CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205474Orig1s000

PHARMACOLOGY REVIEW(S)
Secondary Pharmacology and Toxicology Review for NDA 205-474

TO: NDA 205-474 (Sovereign Pharmaceuticals, LLC)

FROM: Marcie Wood, Ph.D.
Supervisory Pharmacologist
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: October 17, 2014

NDA 205-474, submitted as a 505(b)(2) application on January 14, 2014, proposed to register Guaifenesin and Hydrocodone Bitartrate Oral Solution for the symptomatic relief of cough associated with the common cold. Dr. Nikunj Patel was the nonclinical reviewer for this NDA. No nonclinical studies were submitted for review for either the individual monoproduts or the combination drug product. The application relies on previously approved NDAs for hydrocodone and the OTC monograph reviews and labeling for guaifenesin. Reference is made to NDA 05213 (Hycodan) for hydrocodone bitartrate and to the OTC monograph 21 CFR 341.18 for guaifenesin. Additionally, 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive with any single monograph expectorant.

Labeling: Dr. Patel reviewed the nonclinical sections of the label, including 8.1, 10, 12.1, and 13.1, and recommended changes to sections 8.1 and 13.1. See Dr. Patel’s review dated October 10, 2014, for complete details.

Extractable evaluation: Dr. Patel completed a safety evaluation of extractables at the request of CMC reviewer Dr. Ying Wang and determined that the identified extractables do not pose a safety concern. See Dr. Patel’s extractables review, also dated October 10, 2014, for complete details.

There are no outstanding Pharmacology and Toxicology issues for this product, and the NDA is recommended for approval from the nonclinical perspective.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARCIE L WOOD
10/17/2014
PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 205-474
Supporting document/s: SDN 1
Applicant’s letter date: January 13, 2014
CDER stamp date: January 14, 2014
Product: Guaifenesin and Hydrocodone Bitartrate Oral Solution
Indication: Symptomatic relief of cough associated with the common cold
Applicant: Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, TX 76118
Review Division: Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer: Nikunj S. Patel, Ph.D.
Supervisor/Team Leader: Marcie L. Wood, Ph.D.
Division Director: Badrul Chowdhury, MD, Ph.D.
Project Manager: Laura Musse, R.N., M.S., C.R.N.P

Template Version: September 1, 2010

Disclaimer

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Reference ID: 3642455
available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205-474.
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1 Executive Summary

1.1 Introduction
This review evaluates the nonclinical information to support safety of guaifenesin and hydrocodone bitartrate. Sovereign Pharmaceuticals, LLC submitted a 505(b)(2) New Drug Application (NDA) on January 14, 2014, for guaifenesin and hydrocodone bitartrate (200 mg and 5 mg per 5 mL, respectively) oral solution. Guaifenesin and hydrocodone bitartrate oral solution is indicated for the symptomatic relief of cough associated with common cold.

1.2 Brief Discussion of Nonclinical Findings
No nonclinical pharmacology or toxicology studies were conducted with the proposed guaifenesin and hydrocodone bitartrate combination product. The sponsor is relying on the previous approval of hydrocodone bitartrate and the guaifenesin OTC monograph for safety and efficacy of the proposed combination product.

Guaifenesin is an accepted expectorant in the OTC monograph (21CFR 341.18 for “Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Use”). Guaifenesin was approved as Mucinex extended release tablets on July 12, 2002 (Reckitt Benckiser, NDA 21282). Chronic toxicity studies with guaifenesin have demonstrated no adverse pathological findings based on the OTC monograph review. Animal studies to assess carcinogenicity, genotoxicity, and reproductive toxicology have not been conducted.

Hydrocodone bitartrate is a generally recognized antitussive, with efficacy established in DESI notice #5213 (dated June 1, 1982). Hydrocodone bitartrate was originally approved and marketed as Hycodan syrup and tablets (Endo Pharmaceuticals Inc., NDA 05213, approved on March 23, 1945). Endo Pharmaceuticals has since withdrawn Hycodan from the market, however a number of approved marketed generics of hydrocodone bitartrate and homatropine methylbromide syrup currently exist (ANDAs 40613, 88008, and 88017). Hydrocodone has been shown to be teratogenic in hamsters.

1.3 Recommendations

1.3.1 Approvability
From a nonclinical pharmacology and toxicology standpoint, the application is recommended for approval.

