CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208085Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208085

COMPLETE RESPONSE

ECI Pharmaceuticals, LLC
5311 N.W. 35th Terrace
Fort Lauderdale, FL 33309

Attention: John Copanos
Chief Executive Officer

Dear Mr. Copanos:

Please refer to your New Drug Application dated April 13, 2016, received April 13, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [redacted] (b) (4) (Hydrocodone Bitartrate and Guaifenesin, 5mg/400mg) Tablets.

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

1. The development program for this application was based on demonstration of comparative bioavailability to the listed drug relied upon for the hydrocodone bitartrate aspect of the combination product and a guaifenesin product that complies with the over-the-counter (OTC) monograph (the reference guaifenesin product). The clinical pharmacology study submitted to support this application (study 102-13-US) showed that the guaifenesin component of the proposed combination product provided AUC comparable to the reference guaifenesin product, but the 90% CI of the geometric mean ratio of the Cmax for guaifenesin in the proposed product was lower (76.68%) than what the Agency considers to be acceptable to establish comparative bioavailability. As a result, this application cannot rely on the OTC monograph for guaifenesin without additional data or an alternative justification that scientifically bridges the guaifenesin component of the proposed product to that monograph. A bridge is necessary to demonstrate that reliance on the guaifenesin OTC monograph is appropriate.

This deficiency may be addressed by performing the following:

a. Repeat the single-dose clinical pharmacology study to evaluate the relative bioavailability of your proposed hydrocodone 5 mg/guaifenesin 400 mg immediate release tablet compared to the individual reference products under the fasted state. If you choose to repeat the relative bioavailability study, the study should be designed carefully with considerations of the PK variability observed in your current program, or

b. Because comparative bioavailability of the proposed combination product was not established, conduct a clinical development program with clinical efficacy and safety studies to support your combination product, or

c. Evaluate whether there is a need to reformulate your combination product. If you reformulate the product, you must repeat the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the individual reference products under fasted state to demonstrate comparative bioavailability. You may also need to repeat the food effect study if the product is reformulated.

PRODUCT QUALITY

2. Provide the following data to the NDA for at least one commercial scale drug product batch:

   a. Data from the [redacted] (b) (4) per your submission Sections 3.2.P.3.4 and 3.2.P.5.2 (Version 09).

   b. Drug product certificate of analysis against the current release specification.

   c. Certificate of analysis for the APIs [used for that drug product batch(es)] per your current specification for drug substance.

FACILITY INSPECTIONS

3. During a recent inspection of the **ECI Pharmaceuticals LLC, FEI 3008798439, in Fort Lauderdale, Florida** manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved. Please list communications submitted to, or held with, the agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

PRESCRIBING INFORMATION

4. 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

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. 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 LeAnn Brodhead, Regulatory Project Manager, at (240) 402-2605.

Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, M.D.
Deputy Director
Division of Pulmonary, Allergy, and Rheumatology 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/

LYDIA I GILBERT MCCLAIN
02/13/2017