DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22439/S-009
NDA 22442/S-009
NDA 204307/S-003

SUPPLEMENT APPROVAL

Cypress Pharmaceutical, Inc.
10 North Park Place, Suite 210
Morristown, NJ 07960

Attention: Blanche Reynolds
Regulatory Project Manager

Dear Ms. Reynolds:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 21, 22, and 23, 2016 and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 22439/S-009/Zutripro (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine), NDA 22442/S-009/Rezira (hydrocodone bitartrate and pseudoephedrine), and NDA 204307/S-003/Vituz (hydrocodone bitartrate and chlorpheniramine maleate) Oral Solutions, respectively.

We also refer to our letter dated August 31, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Zutripro, Rezira, and Vituz Oral Solutions This information pertains to the serious risks of profound sedation, respiratory depression, coma, and death associated with the concomitant use of opioids and benzodiazepines or other central nervous system depressants, including alcohol.

These supplemental new drug applications provide for revisions to the labeling for Zutripro, Rezira, and Vituz Oral Solutions, consistent with our August 31, 2016 correspondence.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the revision listed below and included in the enclosed labeling.

> Per the Physician Labeling Rule, in the Highlights of the prescribing information, the Recent Major Changes section is limited to five labeling sections in the Full Prescribing Information, these are Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions. Because of this rule,

Drug Interactions and Patient Counseling Information were removed from the Recent Major Changes section.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert and text for the Medication Guide, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

IMMEDIATE CONTAINER LABELS

Submit the final printed immediate container labels that are identical to the enclosed immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* For administrative

purposes, designate this submission "**Final Printed Container Labels for approved NDA 22439/S-009, NDA 22442/S-009 and NDA 204307/S-003**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager for Safety, at (301) 301-796-1226.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Container Labeling

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

/s/

SALLY M SEYMOUR
01/13/2017