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APPLICATION NUMBER:

204307Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	February 20, 2013
From	Lydia I Gilbert-McClain, MD, FCCP
Subject	Division Director Summary Review
NDA/BLA # Supplement#	204307
Applicant	Cypress Pharmaceuticals
Date of Submission	April 24, 2012
PDUFA Goal Date	February 24, 2013
Proprietary Name / Established (USAN) names	Vituz/hydrocodone bitartrate and chlorpheniramine maleate
Dosage forms / Strength	Oral Solution/5 mg and 4 mg, respectively, in each 5 ml
Proposed Indication(s)	Relief of cough and symptoms associated with upper respiratory allergies or the common cold
Recommended Action:	Approval

1. Introduction

This 505(b) (2) new drug application (NDA 204307) submission by Cypress Pharmaceuticals received April 24, 2012, for a hydrocodone bitartrate (HC) and chlorpheniramine maleate (CPM) combination oral solution with a proposed indication for the temporary relief of cough and symptoms associated with upper respiratory allergies or a common cold. This is a clinical pharmacology-based program that relies on the demonstration of bioequivalence of the proposed HC and CPM combination product to that of approved reference product, Hycodan (the actual hydrocodone product used was a generic version of Hycodan since that product is no longer marketed) and the OTC monograph product chlorpheniramine.

This product is related to and shares the same clinical pharmacology program as two other NDAs previously submitted by Cypress, NDA 22-439, a 3-ingredient combination product comprised of hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride (tradename Zutripro) and NDA 22-442, a 2-ingredient combination product of hydrocodone bitartrate and pseudoephedrine hydrochloride (tradename Rezira). After two complete response actions based on a lack of demonstration of bioequivalence and failure of an inspection by the Division of Scientific Investigations, the two products were approved on June 8, 2011. As mentioned, the clinical pharmacology study data used to support approval of Zutripro (demonstration of the equivalence of each component of the 3-ingredient cough/cold combination oral solution test drug to each of the respective reference drugs (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride) is being used to support approval of this 2-ingredient HC and CPM combination product. This review will briefly summarize the clinical pharmacology program used to support approval as well as summarize applicable discipline-specific issues.

2. Background

As part of the FDA's compliance efforts to remove illegally marketed products from the market, the Agency issued a Federal Register notice [(published on October 1, 2007 [Docket No. 2007N-0353], regarding illegally marketed hydrocodone-containing combination products. The FR notice stated that all manufacturers of hydrocodone-containing products had to stop manufacturing these products by December 31, 2007. The Agency has encouraged manufacturers of these and other unapproved products to submit NDAs to obtain approval for marketing these products in the United States. This application is to market a combination product containing hydrocodone bitartrate and chlorpheniramine maleate, as an immediate release oral solution containing 5 mg and 4 mg of HC and CH, per 5 mL respectively. Chlorpheniramine is a well known antihistamine used to treat symptoms associated with upper respiratory allergies and is listed in the OTC monograph (21 CFR 341.12). There is an approved extended release HC/CPM combination product (Tussionex Pennkinetic) that was FDA approved on December 31, 1987 (NDA 19-111).

The development program for this application is based on demonstration of bioequivalence to the reference ingredients of the combination product. Since hydrocodone is not a monograph product, clinical studies would normally be required to support a combination product containing hydrocodone and other active ingredients in order to demonstrate the contribution of each component to the combination product as required by regulation (21CFR 300.50). However, because of the prior regulatory precedent of approving Tussionex Pennkinetic with clinical pharmacology data only, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combinations have been allowed to be developed under a clinical pharmacology program only. Therefore, clinical efficacy and safety studies may not be necessary to support this combination product provided that the applicant carries out a satisfactory clinical pharmacology program.