1.3.2 Additional Non Clinical Recommendations
None

1.3.3 Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects: Pregnancy Category C
There are no adequate and well controlled studies of Guaifenesin and Hydrocodone Bitartrate Oral Solution in pregnant women. Reproductive toxicity studies have not been conducted with Guaifenesin and Hydrocodone Bitartrate Oral Solution; however, studies are available with an individual active ingredient or related active ingredient. Hydrocodone was teratogenic in hamsters. Codeine, an opiate related to hydrocodone, increased resorptions and decreased fetal weight in rats. Because animal reproduction studies are not always predictive of human response, Guaifenesin and Hydrocodone Bitartrate Oral Solution should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Hydrocodone:
Hydrocodone has been shown to be teratogenic in hamsters when given in a dose approximately 27 times the maximum recommended human daily dose (MRHDD) (on a mg/m² basis at a single subcutaneous dose of 102 mg/kg on gestation day 8). Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In a study in which pregnant rats were dosed throughout organogenesis, a dose of codeine approximately 40 times the MRHDD of hydrocodone (on a mg/m² basis at an oral dose of 120 mg/kg/day of codeine) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, doses of codeine up to approximately 20 and 100 times, respectively, the MRHDD of hydrocodone (on a mg/m² basis at oral doses of 30 and 600 mg/kg/day, respectively), produced no adverse developmental effects.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

10 OVERDOSAGE
No human overdosage data are available for Guaifenesin and Hydrocodone Bitartrate Oral Solution.

Hydrocodone:
Overdosage with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, dizziness, ringing in the ears, confusion, blurred vision, eye problems, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

Guaifenesin:
Overdosage with guaifenesin can cause depression of the central nervous system. While present in polypharmacy overdoses, one case of overdose with only significant
levels of guaifenesin has been reported. Symptoms included slurred speech, shallow respirations, reduced heart rate with rhythm sinus bradycardia, followed by asystole.

Treatment of overdosage consists of discontinuation of Guaifenesin and Hydrocodone Bitartrate Oral Solution together with institution of appropriate therapy. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual sensitivity to opioids including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Hydrocodone is an opioid antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and physiological dependence.

Guaifenesin is an expectorant the action of which promotes or facilitates the removal of secretions from the respiratory tract. The precise mechanism of action of guaifenesin is not known; however, it is thought to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi. In turn, this may increase the efficiency of the cough reflex and facilitate removal of the secretions.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with Guaifenesin and Hydrocodone Bitartrate Oral Solution; however, published information is available for the individual active ingredients or related active ingredients.

Hydrocodone:
Carcinogenicity studies were conducted with codeine, an opiate related to hydrocodone. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 23 and 65 times, respectively, the MRHDD of hydrocodone on a mg/m² basis).

Guaifenesin:
No carcinogenicity studies were conducted in animals with guaifenesin. No chronic animal toxicity studies were identified.
2 Drug Information

2.1 Drug

Generic Name: Guaifenesin and Hydrocodone Bitartrate Oral Solution

Two active pharmaceutical ingredients (APIs) as follows:

Generic Name: Guaifenesin

CAS Registry Number: 93-14-1

Code Name: Not applicable

Chemical Name: (±)-3-(o-Methoxyphenoxy)-1,2-propanediol

Molecular Formula/Molecular Weight: C\textsubscript{10}H\textsubscript{14}O\textsubscript{4} / 198.22

Structure or Biochemical Description:

Figure 1: Guaifenesin

\[
\begin{align*}
&\begin{array}{c}
\text{O} \\
\text{OH} \\
\text{OH} \\
\text{OCH}_3
\end{array}
\end{align*}
\]

Pharmacologic Class: Expectorant

Generic Name: Hydrocodone Bitartrate

CAS Registry Number: 34195-34-1 Hydrate

Code Name: Not applicable

Chemical Name: Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5α)-, [R-(R*,R*)]-2,3-dihydroxybutanedioante (1:1), hydrate (2:5)

Molecular Formula/Molecular Weight: C\textsubscript{18}H\textsubscript{21}NO\textsubscript{3} · C\textsubscript{4}H\textsubscript{6}O\textsubscript{6} · 2.5 H\textsubscript{2}O / 494.5

Structure or Biochemical Description:
2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 101683, hydrocodone bitartrate and guaifenesin)
NDA 05213 (Hycozan, hydrocodone bitartrate and homatropine)
ANDAs 40613, 88008, and 88017 (hydrocodone bitartrate and homatropine methylbromide)

