CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206976Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206976

COMPLETE RESPONSE

Institut Biochimique SA (IBSA)
c/o Clarence E. Jones
4249 Via Encanto
Thousand Oaks, CA 91320

Attention: Clarence E. Jones, PhD
U.S. Agent

Dear Dr. Jones:

Please refer to your New Drug Application (NDA) dated and received, May 26, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for diclofenac epolamine topical system 1.3%.

We have completed our review of this application, as amended, and 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

1. The product used in the clinical studies was manufactured at a different facility than the to-be-marketed product. You have not provided adequate information (refer to the Biopharmaceutics section below) to bridge these two products in order to establish the safety and effectiveness of the to-be-marketed product.

   Information needed to resolve the deficiency
   Conduct at least one adequate and well-controlled clinical efficacy trial to demonstrate the safety and effectiveness of the to-be-marketed product manufactured at the proposed commercial manufacturing site, (b) (4) We recommend that you discuss the design of this study with the Division in advance.

NONCLINICAL

2. Your application did not include an adequate justification to support the safety of the (b) (4) leachable compounds whose structures were not fully elucidated in the leachables studies but were detected at levels exceeding the qualification threshold of 5 mcg/day.
   a. (b) (4)

b. [redacted]

c. [redacted]

Information needed to resolve the deficiency

To address this deficiency, identify all unknown leachable compounds detected at levels that exceed 5 mcg/day and provide a toxicological risk assessment to justify the safety of these identified compounds. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s), unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

- If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.

- Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation.

- Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the

compounds and an adequate scientific bridge to interpolate a NOAEL for the novel leachable.

Alternatively, you may provide evidence that none of the compounds can penetrate skin and, therefore, would not pose any risk to patients based on an accurate and reliable method to demonstrate compound size. Submit any literature articles that are intended to support this argument .

PRODUCT QUALITY

3. (b) (4)

4. (b) (4)

(b) (4)

5. (b) (4)

(b) (4)

6. (b) (4)

(b) (4)

(b) (4)

7. (b) (4)

(b) (4)

8. (b) (4)

(b) (4)

9. (b) (4)

(b) (4)

10. (b) (4)

11. (b) (4)

(b) (4)

Process

12. (b) (4)

(b) (4)

13. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Biopharmaceutics

14. The weight-of-evidence approach (risk-based approach) to support the manufacturing site change from Teikoku (b) (4) is inadequate due to the following deficiencies:

a) (b) (4)

b)

Information needed to resolve the deficiencies

Given the inadequate data to support a risk-based approach, as a path forward for the evaluation of the proposed site change and as per SUPAC-MR guidance, in vivo data are needed for bridging the manufacturing site change. Because there is no unexpired drug product manufactured at Teikoku available to perform a head-to-head comparison of the two sites via a pharmacokinetic study, conduct one adequate and well-controlled clinical efficacy and safety study to bridge the products manufactured at different sites and to demonstrate the safety and effectiveness of the product manufactured at the proposed commercial manufacturing site, (b) (4). Also see Clinical comments.

15. (b) (4)

(b) (4)

Information needed to resolve the deficiency
Provide additional data demonstrating the discriminating ability of the method towards meaningful changes of the critical material attributes or process parameters. These data are needed to support the adequacy of the method as a QC tool for drug product release and stability testing.

PRESCRIBING INFORMATION

16. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* 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.

    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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, August 30, 2016, which addresses the proposed proprietary name, Licart. 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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

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 Spiros Nicols, Regulatory Project Manager, at (240) 402-5988.

Sincerely,

{See appended electronic signature page}

Ellen Fields, MD, MPH
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

ELLEN W FIELDS
03/24/2017