APPLICATION NUMBER:

208085Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
# NDA/BLA Multi-Disciplinary Review and Evaluation

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<td>Priority or Standard</td>
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<tr>
<td>Submit Date(s)</td>
<td>October 30, 2017</td>
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<tr>
<td>Received Date(s)</td>
<td>October 30, 2017</td>
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<td>PDUFA Goal Date</td>
<td>April 30, 2018</td>
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<tr>
<td>Division/Office</td>
<td>Division of Pulmonary, Allergy, and Rheumatology Products</td>
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<tr>
<td>Review Completion Date</td>
<td>April 13, 2018</td>
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<tr>
<td>Established Name</td>
<td>Hydrocodone Bitartrate/Guaifenesin 5mg/400mg</td>
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| Pharmacologic Class     | Opioid agonist                           |
| Code name               |                                          |
| Applicant               | ECI Pharmaceuticals                      |
| Formulation(s)          | Tablet                                   |
| Dosing Regimen          | 1 tablet every 4 to 6 hours, not to exceed 6 doses in 24 hours |
| Applicant Proposed Indication(s)/Population(s) | For use in symptomatic relief of cough, to loosen mucus (mucus) |
|                         | For use in symptomatic relief of cough and to loosen mucus associated with the common cold in patients 18 years of age and older |

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1 There is no approved tradename for this product. FDA issued a proprietary name denied letter to ECI Pharmaceuticals on February 28, 2018. There have been no new proprietary name review requests submitted by the applicant.
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NDA Multi-Disciplinary Review and Evaluation (NDA 208085)
Hydrocodone Bitartrate/Guaifenesin 5mg/400mg

**Reviewers of Multi-Disciplinary Review and Evaluation**

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<tr>
<td>Regulatory Project Manager</td>
<td>LeAnn Brodhead, Pharm D</td>
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<tr>
<td>Nonclinical Reviewer</td>
<td>Yu-Mee Kim, PhD</td>
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<tr>
<td>Nonclinical Team Leader</td>
<td>Carol Galvis, PhD</td>
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<td>Office of Clinical Pharmacology Reviewer(s)</td>
<td>Suryanarayana Sista, PhD</td>
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<tr>
<td>Office of Clinical Pharmacology Team Leader(s)</td>
<td>Bhawana Saluja, PhD</td>
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<tr>
<td>Clinical Reviewer</td>
<td>Xu Wang, MD</td>
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<tr>
<td>Clinical Team Leader</td>
<td>Stacy Chin, MD</td>
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<tr>
<td>Cross-Disciplinary Team Leader</td>
<td>Bhawana Saluja, PhD</td>
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<td>Division Director (DPARP)</td>
<td>Lydia Gilbert-McClain, MD</td>
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**Additional Reviewers of Application**

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<tr>
<td>OPQ</td>
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<tr>
<td>Microbiology</td>
<td>Xiaoying Zhang</td>
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<tr>
<td>OPDP</td>
<td>Kyle Snyder</td>
</tr>
<tr>
<td>OSE/DMEPA</td>
<td>Lissa Owens/Sarah Vee</td>
</tr>
<tr>
<td>Patient Labeling Team</td>
<td>Nyedra Booker/Marcia Britt Williams</td>
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OPQ=Office of Pharmaceutical Quality  
OPDP=Office of Prescription Drug Promotion  
OSE= Office of Surveillance and Epidemiology  
DMEPA=Division of Medication Error Prevention and Analysis
Glossary