2.3 Drug Formulation

The drug product is an oral solution of 5 mL containing 200 mg guaifenesin and 2.5 mg hydrocodone bitartrate. The composition of the drug product is summarized in the tables below. The sponsor is proposing an original flavor (cherry punch) and an alternate flavor (raspberry) for the liquid. The levels of all excipients are within limits set in the inactive ingredients guide or are present at similar or higher levels in approved oral products.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight (mg) per 5 mL</th>
<th>% (w/w)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone Bitartrate, USP</td>
<td>2.500</td>
<td>0.044</td>
<td>Active ingredient</td>
</tr>
<tr>
<td>Guaifenesin, USP</td>
<td>200.00</td>
<td>3.518</td>
<td>Active ingredient</td>
</tr>
<tr>
<td>Propylene Glycol, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylparaben, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylparaben, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cherry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium Sorbate, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium Citrate, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saccharin Sodium, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citric Acid, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycerin, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purified Water, USP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Weight, 5 mL dose</td>
<td>5685.0 mg</td>
<td>100%</td>
<td>---</td>
</tr>
</tbody>
</table>

Reference ID: 3642455
Table 2: Summary of excipients in alternate raspberry flavor formulation

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight (mg) per 5 mL</th>
<th>% (w/w)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone Bitartrate, USP</td>
<td>2.560</td>
<td>0.044</td>
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</tr>
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<td>200.00</td>
<td>3.518</td>
<td>Active ingredient</td>
</tr>
<tr>
<td>Propylene Glycol, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylparaben, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylparaben, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raspberry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium Sorbate, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium Citrate, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saccharin Sodium, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citric Acid, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycerin, NF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purified Water, USP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Weight, 5 mL dose</strong></td>
<td><strong>5685.0 mg</strong></td>
<td><strong>100%</strong></td>
<td><strong>---</strong></td>
</tr>
</tbody>
</table>

2.4 Comments on Novel Excipients

The artificial flavoring raspberry is not listed in the IIG database however it is present in Liquituss GG, an OTC oral guaifenesin solution. The sponsor provided a list of ingredients contained in the raspberry flavoring from the manufacturer in addition to a letter of authorization for DMF #. The ingredients listed by the manufacturer in the raspberry flavoring are . This flavoring is also stated by the manufacturer as Generally Recognized As Safe (GRAS).

The CMC reviewer has confirmed that the proposed flavorings are all stated as GRAS with each ingredient having a FEMA number in the DMF (email communication with Dr. Ying Wang, dated May 30, 2014).

2.5 Comments on Impurities/Degradants of Concern

All impurities and degradants are within limits in ICH Qualification Thresholds for drug substances (ICH Q3A(R)) and drug products (ICH Q3B(R)).
2.6 Proposed Clinical Population and Dosing Regimen

5 mL of the solution for oral administration contains 2.5 mg of hydrocodone bitartrate and 200 mg of guaifenesin. The dosing regimen is 10 mL every 4 to 6 hours for patients 18 years of age and older, not to exceed 6 doses (60 mL) in 24 hours.

Table 3: Proposed clinical dosing regimen

<table>
<thead>
<tr>
<th>Subject Age</th>
<th>Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 18 years</td>
<td>400 mg guaifenesin / 5 mg hydrocodone bitartrate every 4 to 6 hours (10 mL)</td>
</tr>
</tbody>
</table>

2.7 Regulatory Background

IND 101683: A pre-IND meeting was held on April 14, 2008 (for details see meeting minutes dated March 30, 2008). The Agency agreed that no additional nonclinical studies would be required for IND/NDA submission based upon the approved NDA products and the OTC monograph. The Agency also noted that the sponsor should monitor impurities and degradants during product development, particularly for structures similar to hydrocodone which may have genotoxic potential. The sponsor submitted IND 101683 on February 27, 2009 (for details see nonclinical review by Dr. Marcie L. Wood, dated March 25, 2009) for a fixed-dose combination product of hydrocodone bitartrate and guaifenesin.

NDA 205474: A pre-NDA meeting was held on November 9, 2011 (for details see meeting minutes dated December 8, 2011). There were no nonclinical questions, however the Agency requested that the sponsor provide information pertaining to the approved use of the proposed new flavoring agent in drugs or food in the U.S. and/or safety information for the flavoring agent as a whole or all individual ingredients. The Agency again reminded the sponsor of the requirement to address impurities and degradants, as necessary. The sponsor submitted NDA 205474 on January 14, 2014, for a fixed-dose combination product of hydrocodone bitartrate and guaifenesin. The CMC reviewer requested a Pharmacology/Toxicology consult for evaluation of extractables (Email correspondence from Dr. Ying Wang dated 6/11/14). The Pharmacology/Toxicology assessment of extractables is addressed in a separate review.

