CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209388Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209388

COMPLETE RESPONSE

Evoke Pharma, Inc.
Attention: Marilyn R. Carlson, DMD, MD
Chief Medical Officer
420 Stevens Avenue, Suite 370
Solana Beach, CA 92075

Dear Dr. Carlson:

Please refer to your New Drug Application (NDA) dated May 30, 2018, received June 1, 2018, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Gimoti (metoclopramide nasal spray).

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 PHARMACOLOGY

Your pharmacokinetic (PK) bridge between the Gimoti 15 mg dose and the Reglan tablet 10 mg is insufficient to justify the reliance on the findings of safety and efficacy for Reglan to assure comparable safety and efficacy between Gimoti and Reglan.

We have concerns that your product is not able to deliver metoclopramide in a reliable and consistent manner. Several subjects demonstrated low Cmax (<5 ng/ml) for metoclopramide with one or more Gimoti administrations. This was not observed with Reglan tablet administration. The overall lower mean Cmax was driven by these individuals who appeared to receive very little drug. The reason for this observation is unclear.

Recommendations to Address Deficiencies:
To address the clinical pharmacology deficiency, we recommend that you investigate the root cause(s) for the variability in PK for Gimoti, including the issue of inconsistent and incomplete delivery. You will need to provide evidence supporting your conclusions from the root cause analysis and provide mitigation strategies that will address the(se) issue(s). Depending on the identified cause(s), you may need to conduct additional in vitro and/or in vivo studies.

PRODUCT QUALITY/DEVICE QUALITY

Your proposed specification for the drug product is inadequate since insufficient evidence has been provided to ensure that the quality control and essential performance characteristics of the combination product do not contribute to the observed clinical variability and lack of efficacy. Specifically, the method and acceptance criterion for droplet size distribution is not deemed robust enough to guarantee consistent delivery of the drug to the patient with each actuation. The proposed acceptance criterion for droplet size distribution of the 15 mg/mL strength (i.e., the mean droplet sizes and calculated ranges) are not justified particularly given the observed variability of PK data.

Recommendations to Address Deficiencies:
Upon resubmission, all proposed tests and acceptance criteria including the droplet sizes and other essential performance characteristics for the commercial product specification should be supported by three batches of drug product using the selected commercial formulation (including strength of the product) and the commercial device. We recommend that the three registration batches be manufactured at the proposed commercial manufacturing site, manufactured by the proposed commercial process, and tested using validated analytical methods at the proposed analytical site.

ADDITIONAL COMMENTS

The following comments are not approvability issues but should be addressed in the complete response submission.

PRODUCT QUALITY/DEVICE QUALITY

A. We recommend that actuation force be considered an essential performance requirement and to include a test and acceptance criterion for actuation force for the to-be-marketed combination product in the product release and stability specification. You should include verification and validation data to support that specification and describe why this force is appropriate for the intended user population. Alternatively, provide a rationale for why you do not consider actuation force an essential performance requirement for the device constituent and how you will control the product to assure this essential performance will be consistently achieved.

B. You provided a specification for the lowest allowable cap removal force, but without the highest allowable cap removal force. This information is recommended to demonstrate that the cap will not be too difficult for the user to remove. We recommend the upper cap removal force specification be defined.

C. The proposed shelf-life of (b) (4) months is not supported by the data submitted. Upon resubmission the proposed shelf life should be supported by three batches of the drug product using the selected commercial formulation (including strength of the product) and the proposed commercial device.

D. It is premature to agree to a reduced reporting category for an additional release and stability facility as proposed in your comparability protocol.

CLINICAL PHARMACOLOGY

E. (b) (4) (b) (4) We recommend that you develop a lower dosage strength to address the dosage adjustment for patients who may need lower dose.

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 *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 7, 2018 which addresses the proposed proprietary name, Gimoti. 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," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

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 Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
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/

JOYCE A KORVICK
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