CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205474Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 14, 2014
From	Lydia I Gilbert-McClain, MD, FCCP
Subject	Division Director Summary Review
NDA#	205-474
Applicant	Sovereign Pharmaceuticals, LLC
Date of Submission	January 14, 2014
PDUFA Goal Date	November 14, 2014
Proprietary Name / Established (USAN) names	Obredon/hydrocodone bitartrate and guaifenesin
Dosage forms / Strength	Oral Solution/2.5 mg and 200 mg, respectively, in each 5 ml
Indication(s)	Symptomatic relief of cough and to loosen phlegm (mucus) associated with the common cold
Recommended Action:	Approval

1. Introduction

This is a 505(b) (2) new drug application (NDA 205-474) submitted by Sovereign Pharmaceuticals and received January 14, 2014, for a hydrocodone bitartrate (HC) and guaifenesin (GUA) combination oral solution with a proposed indication of "the symptomatic relief of (b) (4) cough (b) (4) This is a clinical pharmacology-based program that relies on the demonstration of bioequivalence of the proposed HC and GUA combination product to that of the approved reference product, Hycodan (the actual hydrocodone product used in the clinical pharmacology studies was a generic to Hycodan developed by High-Tech pharma [ANDA 40-613] since Hycodan is no longer marketed and the OTC monograph for guaifenesin.

This product is similar to several other HC-containing immediate release oral solution combination products that the Agency has approved within the last 3 years for cough/cold indications [**Zutripro** (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride); **Rezira** (hydrocodone bitartrate and pseudoephedrine hydrochloride); and **Vituz** [hydrocodone bitartrate and chlorpheniramine maleate). These programs all relied on establishment of bioequivalence of the individual ingredients to reference products. This application is similar and the clinical pharmacology program supports approval of the product. This review provides a high level summary of some key aspects of the application.

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 guaifenesin, as an immediate release oral solution containing 2.5 mg and 200 mg of HC and GUA, per 5 mL respectively. HC is an opioid that is used as an antitussive in low doses and GUA is used as an expectorant according to the OTC monograph (21 CFR 341.18).

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 were not necessary to support this combination product because the sponsor was able to establish bioequivalence in a satisfactory clinical pharmacology program.

Hycodan [ENDO Pharmaceuticals] is the hydrocodone reference product [NDA 05-213] however, ENDO Pharmaceuticals discontinued marketing Hycodan solution [not for reasons of efficacy or safety] and the Orange Book now lists the hydrocodone product from Hi Tech Pharma (ANDA 040613) as the RLD for hydrocodone bitartrate syrup. Although the Applicant used Hi-Tech Pharma's product as the reference for hydrocodone in their bioavailability studies 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 non-sterile oral solution containing hydrocodone bitartrate 2.5 mg and guaifenesin 200 mg per 5 mL as an immediate release formulation. Inactive ingredients include citric acid, potassium sorbate, potassium citrate, saccharin sodium, (b) (4) glycerin, propylene glycol, and methylparaben and propylparaben (b) (4) There are no outstanding CMC issues and 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. However, a study was conducted to evaluate potential extractables for the HDPE

container closure system for the proposed product. Extractables belonging to 3 chemical classes were identified following isopropanol and hexane extraction - alkanes, fatty acids and [redacted] (b) (4) but no extractables were detected following water extraction. These extractables do not pose a safety concern and further preclinical studies are not warranted.

5. Clinical Pharmacology/Biopharmaceutics

Support for the NDA is based on data from 2 clinical pharmacology studies in this application.

Study 11244403 was a single-dose open label 4-way crossover study in 56 adult healthy volunteers designed to compare the relative bioavailability of the proposed drug product with the reference drugs HC and GUA and with co-administration of hydrocodone bitartrate solution + guaifenesin solution. The study was conducted in the fasting state with treatment periods separated by a 7-day washout period. The results of this study established bioequivalence of the proposed product to the reference drugs [90% CI of the ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the 80 – 125% bounds for bioequivalence] and showed that there was no drug interaction between the immediate release HC and GUA when co-administered.