3 Studies Submitted

None

4 Pharmacology

No studies were submitted or reviewed.
5 Pharmacokinetics/ADME/Toxicokinetics
No studies were submitted or reviewed.

6 General Toxicology
No studies were submitted or reviewed.

7 Genetic Toxicology
No studies were submitted or reviewed.

8 Carcinogenicity
No studies were submitted or reviewed.

9 Reproductive and Developmental Toxicology
No studies were submitted or reviewed.

10 Special Toxicology Studies
No studies were submitted or reviewed.

11 Integrated Summary and Safety Evaluation
The proposed fixed dose combination product in the current 505(b)(2) NDA is an aqueous oral solution containing guaifenesin and hydrocodone bitartrate. Guaifenesin is a recognized expectorant and hydrocodone is an opioid antitussive and analgesic derived from codeine. No nonclinical pharmacology and toxicology studies were conducted with the proposed combination of guaifenesin and hydrocodone bitartrate. The sponsor is relying upon the previously approved product NDAs, OTC monograph reviews, and labeling from the individual products. Both guaifenesin and hydrocodone bitartrate are widely used in the United States.

The OTC monograph 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive drug with any single monograph nasal decongestant and any single expectorant to be a permitted combination in OTC cough/cold products. Although hydrocodone is not an OTC monograph antitussive, hydrocodone combination products containing monograph active ingredients have been accepted based on the prior regulatory precedent approval of Tussionex® (the combination of hydrocodone and chlorpheniramine; NDA 19-111).
Guaifenesin:
Guaifenesin has been widely used for many years in the US. It is recognized in OTC monograph 21CFR 341.18 as an expectorant. Guaifenesin is a Pregnancy Category C drug. Chronic toxicity studies with guaifenesin have demonstrated no adverse pathological findings based on the OTC monograph review. Animal studies to assess carcinogenicity, genotoxicity, fertility, developmental or teratogenic effects of guaifenesin have not been conducted.

Hydrocodone bitartrate:
Hydrocodone bitartrate is a narcotic antitussive and analgesic that has been widely used in the United States for many years. Hydrocodone bitartrate is a recognized antitussive, with efficacy established in Drug Efficacy Study Implementation (DESI) Notice 5213, dated June 1, 1982. Although the exact mechanism of action of hydrocodone is not known, it is believed to directly act on the cough center in the medulla of the brain.

The proposed combination oral solution is intended to provide symptomatic relief of cough associated with the common cold. The proposed doses and dosing regimen are within the dosage limits recommended in the OTC monograph for guaifenesin (21CFR 341.78) and in approved products containing hydrocodone. The table below summarizes the recommended dosages for guaifenesin and hydrocodone.

Table 4: Recommended dosing for guaifenesin and hydrocodone bitartrate monoprodutcs

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>(b) (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guaifenesin Dosage</td>
<td>200 – 400 mg</td>
<td></td>
</tr>
<tr>
<td>NTE in 24 hours</td>
<td>2400 mg</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone bitartrate Dosage</td>
<td>5 mg</td>
<td></td>
</tr>
<tr>
<td>NTE in 24 hours</td>
<td>30 mg</td>
<td></td>
</tr>
</tbody>
</table>

NTE, not to exceed

Recommendation: From a nonclinical perspective, approval is recommended for the application. There are no unresolved nonclinical issues.

Labeling Review

Review of labeling is based upon comparison to labeling contained in other approved products containing hydrocodone bitartrate (Zutripro® Oral Solution, NDA 22439). The following nonclinical sections were reviewed to verify that the language for hydrocodone bitartrate mirrors the June 8, 2011, approved labeling for Zutripro® Oral Solution. Changes to the proposed labelling are indicted in the table below. Changes included the following:
1. Hydrocodone dose ratios in sections 8.1 and 13.1 were updated and based upon the maximum daily dose of hydrocodone for Guaifenesin and hydrocodone oral solution (i.e. 30 mg/day).

2. (b)(4)

3. (b)(4)

4. A statement was added to indicate that no information on the carcinogenicity, genotoxicity, or reproductive toxicology of guaifenesin is available.

