

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22442Orig1s000

OTHER ACTION LETTER(s)



NDA 022442

COMPLETE RESPONSE

Cypress Pharmaceutical, Inc.
c/o Beckloff Associates, Inc.
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Attention: William Putman, Ph.D., R.A.C.
Director, Executive Consultant

Dear Dr. Putman:

Please refer to your New Drug Application (NDA) dated November 7, 2008, received November 10, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Rezira (hydrocodone and pseudoephedrine) Oral Solution

We acknowledge receipt of your submissions dated December 10, 2009 and April 9 and 20, and May 6, 17 and 19, 2010. The December 10, 2009, submission constituted a complete response to our September 18, 2009, action letter.

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. An audit performed by the Agency of the bioequivalence studies S08-0179 and SAM 09-1010 designed to establish bioequivalence of the active ingredients hydrocodone and pseudoephedrine in your drug product to the reference products identified deficiencies both in the conduct of the study and in the methods used at the analytical sites. Because of these deficiencies, the bioequivalence studies cannot be relied upon to establish bioequivalence of your proposed drug product to the reference products.

This deficiency may be addressed by doing the following:

- a. Conduct another single-dose clinical pharmacology study to establish the bioequivalence of your proposed hydrocodone 5 mg/chlorpheniramine 4 mg/pseudoephedrine 60 mg/ per 5 ml oral solution to the reference products.

OR

- b. Conduct a clinical development program with clinical efficacy and safety studies to support your combination product

LABELING

2. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit 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>.
3. Please submit draft carton and container labeling revised as follows:
 - a. Harmonize the drug substance established name on the carton and container labeling to match the format used in the package insert, such that “Oral Solution” remains outside of the parentheses.

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.

OTHER

The following comments are not related to the approvability of the application.

4. It is acceptable to remove the identified impurity (b) (4) from the commercial product specifications.
5. The Agency does not agree with your approach of removing specified impurities (b) (4) from the commercial product specifications. These impurities should be reported when they are at or above the ICH reporting threshold of 0.1%.
6. Change to specifications of commercial products should be handled in a post-approval supplement.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.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 Philantha M. Bowen, Senior Regulatory Health Project Manager, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Package Insert

15 pages of draft labeling has been withheld in full as B
(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA (hydrocodone bitartrate and PSEU)

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
06/11/2010
Deputy Division Director



NDA 22442

COMPLETE RESPONSE

Cypress Pharmaceutical, Inc.
c/o Beckloff Associates, Inc.
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

Attention: William Putman, Ph.D., R.A.C.
Director, Executive Consultant

Dear Dr. Putman:

Please refer to your new drug application (NDA) dated November 7, 2008, received November 10, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Rezira® (hydrocodone and pseudoephedrine) Oral Solution.

We acknowledge receipt of your amendments dated January 28, March 4, April 8, May 18, and July 10, 2009.

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

1. The clinical pharmacology study submitted to support this application show that the hydrocodone component of your oral solution product is not bioequivalent to the reference Hycodan® oral solution, in that the 90% CIs of the geometric mean ratio of C_{max} for hydrocodone bitartrate in your product is outside of the 80 -125% goal post for bioequivalence.

This deficiency may be addressed by doing the following:

- a. Conduct a single-dose clinical pharmacology study to establish the bioequivalence of your proposed Rezira® (hydrocodone 5 mg and pseudoephedrine 60 mg/ per 5 mL) oral solution to the reference products.

OR

- b. Conduct a clinical development program with clinical efficacy and safety studies to support your combination product.

PRODUCT QUALITY

2. In the SPL data element table:
 - a. Provide “Product Characteristics” information relevant to your product, such as color, shape, and flavor;
 - b. Correct “purified water” to “water” in the ingredient table;
 - c. Add NDC entry of the professional sample into the Packaging section.
3. Submit revised specification limits based on the available batch analysis. The batch analysis indicated that there is no detectable total impurity, and the one year long term stability data showed (b) (4) total impurity.
4. Submit stability and microbial limit testing results (b) (4)
5. Submit the analytical method developed for detection and quantification of (b) (4) in the Rezira drug product and the method validation results.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, 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/oc/datacouncil/spl.html>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22442

ORIG-1

CYPRESS
PHARMACEUTICA
L INC

REZIRA^(b)₍₄₎ (HYDROCODONE
BITARTRATE AND PSEU

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
09/18/2009