- **AC**: advisory committee
- **ADME**: absorption, distribution, metabolism, excretion
- **AE**: adverse event
- **BLA**: biologics license application
- **BPCA**: Best Pharmaceuticals for Children Act
- **BRF**: Benefit Risk Framework
- **CBER**: Center for Biologics Evaluation and Research
- **CDER**: Center for Drug Evaluation and Research
- **CDRH**: Center for Devices and Radiological Health
- **CDTL**: Cross-Discipline Team Leader
- **CFR**: Code of Federal Regulations
- **CMC**: chemistry, manufacturing, and controls
- **COSTART**: Coding Symbols for Thesaurus of Adverse Reaction Terms
- **CRF**: case report form
- **CRO**: contract research organization
- **CRT**: clinical review template
- **CSR**: clinical study report
- **CSS**: Controlled Substance Staff
- **DHOT**: Division of Hematology Oncology Toxicology
- **DMC**: data monitoring committee
- **ECG**: electrocardiogram
- **eCTD**: electronic common technical document
- **ETASU**: elements to assure safe use
- **FDA**: Food and Drug Administration
- **FDAAA**: Food and Drug Administration Amendments Act of 2007
- **FDASIA**: Food and Drug Administration Safety and Innovation Act
- **GCP**: good clinical practice
- **GRMP**: good review management practice
- **ICH**: International Conference on Harmonization
- **IND**: Investigational New Drug
- **ISE**: integrated summary of effectiveness
- **ISS**: integrated summary of safety
- **ITT**: intent to treat
- **MedDRA**: Medical Dictionary for Regulatory Activities
- **mITT**: modified intent to treat
- **NCI-CTCAE**: National Cancer Institute-Common Terminology Criteria for Adverse Event
- **NDA**: new drug application
- **NME**: new molecular entity
<table>
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<th>Acronym</th>
<th>Description</th>
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<td>Office of Surveillance and Epidemiology</td>
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<td>OSI</td>
<td>Office of Scientific Investigation</td>
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<td>PBRER</td>
<td>Periodic Benefit-Risk Evaluation Report</td>
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<td>pharmacodynamics</td>
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<td>PI</td>
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<td>post-marketing commitment</td>
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<td>PMR</td>
<td>post-marketing requirement</td>
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<tr>
<td>PP</td>
<td>per protocol</td>
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<tr>
<td>PPI</td>
<td>patient package insert</td>
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<tr>
<td>PREA</td>
<td>Pediatric Research Equity Act</td>
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<tr>
<td>PRO</td>
<td>patient reported outcome</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update report</td>
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<tr>
<td>REMS</td>
<td>risk evaluation and mitigation strategy</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SGE</td>
<td>special government employee</td>
</tr>
<tr>
<td>SOC</td>
<td>standard of care</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment emergent adverse event</td>
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</table>
Executive Summary

1.1. Product Introduction

This current resubmission by the Applicant, ECI Pharmaceuticals, LLC, received October 30, 2017, is a 505(b)(2) new drug application based on a clinical pharmacology program for a hydrocodone bitartrate and guaifenesin combination immediate-release oral tablet with a proposed indication for the symptomatic relief of cough and to loosen mucus associated with the common cold. This is the second submission for this proposed cough and cold product. The previous submission, dated April 13, 2016, contained data from two clinical pharmacology study (Study 102-13-US and 099-14-US). These studies were reviewed and a CR action was taken due to failure to demonstrate bioequivalence (BE) for the guaifenesin drug component.

For this submission, the Applicant submitted a new relative bioavailability study (Study 11774901) to support the BE of the hydrocodone and guaifenesin component of their proposed product to that of an approved reference product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

As the Applicant has not conducted clinical trials to assess the safety and efficacy of their proposed combination product, the development program for this application is based on demonstration of BE to the reference ingredients of the combination product. In this submission, the Applicant submitted one clinical pharmacology study (Study 11774901) to support BE of hydrocodone and guaifenesin to the listed reference product. The BE for hydrocodone and guaifenesin was demonstrated (the 90% CI for the ratio of the geometric means of the test/reference products for the AUC and $C_{\text{max}}$ were within $80 – 125\%$) in Study 11774901, a single-dose, randomized, three-treatment crossover study under fasting condition in 42 male and female healthy volunteers aged 18 to 45 years. In this study, the geometric mean ratio (test/listed) of $AUC_{0-\infty}$, $AUC_{0-t}$, and $C_{\text{max}}$ for hydrocodone were 0.97 (90% CI = 0.94, 1.00), 0.97 (90% CI = 0.94, 1.00) and 0.92 (90% CI = 0.87, 0.96), respectively. The geometric mean ratio (test/listed) of $AUC_{0-\infty}$, $AUC_{0-t}$, and $C_{\text{max}}$ for guaifenesin were 1.01 (90% CI = 0.96, 1.06), 1.00 (90% CI = 0.95, 1.06) and 0.99 (90% CI = 0.89, 1.10), respectively (see the clinical pharmacology section of the Unireview by Dr. Sury Sista).