<table>
<thead>
<tr>
<th>Section of label</th>
<th>Sponsor's proposed wording</th>
<th>Reviewer's changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 USE IN SPECIFIC POPULATIONS</td>
<td>(b)(4)</td>
<td><strong>Teratogenic Effects:</strong> Pregnancy Category C. There are no adequate and well controlled studies of Guaifenesin and Hydrocodone Bitartrate Oral Solution in pregnant women. Reproductive toxicity studies have not been conducted with Guaifenesin and Hydrocodone Bitartrate Oral Solution; however, studies are available with an individual active ingredient or related active ingredient. Hydrocodone was teratogenic in hamsters. Codeine, an opiate related to hydrocodone, increased resorptions and decreased fetal weight in rats. Because animal reproduction studies are not always predictive of human response, Guaifenesin and Hydrocodone Bitartrate Oral Solution should be used during pregnancy only if the benefit justifies the potential risk to the fetus. <strong>Hydrocodone:</strong> Hydrocodone has been shown to be teratogenic in hamsters when given in a dose approximately 27 times the</td>
</tr>
</tbody>
</table>
maximum recommended human daily dose (MRHDD) (on a mg/m² basis at a single subcutaneous dose of 102 mg/kg on gestation day 8). Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In a study in which pregnant rats were dosed throughout organogenesis, a dose of codeine approximately 40 times the MRHDD of hydrocodone (on a mg/m² basis at an oral dose of 120 mg/kg/day of codeine) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, doses of codeine up to approximately 20 and 100 times, respectively, the MRHDD of hydrocodone (on a mg/m² basis at oral doses of 30 and 600 mg/kg/day, respectively), produced no adverse developmental effects.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use.
<table>
<thead>
<tr>
<th>10 OVERDOSAGE</th>
<th>No changes</th>
</tr>
</thead>
</table>

or dose.
## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

No changes
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with Guaifenesin and Hydrocodone Bitartrate Oral Solution; however, published information is available for the individual active ingredients or related active ingredients.

Hydrocodone:
Carcinogenicity studies were conducted with codeine, an opiate related to hydrocodone. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 23 and 65 times, respectively, the MRHDD of hydrocodone on a mg/m² basis).

Guaifenesin:
Carcinogenicity, genotoxicity, or reproductive toxicology studies have not been conducted with guaifenesin.
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/s/

NIKUNJ S PATEL
10/10/2014

MARCIE L WOOD
10/10/2014
Nonclinical Safety Evaluations of Extractables in guaifenesin and hydrocodone bitartrate oral solution (NDA 205-474)

General Information
Submissions: SDN 1, submitted on January 14, 2014, and SDN 20, submitted on August 11, 2014
Applicant: Sovereign Pharmaceuticals, LLC
Drug Product: Guaifenesin and hydrocodone bitartrate oral solution
Request From: Ying Wang, CMC Reviewer, ONDQA
Date of Request: June 11, 2014
Date Received: June 11, 2014
Materials Reviewed: HDPE Container Closure System: Safety of Extractable and Leachables (SDN1, Tab 3.2.P.7)

Sovereign’s response to the Agency’s information request issued on July 21, 2014. The response was submitted on August 11, 2014 (SDN 20).

Summary
This review evaluates the safety of extractables for guaifenesin and hydrocodone bitartrate oral solution proposed by Sovereign Pharmaceuticals. Sovereign Pharmaceuticals conducted a study to assess potential extractables from the container closure system for their proposed combination product guaifenesin and hydrocodone bitartrate oral solution. The solvents used in the study were isopropanol, hexane, and water. The proposed drug product is formulated in .

A total of 11 and 12 compounds were identified following isopropanol and hexane extraction, respectively. No extractables were detected following water extraction. The extractables belong to 3 chemical classes: higher . No further nonclinical studies are recommended based upon the extractables identified as they are not considered to pose a safety concern using a weight of evidence approach. In addition, none of the identified extractables are water soluble and therefore would not be expected to be found in the aqueous drug product.
Background

The sponsor submitted a 505(b)(2) NDA for guaifenesin and hydrocodone bitartrate oral solution on January 14, 2014. This review conducts nonclinical safety evaluations of the extractables in the container closure system of the proposed drug product guaifenesin and hydrocodone bitartrate oral solution. The review was requested by Dr. Ying Wang of ONDQA on June 11, 2014.