Of note is that Hycodan [ENDO Pharmaceuticals] was the hydrocodone reference product initially agreed to during the course of the development period for the 3 related combination products. However, ENDO Pharmaceuticals subsequently discontinued marketing Hycodan solution, but not because of safety or efficacy concerns. The Orange Book then listed the hydrocodone product from Hi Tech Pharma (ANDA 040613) as the RLD for hydrocodone bitartrate syrup. Subsequently, the Applicant used Hi-Tech Pharma's product as the reference for hydrocodone in their bioavailability studies. However, Hycodan is still the reference drug to support the 505(b) (2) application for reliance on the Agency's previous findings of safety and efficacy of hydrocodone.

3. CMC/Device

The proposed product is an aqueous clear to light yellow (b) (4) oral solution containing hydrocodone bitartrate 5 mg and chlorpheniramine maleate 4 mg, per 5 mL. The product contains methylparaben and propylparaben at target concentrations of (b) (4)

From the CMC microbiology standpoint, Cypress responded adequately to several requests in the 74-day letter regarding antimicrobial preservative effectiveness testing, microbial limits

testing, and testing for the presence of *B. cepacia*. There are no outstanding CMC microbiology issues with the formulation.

There are no outstanding DMF or inspection issues. The stability data support a 24 month expiry.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology studies were required or performed for this application.

5. Clinical Pharmacology/Biopharmaceutics

Cypress submitted one clinical pharmacology study in this application in order to demonstrate the bioequivalence of the hydrocodone bitartrate and chlorpheniramine maleate components of their proposed HC and CPM combination product to their respective individual reference products. The data generated from the study, which included pseudoephedrine as a third drug component, have been used to support the approval of two other related combination cough and cold products, Zutripro, a hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride triple combination product and Rezira, a hydrocodone and pseudoephedrine 2-ingredient product. The study has been previously reviewed and bioequivalence [defined as the 90% CI of ratios of AUC and C_{max} compared to the individual reference products being within 80 - 125%] was demonstrated for the HC and CPM components (and pseudoephedrine) and been confirmed by the clinical pharmacology review team.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of approved reference products Hycodan (the actual hydrocodone product used was a generic version of Hycodan since that product is no longer marketed) and the OTC monograph product chlorpheniramine. No clinical efficacy studies were conducted, because bioequivalence was demonstrated.

8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to the approved reference products. In addition, for the original NDA submission, the Applicant conducted a review of the literature, and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof, for the period

from October 2007 through March 2008. Subsequent safety updates dated March 31, 2011, and October 15, 2012, submitted during the review of NDA complete responses did not reveal any new safety signals.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this NDA. The active ingredients present in this product are well known as individual drug substances, and as previously discussed, based on the current monograph and the Agency's prior precedent, the combination of products of these classes are accepted for the proposed indications. However, a meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee was held on January 24 & 25, 2013 to discuss the public health benefits and risks, including the potential for abuse, of drugs containing hydrocodone either combined with other analgesics or as an antitussive. The meeting was held in response to a request to the Department of Health and Human Services from the Drug Enforcement Administration for a scientific and medical evaluation and scheduling recommendation for these products in response to continued reports of misuse, abuse, and addiction related to these products. A recommendation for rescheduling these hydrocodone products from Schedule III to Schedule II was brought to the committee.

As part of the background materials for this Advisory Committee, the Controlled Substances Staff (CSS) included a review dated July 30, 2009 completed by the Office of Surveillance and Epidemiology (OSE), Division of Epidemiology (DEPI) that evaluated data from the Drug Abuse Warning Network (DAWN) as well as prescription utilization data for all hydrocodone containing products (including hydrocodone-containing cough/cold products). The OSE review concluded that based on the limited evidence found in DAWN, the abuse of respiratory hydrocodone products appears to be lower than for analgesic hydrocodone products. The executive Summary further stated that given significantly lower rates of drug utilization and evidence that some (albeit much lower) abuse ratios were found with these products, OSE/DEPI recommended that abuse liability studies should be required of sponsors submitting NDAs and that conducting these studies post-approval is appropriate. The OSE review also recommended that the studies should be conducted on all respiratory hydrocodone containing products.