The NDA also provides labeling consistent with the Pregnancy and Lactation Labeling Rule (PLLR).
1.3. **Benefit-Risk Assessment**

**Benefit-Risk Summary and Assessment**
This is a 505(b)(2) application for an immediate-release oral tablet fixed-dose combination drug product containing hydrocodone bitartrate and guaifenesin (5 mg and 400 mg, respectively). The Applicant uses HycoDan (NDA 05213, hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg Tablet) as the reference drug for hydrocodone component of the combination product. The Applicant cites OTC Monograph 21 CFR 341.18 to support guaifenesin component of the combination drug product. The proposed drug product depends on the bioequivalence to the reference drugs to support its safety and effectiveness. No clinical efficacy and safety studies were submitted to support this application.

The clinical pharmacology study demonstrated the bioequivalence between the hydrocodone and guaifenesin of the proposed drug product and the reference drugs. The adverse events in the study were low and revealed no new safety signals. No unexpected adverse events occurred.

The safety and efficacy of the proposed drug product relies primarily on the Agency’s previous findings of approved hydrocodone product HycoDan tablets and the OTC monograph for guaifenesin. Therefore, the safety and efficacy of the proposed drug product is determined by the bioequivalence to the reference drugs. The overall risk-to-benefit profile of this hydrocodone and guaifenesin tablet for symptomatic relief of cough and to loosen mucus associated with the common cold in patients 18 years of age and older is favorable. The pivotal clinical pharmacology study, the OTC monograph, and the reference products all support the efficacy and safety of the hydrocodone and guaifenesin tablets.

---

Bhawana Saluja, PhD
Cross-Disciplinary Team Leader
2 Therapeutic Context

Analysis of Condition

FDA published a final Federal Register (FR) notice of its intention to take enforcement action against illegally marketed cough/cold drug products containing hydrocodone on October 1, 2007 [Docket No. 2007N-0353]. To date, several hydrocodone-containing cough/cold products have been approved.

Hydrocodone is currently available in combination with guaifenesin, chlorpheniramine maleate, and pseudoephedrine HCl in NDAs and multiple generic antitussive drugs. In addition, hydrocodone is available in the United States in tablet and capsule formulations as analgesic medications at higher doses than antitussives, such as Vicoprofen (NDA 20716), Vicodin and Vicodin HP (ANDA 88058, ANDA 40117), Lortab (ANDA 40100, ANDA 87722), and Anexsia (ANDA 40405, ANDA 40409, ANDA [b] 40409, ANDA 40686, ANDA 89160).

Guaifenesin is currently approved in the United States in tablet (Mucinex ER, NDA 21282), in combination with dextromethorphan (Mucinex TM DM, NDA 21620), hydrocodone bitartrate (NDA 205474), and pseudoephedrine HCl (NDA 21585). These products are extended release formulations. Guaifenesin is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

2.2. Analysis of Current Treatment Options

Table 1. Currently Available Treatments for Proposed Indication

<table>
<thead>
<tr>
<th>Product(s) Name</th>
<th>Relevant Indication</th>
<th>Year of Approval</th>
<th>Dosing/Administration</th>
<th>Efficacy Information</th>
<th>Important Safety and Tolerability Issues</th>
<th>Other Comments</th>
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<tr>
<td>Obredon (hydrocodone and guaifenesin) oral solution</td>
<td>For symptomatic relief of cough and to loosen mucus associated with the common cold in patients ≥18 years.</td>
<td>2014</td>
<td>Oral solution 10 mL every 4 to 6 hours, not to exceed 6 doses (60 mL) in 24 hours.</td>
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<tr>
<td>Flowtuss (hydrocodone)</td>
<td>For symptomatic</td>
<td>2015</td>
<td>Oral solution 10 mL every</td>
<td></td>
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<td>Treatment</td>
<td>Description</td>
<td>Dosage</td>
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<tr>
<td>Hydrocodone Bitartrate/Guaifenesin</td>
<td>Oral solution for relief of cough and to loosen mucus associated with the common cold in patients ≥18 years.</td>
<td>4 to 6 hours, not to exceed 6 doses (60 mL) in 24 hours.</td>
<td></td>
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Other Treatments – [Combine by Pharmacologic Class, if relevant]

