoints must include the mean steady state C_{max} and AUC_{0-t} of calcipotriene and betamethasone dipropionate and their main metabolites (MC1080 and

betamethasone 17-propionate) in the subset of patients who are treated under maximal use conditions. Bioanalytical method validation and bioanalysis reports for each assay (which includes both the parent compounds and their metabolites as well as cortisol and calcium) must be included to support the results.

Safety Endpoints:

Safety outcomes must include adverse events, local skin reactions, clinical laboratory assessments, and extent of exposure. All adverse events must be monitored until symptom resolution or until the condition stabilizes.

Adverse Events

The following adverse events must be actively monitored for the duration of the study based on the known adverse event profile of calcipotriene and betamethasone dipropionate:

- Evidence of HPA axis suppression, e.g., headache, diarrhea, vomiting, weakness, and fatigue
- Evidence of hypercalcemia, e.g., arthralgia, fatigue, anorexia, nausea, depression, muscle weakness
- Local adverse events, e.g., striae, telangiectasias, hypopigmentation, secondary infections, burning, stinging, pruritus

In addition, any spontaneous reports related to HPA axis suppression, hypercalcemia or local toxicity must be captured in the study documents.

Findings of hypercalcemia or hypothalamic pituitary adrenal axis suppression in a majority of enrolled patients may require termination of the study before planned completion.

- *Known Drug Safety concerns and monitoring:*
  Hypercalcemia and hypercalciuria are the primary drug specific safety concerns associated with calcipotriene; hypothalamic pituitary adrenal axis suppression with the potential for glucocorticosteroid insufficiency are the primary drug specific safety concerns associated with betamethasone dipropionate. Other safety concerns are related to local skin reactions which include application site irritation, application site pruritus, folliculitis, skin hypopigmentation, allergic contact dermatitis and urticaria, and exacerbation of psoriasis.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - *dosage form:* Foam
  - *route of administration:* Topical
  - *regimen:* Once daily for 4 weeks

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- *Statistical information, including power of study(ies) and statistical assessments:* This study must assess 100 evaluable patients for safety and the effects on calcium metabolism. The reports should include summary statistics for all safety and pharmacokinetic assessments as agreed with the Agency at the time of protocol submission and review prior to initiation of the study.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that calcipotriene 0.005% and betamethasone dipropionate 0.064% foam is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety

Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before January 31, 2019. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at 301-796-5376.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIE G BEITZ
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