Evaluation

This review evaluates the safety of the extractables in guaifenesin and hydrocodone bitartrate oral solution using data provided by the applicant in a report entitled “HDPE Container Closure System: Safety of Extractable and Leachables” and other available information. The applicant provided an extractables profile of the container closure system for the to-be-marketed product. Water, isopropanol, and hexane were used as solvents, with hexane representing the “worst case scenario” for extractables. A total of 12 compounds were identified as extractables using hexane, 11 of which were also identified using isopropanol extraction. No extractables were identified when using water as a solvent. The identified compounds belong to 3 structural groups: [8][4]. It should be noted that the proposed product is formulated in an aqueous solution [6][4] and that none of the extractables identified are water soluble. Table 1 presents expected maximum exposure levels for the 12 extractables identified using hexane and isopropanol.
Table 1: Estimated exposure of extractables following isopropanol or hexane extraction

<table>
<thead>
<tr>
<th>Extractable</th>
<th>CAS #</th>
<th>Isopropanol (µg/day)</th>
<th>Hexane (µg/day)</th>
<th>Isopropanol (µg/day)</th>
<th>Hexane (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

The current review conducts the safety evaluations of the extractables based on maximum anticipated adult daily exposure levels. While the applicant provided a safety evaluation of each of these compounds in the report, maximum daily anticipated exposures for each extractable were not included. Therefore an information request (IR) was sent to the sponsor on July 21, 2014 to request this information. The sponsor responded to the IR on August 11, 2014, with a summary and rationale for calculating the estimated maximum daily exposure levels for each extractable.

The sponsor rationalized that the drug product will be exposed to only the inner surface of the container closure system and therefore estimated the maximum daily exposure to be half of the total amount of each compound extracted. This review, however, considered the total amount of each compound extracted as a worst case scenario. Therefore the values calculated in table 1 are based upon anticipated exposure to all surfaces of the container closure system.

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Conclusion
There is no nonclinical safety concern for the 12 extractable compounds identified under the conditions of the study.

Recommendation
The weight of evidence indicates that the extractables identified under the conditions of the study do not pose a safety concern, therefore further nonclinical studies to address the safety of the container closure system are not recommended.
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/s/

NIKUNJ S PATEL
10/10/2014

MARCIE L WOOD
10/10/2014
**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement**

**NDA Number:** 205474  
**Applicant:** Sovereign Pharmaceuticals, Inc.  
**Stamp Date:** 1/14/2014  
**Drug Name:** Hydrocodone bitartrate/guaifenesin oral solution  
**NDA/BLA Type:** Standard

On **initial** overview of the NDA/BLA application for filing:

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?</td>
<td></td>
<td></td>
<td>Not applicable. A pharmacology/toxicology section was not included in this 505(b)(2) submission.</td>
</tr>
<tr>
<td>2 Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?</td>
<td></td>
<td></td>
<td>Not applicable. Refer to comment under #1.</td>
</tr>
<tr>
<td>3 Is the pharmacology/toxicology section legible so that substantive review can begin?</td>
<td></td>
<td></td>
<td>Not applicable. Refer to comment under #1.</td>
</tr>
<tr>
<td>4 Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?</td>
<td></td>
<td></td>
<td>Not applicable as no toxicology studies were requested or submitted.</td>
</tr>
<tr>
<td>5 If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).</td>
<td></td>
<td></td>
<td>Not applicable. Refer to comment under #4.</td>
</tr>
<tr>
<td>6 Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?</td>
<td></td>
<td></td>
<td>Not applicable. Refer to comment under #4.</td>
</tr>
<tr>
<td>7 Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?</td>
<td></td>
<td></td>
<td>Not applicable. Refer to comment under #4.</td>
</tr>
</tbody>
</table>
### PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

<table>
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<tr>
<td>8</td>
<td></td>
<td></td>
<td>Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?</td>
</tr>
<tr>
<td>9</td>
<td>X</td>
<td></td>
<td>Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57?</td>
</tr>
<tr>
<td>10</td>
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<td></td>
<td>Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)</td>
</tr>
<tr>
<td>11</td>
<td>X</td>
<td></td>
<td>Has the applicant addressed any abuse potential issues in the submission?</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td>If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?</td>
</tr>
</tbody>
</table>

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? **Yes**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

No comments.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No issues from the nonclinical perspective.

---

Nikunj S. Patel, Ph.D.
Reviewing Pharmacologist Date

Marcie L. Wood, Ph.D.
Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3470852
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/s/

NIKUNJ S PATEL
03/13/2014

MARCIE L WOOD
03/14/2014

Reference ID: 3470852