**CFR 21 341.14 Antitussive**

(a) Oral antitussives

(1) Chlophedianol hydrochloride

(2) Codeine ingredients
   (i) Codeine
   (ii) Codeine phosphate
   (iii) Codeine sulfate

(3) Dextramethorphan

(4) Dextromethorphan hydrobromide

(5) Diphenhydramine citrate

(6) Diphenhydramine hydrochloride

(b) Topical antitussives

(1) Camphor

(2) Menthol

**CFR 21 341.18 Expectorant**

Guaifenesin
3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Hydrocodone is a commonly used antitussive. The safety and effectiveness of hydrocodone as a prescription drug for the symptomatic relief of cough are supported by DESI review and by the FDA approved product Hycodan (NDA 05213). Hydrocodone is an opioid, a schedule II controlled substance as a single ingredient (21 CFR 1308.12). Also, according to 21 CFR 1308 published on February 27, 2014 in Federal Register Volume 79, Number 39, all HC combination products (analgesic and antitussive) are placed into schedule II controlled substance as well.

Hydrocodone, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of hydrocodone and guaifenesin is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50).

However, there is a regulatory precedent regarding the combination of hydrocodone with an OTC monograph product. Briefly, during the FDA deliberations on the approvability of Tussionex Penkkinetic extended release suspension (NDA 19-111) at the Center Level the FDA determined that clinical studies are not necessary for the combination of hydrocodone and a permitted OTC monograph ingredient. The development program for Tussionex Penkkinetic was comprised of 3 bioavailability studies and no clinical studies. Based on this prior precedent, the Division has accepted the conclusion that for a hydrocodone combination product containing monograph active ingredients, a drug development plan does not need to establish the efficacy, safety, or the contribution of hydrocodone or an OTC monograph ingredient to the efficacy and safety of the combination product, and that approval can be based on establishment of bioequivalence.

Guaifenesin (GU) is considered to be generally recognized as safe and effective (GRASE) as an expectorant [21 CFR 341.18].

3.2 Summary of Presubmission/Submission Regulatory Activity

6/23/2010: ECI submitted a pre-IND meeting request (pre-IND 109,251). Upon review of the briefing document submitted on 8/21/2010, the Division cancelled the meeting, but provided comments on the drug development program in a facsimile dated 9/21/2010. The Division’s comments stated that for the proposed immediate release hydrocodone and guaifenesin tablet 505 (b)(2) would be an appropriate pathway, and a single dose bioequivalence (BE) study comparing the proposed drug product against each of the active individual components administered separately under fasted state and a food effect study to evaluate the effect of food ion the proposed drug product would be required.

02/25/2011: ECI had a Type B meeting with the Division further discuss the drug development program for the proposed drug product. In addition to comments on issues of product quality
and stability for the proposed drug product and reference drugs for the pharmacology studies, the Division advised that additional studies might be necessary to support efficacy and safety of the proposed product in pediatric population.

11/11/2013: ECI submitted an opening IND (IND 109,251) including protocols for 2 clinical pharmacology studies (a single dose BE study 102-13-US and a food effect study).

04/13/2016: NDA 208085 N000 was filed for the proposed drug product.

02/23/2017: Complete Response Letter was issued. The clinical pharmacology study submitted to support this application (study 102-13-US) showed that the guaifenesin component of the proposed combination product provided AUC comparable to the reference guaifenesin product, but the 90% CI of the geometric mean ratio of the Cmax for guaifenesin in the proposed product was lower (76.68%) than what the Agency considers to be acceptable to establish comparative bioavailability. As a result, this application cannot rely on the OTC monograph for guaifenesin without additional data or an alternative justification that scientifically bridges the guaifenesin component of the proposed product to that monograph. A bridge is necessary to demonstrate that reliance on the guaifenesin OTC monograph is appropriate. See Section 6 Clinical Pharmacology for details of the requirements to address the deficiency.