The question of the need for abuse liability studies for hydrocodone-containing products for cough/cold was discussed during the initial review cycles of Zutripro and Rezira, at a CDER regulatory briefing held on June 12, 2009. The CSS had recommended that this abuse potential be studied with animal and/or human studies. The consensus from the regulatory briefing was that abuse potential assessment was not required for these combination products prior to approval. These combinations would remain in Schedule III by virtue of the hydrocodone component and would have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for several years and there have been no safety concerns raised regarding an increase in the abuse potential of these combinations. The recommendation from the regulatory briefing was that a postmarketing signal could trigger the need for abuse potential studies for these products in the future. The CSS staff subsequently wrote an addendum to the consultation noting that the sponsors of these products could

conduct active surveillance and monitoring for signals of abuse, misuse, overdose, and addiction and provide periodic summaries post approval.

The recommendation from the January DSaRM advisory committee meeting was in favor of rescheduling all hydrocodone-containing products from Schedule III to Schedule II of the Controlled Substances Act. The thought is that more restrictive scheduling would lead to a reduction in the abuse and misuse of hydrocodone containing products. At the time of the completion of this Summary Review, the CSS is still in the process of summarizing information from the docket comments for the DSaRM advisory committee meeting (over 575 comments were received). The reviewer requested input from the Division regarding the consequences of upscheduling cough and cold hydrocodone containing products (*email correspondence February 5, 2013*). There are no expected negative consequences with the upscheduling of hydrocodone containing cough/cold products. These products are indicated for the temporary relief of symptoms of colds and upper respiratory allergies. These symptoms are usually self-limiting and so the utilization of these products is expected to be generally low considering that there are multiple over the counter products available for the same indications.

Since the Agency has not yet finalized the action of changing the scheduling of hydrocodone, this product will be approved as a Schedule III product; however, the sponsor will need to submit a labeling supplement to change the labeling to reflect the change in Schedule from Schedule III to Schedule II if the Agency ultimately follows the recommendation of the DSaRM Advisory Committee.

10. Pediatrics

The pediatric plan for this HC/CPM combination product (Vituz) was previously agreed to with Cypress at the time of approval of their 2 related cough and cold combination products, Zutripro and Rezira, which contain hydrocodone, chlorpheniramine, and pseudoephedrine and hydrocodone and pseudoephedrine, respectively. The rationale for the plan is as follows. The current proposed indication for Vituz is for adults 18 years of age and older, and the Applicant requested a deferral for children 6-17 years of age and a waiver for children under 6 years of age. The request for waiver for children under 6 years of age is based on the fact that the proposed product contains hydrocodone which is contraindicated for use in children less than 6 years of age (because of the risk of respiratory depression). It is appropriate to waive studies for pediatric patients less than 6 years of age because of this safety concern. However, although hydrocodone is currently labeled for use in children down to 6 years of age, safety concerns regarding dose-related respiratory depression identified over the last few years raises the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression including fatalities due to respiratory failure has been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children less than 6 years of age and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, the Applicant will need to establish the appropriate dose of hydrocodone for children between 6 and 17 years of age.

Hydrocodone was approved under Drug Efficacy Study Implementation (DESI) review and the basis for the dose selection for the pediatric population is unclear. The dose of chlorpheniramine (and pseudoephedrine for the Zutripro product) in the combination product is the same as the doses in the Agency's approved OTC cough/cold monograph. Since the Agency is not aware of any new safety concerns with chlorpheniramine at the established dose and the current monograph is still in effect, the proposed dose for chlorpheniramine in this combination solution should be acceptable. However, pharmacokinetic (PK) data for adequate dose selection and additional safety data in the pediatric population will be required for the hydrocodone component.

