CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213976Orig1s000

OTHER ACTION LETTERS

NDA 213976

COMPLETE RESPONSE

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Matthew Wang, Pharm.D.
Director, Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Wang:

Please refer to your new drug application (NDA) dated and received October 15, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Eohilia (budesonide oral suspension).

We recognize that eosinophilic esophagitis is a rare and serious disease with a high unmet need and no approved therapies. In situations such as this one we must incorporate regulatory flexibility, while still ensuring there is substantial evidence of effectiveness. Based upon our review of your submitted data, we are unable to conclude that there is substantial evidence of effectiveness. As such, we have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/ STATISTICAL:

As was conveyed in the Filing Communication – Filing Review Issues Identified Letter dated December 14, 2020, and subsequently communicated in the Discipline Review Letter dated March 19, 2021, our review identified deficiencies with the ability of the submitted data to demonstrate the short- and long-term efficacy of BOS for the treatment of EoE. We have completed our review of NDA 213976, and have determined that neither the data submitted in the NDA, nor the data submitted to the NDA during review of the application, are adequate to support the demonstration of efficacy of BOS for the treatment of EoE in adult and adolescent patients 11 years and older.

1. The results from the evaluation of the symptomatic coprimary endpoint in trial SHP621-301, while statistically significant, were not representative of clinically meaningful change. Throughout the conduct of the development program and the course of the review, we expressed our concerns with the selection of the ≥30 percent Dysphagia Symptom Questionnaire (DSQ) responder threshold and cautioned you that evidence was needed to support its clinical meaningfulness. The anchor-based analyses that you provided, conducted using the data from the

12-week initial treatment phase 3 trial SHP621-301, do not support that the selected threshold constituted a clinically meaningful within-patient change.

In addition, although a statistically significant response was observed on the histologic coprimary endpoint in trial SHP621-301, the contribution of that finding to support a determination of benefit is unclear due to the lack of sustained histologic response observed in subjects maintained on treatment with BOS in trial SHP621-302. Further, there are inadequate data to demonstrate that short-term improvement in histologic response predicts improvement in meaningful clinical outcomes.

2. The evaluation of the key secondary efficacy endpoint of absolute change from baseline in 14-day DSQ combined score for trial SHP621-301 did not demonstrate that subjects treated with BOS had meaningful benefit compared to those treated with placebo. Although statistically significant results were reported on this prespecified alpha-controlled symptomatic secondary endpoint, the treatment difference between BOS and placebo groups was small, and the assessment period was not supported by the 7-day Patient Global Impression of Severity (PGIS). A treatment difference was not observed on evaluation of the change in 7-day DSQ absolute combined score (conducted to match the 7-day assessment period of the PGIS).

3. As EoE is a chronic relapsing condition, data to establish the benefit of long-term treatment for a candidate therapeutic is needed to support a determination of durability of effect. The need for long-term efficacy data to support your application has been emphasized throughout the development program, and we refer you to the following communications under IND 103173:

    - November 12, 2014 Type B End-of-Phase 2 meeting (meeting minutes finalized on November 30, 2014)
    - July 13, 2015 Type C meeting (meeting minutes finalized on July 15, 2015)
    - November 2, 2016 ‘Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting’ (meeting minutes finalized on November 4, 2016)
    - June 25, 2019 Type B Pre-NDA face-to-face meeting (meeting minutes finalized on June 27, 2019)
    - May 20, 2020 Type B Pre-NDA teleconference (meeting minutes finalized on June 2, 2020)

    On review of your submitted phase 3 trial SHP621-302 efficacy data, the benefit of long-term treatment with BOS for patients with EoE was not established. The trial did not yield statistically significant results on the pre-specified long-term efficacy endpoint of relapse on both histology and symptoms in the individual

subject.

4. The data submitted to the NDA during review of the application from post hoc subgroup analyses of subjects without prior history of dilation for the 12-week initial treatment period are inadequate to support the demonstration of efficacy for BOS for the treatment of patients with EoE. Dilation status was collected during screening for eligibility criteria, and dilation-naïve status was identified as a subgroup of interest for efficacy analyses only *after* data unblinding and completion of the SAP-specified analyses. The variable (i.e., dilation status) used to identify the subpopulation in trial SHP621-301 is not reliable, as a substantial portion of these subjects were identified by self-report, and it was not possible to confirm the dilation status for these subjects from medical records. On analysis of the 7-day DSQ combined score (to match the 7-day PGIS anchor) in subjects with medical record confirmation of dilation status, minimal separation between treatment groups over the 12-week treatment period was observed.

Information needed to resolve the deficiencies:

To resolve the above-noted deficiencies, we recommend you leverage the existing data to inform the design of a new adequate and well-controlled study including adolescent and adult subjects with EoE in a prespecified subpopulation (e.g., subjects without a prior history of dilation, subjects with more severe dysphagia symptoms at baseline) to support chronic administration of BOS. If subjects with a prior history of dilation are to be included for analysis, medical record documentation of the procedure should be available for these subjects.

We recommend a treatment period of at least 24 weeks' duration to assess efficacy for both clinical and histologic endpoints, followed by an extension period to provide a total treatment period of at least 52 weeks' duration to ensure adequate exposure to allow for characterization of the safety profile and the durability of response in the intended population.

This new study should assess prespecified symptomatic and histologic coprimary endpoints. To aid in the interpretation of the DSQ results, an appropriate range of within-patient score change that patients consider to be clinically meaningful should be proposed using anchor-based methods (e.g., patient global impression scale as an anchor), supplemented with empirical cumulative distribution function (eCDF) curves using data pooled across treatment arms. You should complete this study before resubmitting the application.

We look forward to engaging with you as you consider the study design and population selection for a future trial of BOS in patients with EoE and advise you to continue to benefit from the frequent interactions with FDA available to you under your granted breakthrough therapy designation. This application may need discussion at an advisory committee meeting during the next review cycle.

ADDITIONAL COMMENTS:

We have the following additional comments/recommendations that are not approvability issues:

1. You did not conduct a food effect study with either the phase 3 formulation or the to-be-marketed (TBM) formulation of your proposed product. Therefore, the effect of food on the pharmacokinetics (PK) and safety of your drug product to inform dosing instructions in relation to meal intake is unknown. We have determined that the potential effect of food on budesonide exposure from BOS cannot be predicted based on available data/rationale, and a dedicated food effect study is needed. Your product is an oral suspension of corticosteroid budesonide, where adverse events including hypercortisolism and adrenal axis suppression have been shown to be concentration dependent. Considering this, assessing any factor that could potentially increase budesonide exposure is critical. Therefore, you should conduct a dedicated food effect study to inform the prescribing information for BOS and include the results of this study in the resubmission.

2. In the current submission, you provided limited dissolution data with the proposed dissolution method collected at the time of batch release. If approval of your proposed product needs manufacturing any new batch to resolve the deficiencies, provide full-profile dissolution data (n= 12) from that newly manufactured batch collected at the time of batch-release in the next submission. If no new batch manufacturing is required for approval of your product in terms of resolving the deficiencies, only upon approval of the proposed drug product, collect full-profile dissolution data (n= 12) for the first six commercial batches at the time of batch-release and provide these data to the FDA in your annual report.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, November 25, 2020, which addresses the proposed proprietary name, Eohilia. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, M.D., M.M.Sc.
Director
Division of Gastroenterology
Office of Immunology and Inflammation
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/

JESSICA J LEE
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