Study 92001 was a single-center, single dose food effect study in 25 healthy adults and showed that the bioavailability of HC is comparable between the fed and fasted state however, a food effect (reduced AUC and C_{max}) was noted for guaifenesin as shown in the table below.

Food Effect Assessment for Hydrocodone (HC) and Guaifenesin (GUA)

	AUC_{0-inf} (pg hr/mL)	AUC_{0-t} (pg hr/ml)	C_{max} (pg/mL)
Test drug HC/GUA (Fed)	81158/2529	77609/2495	10958/1658
Test drug HC/GUA (fasted)	70109/4821	67323/4789	12450/5295
Fed/fasted HC	1.158 (1.12, 1.19)	1.153 (1.12,1.18)	0.880 (0.82,0.94)
Fed/fasted GUA	0.525 (0.45, 0.60)	0.521 (0.44, 0.60)	0.31 (0.16,0.46)

While this degree of food effect is notable, it must be taken into account that guaifenesin is not labeled with food restrictions in the monograph. The actual clinical significance of this observed food effect is unknown but it is worth noting in the label that a food effect was observed in this study.

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 for guaifenesin. 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, the following adverse effects were observed following single dose administration – headache, somnolence, dizziness, and nausea. These events have all been previously reported for these ingredients HC and GUA and do not raise any new safety concerns.

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.

10. Pediatrics

Currently, approved HC-combination products for cough/cold indications are approved in adults only (18 years of age and older) and Applicants are conducting safety and PK studies to support dosing down to 6 years of age. A similar age restriction will be applied to this application, and a deferral for pediatric studies in children 6 – 17 years of age is appropriate. Studies in children under 6 years of age will be waived because HC is contraindicated in children less than 6 years of age because of the safety concern for respiratory depression in this younger age group.

The Applicant's pediatric plan was discussed at a PeRC meeting on May 7, 2014 and 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 (primary assessment) and efficacy (secondary assessment) in the pediatric population.

11. Other Relevant Regulatory Issues

Inspections

The Division of Scientific Investigation (DSI) conducted an audit for the analytical sites used for study 11244403 (pivotal BE study) in the clinical pharmacology program. The inspection was conducted at (b) (4) and did not identify any deficiencies.

Compliance with Good Clinical Practices

The clinical pharmacology study in this application was conducted in accordance with Good Clinical Practices, and 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 Agency has agreed with the Applicant's proposed trade name Obredon.

Physician Labeling

The physician labeling was reviewed and revised based on similar approved labels for the related cough and cold combination products. Changes were made to the Indication section to reflect the population for which it would be used, and to streamline the language for the guaifenesin component.

Carton and Immediate Container Labels

The carton and immediate container labels have been reviewed and agreed upon.

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 application can be approved for the revised indication as follows:
Symptomatic relief of cough and to loosen (b) (4) associated with the common cold.

The proposed HC and GUA combination product, does not pose an unfavorable risk benefit for these individual ingredients for the adult (18 years and older) population. Additional PK and safety data to support the appropriate dose in the pediatric population are necessary prior to extending the indication to patients less than 18 years.

- 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 II (new schedule based on Oct 6, 2014 final rule)[1] narcotic and available by prescription only. At this time, the abuse

[1] Federal Register/Vol. 79, No.163/Friday, August 22, 2014
Drug Enforcement Administration 21CFR Part 1308 [Docket No. DEA-389]

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). We are requesting the following post-marketing requirements.

2826-1 Conduct a study to assess the pharmacokinetics of each active component in hydrocodone bitartrate and guaifenesin oral solution in children ages 6-17 years with symptoms of the common cold.

Final Protocol Submission:	03/ 2015
Trial Completion:	09/2016
Final Report Submission:	03/2017

2826-2 Conduct a study to assess the safety of hydrocodone bitartrate and guaifenesin in children with symptoms of the common cold. The dose used in this study will be based upon the pharmacokinetic study in children ages 6-17 years (PMR 2826-1).

Final Protocol Submission:	09/2018
Trial Completion:	03/2022
Final Report Submission:	09/ 2022

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/s/

LYDIA I GILBERT MCCLAIN
11/14/2014