This rationale and pediatric plan were discussed at a PeRC meeting for the related Zutripro and Rezira products on May 26, 2010, at which time the committee agreed with the proposed plan to waive studies in children less than 6 years of age and to conduct PK and safety studies in patients 6 to 17 years of age with the intent of arriving at an appropriate dose and collecting additional safety data in the pediatric population. The committee recommended that efficacy assessments and population PK measurements be included in the proposed safety study as well, which is acceptable for a safety and PK study. Even though this product's efficacy is supported by the same relative bioequivalence study as the two related Zutripro and Rezira products, because it is a separate application, the same pediatric plan as previously accepted by PeRC and agreed to with the Applicant was once again presented to PeRC on October 10, 2012. While the PeRC agreed with the waiver of studies in children less than 6 years of age since hydrocodone is contraindicated in children less than 6 years of age, the PeRC changed their recommendation from the previously agreed to PK and safety studies in patients 6 to 17 years of age that cover the other triple and double combination products. Instead the PeRC recommended that the Division require the Applicant conduct a full development program including dose-ranging and replicate factorial design efficacy studies designed to demonstrate the contribution of each individual component to the efficacy of the combination. The main rationale for this requirement was that the overall efficacy data for cough and cold drugs in the pediatric population were not robust, and a well designed pediatric safety and efficacy development program would provide additional pediatric efficacy data for chlorpheniramine. The Division disagrees with the new PeRC recommendation for the following reasons:

- While one could debate the robustness of the available efficacy data for chlorpheniramine and other cough and cold medications in the pediatric population, the proposed chlorpheniramine doses for children 6-17 years of age are within those contained in the current OTC monograph. Since the monograph remains the legal regulatory basis for the determination of safety and efficacy for cough and cold drugs, including chlorpheniramine, the Applicant is not required to conduct a full clinical program to establish what the monograph already has determined to be the safe and effective doses of chlorpheniramine in children.
- There are no new safety concerns for chlorpheniramine in children that have arisen since the previous approval of the related Zutripro product.
- The Applicant is currently conducting PK and safety studies previously accepted by PeRC and the Division for the hydrocodone component in pediatric patients 6-17 years of age for the Zutripro and Rezira products that would also extend to this Vituz hydrocodone and chlorpheniramine combination product

11. Other Relevant Regulatory Issues

Inspections

The Division of Scientific Investigation (DSI) conducted an audit for both the clinical study and bioanalytics sites used for this clinical pharmacology program. The inspection of the clinical site was conducted at Novum Pharmaceutical Research Services, Houston, TX during February 15-28, 2011 and identified no deficiencies. The inspection of analytical portion was conducted at (b) (4)
DSI identified several deficiencies during this inspection involving improper documentation of sample processing steps and a deviation of the sample storage temperature from that specified. The Applicant responded adequately to the deficiencies outlined as a result of the inspection and, subsequently, DSI issued a Memorandum on April 14, 2011, recommending that the clinical and analytical data generated in study 11058503 be accepted for the review. As such, the data for study 11058503 are judged as acceptable to support the clinical pharmacology program.

Compliance with Good Clinical Practices

The clinical pharmacology study in this application was conducted in accordance with Good Clinical Practices, and in particular with the requirements of 21 CFR Part 314.50(3)(i). The Applicant certified that the clinical contractor conducted the study in compliance with Institutional Review Board regulations and with Informed Consent Regulations.

Financial Disclosures

The Applicant certified that there was no financial arrangement with the clinical investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The clinical investigator certified that he was not a recipient of significant payments defined in 21 CFR 54.2(f).

12. Labeling

Proprietary Name

The initial proposed trade name, (b) (4) was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and deemed unacceptable based on (b) (4) Subsequently, Cypress proposed the tradename, Vituz, which was reviewed by DMEPA and found acceptable.

Physician Labeling

The physician labeling was reviewed and revised based on similar approved labels for the Applicant's related cough and cold combination products, Zutripro and Rezira and current labeling for similar cough and cold combination products. Changes were made to the Indication section to reflect the population for which it would be used; those with respiratory tract symptoms due to the common cold and respiratory allergies.

During this review cycle minor revisions to the Adverse Reaction and Clinical Pharmacology sections were made as well as minor changes in format and grammar. At the time of this review the final draft product labeling has been agreed to by the Applicant and Division.

Carton and Immediate Container Labels

A detailed review of the carton and immediate container labels was conducted by the individual disciplines of the Division in consultation with DMPP and DDMAC. The Division and Applicant have agreed on final carton and container labeling.

Patient Labeling and Medication Guide

There is no separate patient labeling and medication guide for this product.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The Applicant has submitted the clinical pharmacology study report which had previously been used to establish the bioequivalence and support approval of Zutripro, their hydrocodone 5 mg, chlorpheniramine 4 mg, and pseudoephedrine 60 mg/ per 5 mL triple combination oral solution. Because the current proposed drug product exists as a solution with the only difference between it and Zutripro being the lack of pseudoephedrine, the same clinical pharmacology study may be used to establish the bioequivalence the hydrocodone and chlorpheniramine components of the proposed HC and CPM combination product to their respective reference drugs. By establishing bioequivalence, the program is able to rely on previous Agency determinations of the safety and efficacy of hydrocodone bitartrate and chlorpheniramine maleate in the proposed combination product for the relief of cough symptoms associated with upper respiratory tract allergies when administered to adults 18 years of age and older at a dose of 5 mL by mouth every 4-6 hours as needed, not to exceed 4 doses in a 24 hour period. Therefore the recommendation is for Approval for the adult population. As detailed in Section 10 (pediatrics) above, approval for children 6-17 years of age will be dependent upon the results of adequately designed pharmacokinetic and safety studies to be performed as a PREA post-marketing requirement in that population.

- Risk Benefit Assessment

The overall risk and benefit assessment of the proposed hydrocodone and chlorpheniramine combination product, based on establishing bioequivalence to the individual reference products and literature and AERS database searches, does not suggest an unfavorable risk benefit for these individual ingredients for the adult (18 years and older) population. Since dose-related respiratory depression associated with fatalities from the use of hydrocodone has been reported for the younger population (patients under 18 years of age) additional PK and safety data to support the appropriate dose in the pediatric population are necessary prior to extending the indication to the pediatric population.

- Recommendation for Postmarketing Risk Management Activities

Hydrocodone is a controlled substance known to have a certain level of abuse potential. The combination product as proposed will be labeled as a Schedule III narcotic and available by prescription only. At this time, the abuse potential can be managed by appropriate labeling. However, we will monitor for signals of abuse/misuse, overdose, and addiction post approval.

- Recommendation for other Postmarketing Study Commitments

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. For this combination product we are waiving the requirement for children less than 6 years of age based on the fact that the proposed product contains hydrocodone which is contraindicated for use in children less than 6 years of age (because of the risk of respiratory depression). The post-marketing requirements under PREA for this NDA can be satisfied with the ongoing required studies for the other 2 related NDAs Zutripro (NDA 022-439) and Rezira (NDA 022-442). The required studies are listed below.

2017-1 Conduct a study to assess the pharmacokinetics of each Vituz drug component (hydrocodone and chlorpheniramine) in approximately 25-35 children ages 6-17 years with symptoms of the common cold. The study can be conducted with a formulation containing hydrocodone, chlorpheniramine, and pseudoephedrine. The results of this study will be used to determine the appropriate dose of the combination product to evaluate in a safety study in children ages 6-17 years.

Final Protocol Submission:	March 8, 2013
Trial Completion:	December 31, 2013
Final Report Submission:	June 30, 2014

2017-2 Conduct a study to assess the safety of Vituz (hydrocodone and chlorpheniramine) in approximately 400-450 children ages 6-17 years with symptoms of the common cold. The study can be conducted with a formulation containing hydrocodone, chlorpheniramine, and pseudoephedrine. The dose used in this study will be based upon the pharmacokinetic study in children ages 6-17 years.

Final Protocol Submission:	September 30, 2014
Trial Completion:	December 31, 2015
Final Report Submission:	September 30, 2016

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/s/

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