10/30/2017: ECI submitted a Class 2 resubmission. The resubmission presented the findings of a new single dose BE study (Study 11774901).
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Integrity and Surveillance (OSIS)

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) concluded that the clinical data from the audited study to be reliable and no significant deficiencies were observed. OSIS recommends that the data for the clinical portion of study submitted to NDA 208085 be accepted. [NDA 208-085, MEMORANDUM, Arindam Dasgupta, PhD, Division of New Drug Bioequivalence Evaluation Office of Study Integrity and Surveillance (OSIS), 12/6/2016]

4.2 Product Quality

Novel excipients: No
Any impurity of concern: No

The proposed product in this NDA is a fixed-dose combination of 5 mg hydrocodone bitartrate and 400 mg guaifenesin as an immediate-release tablet dosage form (one strength combination). Inactive ingredients include crospovidone, microcrystalline cellulose, stearic acid, talc, and magnesium stearate. The dosage form is an immediate release, white, capsule-shaped tablet, embossed with “ECI” and “601” on opposite sides. The drug substance hydrocodone bitartrate, USP, is manufactured by . The drug substance guaifenesin is manufactured by . The drug product hydrocodone bitartrate and guaifenesin tablets is manufactured, processed, and packaged by ECI Pharmaceuticals, LLC, Fort Lauderdale, Florida.

In the first cycle of review, the CMC reviewers noted that the drug product is manufactured by

Inspection of the hydrocodone and guaifenesin drug substance manufacturing sites yielded acceptable outcomes. During the inspection of the ECI Pharmaceuticals LLC, FEI 3008798439, in Fort Lauderdale, Florida manufacturing facility for this NDA, the field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. These issues have been resolved and the facilities team recommends the application be approved.

Based on the review of the resubmission and recommendations from the drug substance, process, and facilities teams, CMC recommends approval of this application.
4.3. **Clinical Microbiology**

Not applicable.

4.4. **Devices and Companion Diagnostic Issues**

Not applicable.
5 **Nonclinical Pharmacology/Toxicology**

5.1. **Executive Summary**

For nonclinical pharmacology and toxicology support of this application, no new nonclinical data was submitted. The sponsor relied on previous safety and efficacy findings of Tussigon® (hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg) Tablets of king Pharmaceuticals (ANDA088508) for the hydrocodone component and Guaifenesin OTC monograph (21 CFR 314.18) for the guaifenesin component. The full nonclinical review was completed and uploaded into DARRTS on January 4, 2017. The label will be updated with the Opioid Cough/Cold Drug Safety Labeling Changes (SLC).

As the recommended dosage of each active ingredient for this NDA is within the dose ranges recommended in OTC monograph (21 CFR 341.78 for guaifenesin) and the approved products, we recommend this application for approval.

5.2. **Referenced NDAs, BLAs, DMFs**

None

5.3. **Pharmacology**

Not applicable.

5.4. **ADME/PK**

Not applicable.

5.5. **Toxicology**

5.5.1. **General Toxicology**

Not applicable.

5.5.2. **Genetic Toxicology**

See section 5.5.3. Carcinogenicity.
5.5.3. Carcinogenicity

From the Label (section 13.1)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity, mutagenicity, and fertility studies have not been conducted with TRADENAME; 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. Two-year studies in F344/N rats and B6C3F1 mice were conducted to assess the carcinogenic potential of codeine. No evidence of tumorigenicity was observed in male and female rats at codeine dietary doses up to 70 and 80 mg/kg/day (approximately equivalent to 40 and 45 times the MRHD of hydrocodone on a mg/m2 basis, respectively). No evidence of tumorigenicity was observed in male and female mice at codeine dietary doses up to 400 mg/kg/day (approximately equivalent to 110 times the MRHD of hydrocodone on a mg/m2 basis).
Mutagenicity studies with hydrocodone have not been conducted.
Fertility studies with hydrocodone have not been conducted.

Guaifenesin
Carcinogenicity, mutagenicity, and fertility studies with guaifenesin have not been conducted.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
See section 5.4.3. Carcinogenicity for the Label section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Embryo-Fetal Development
From the Label section 8.1 Pregnancy

8.1 Pregnancy
Risk Summary
TRADENAME is not recommended for use in pregnant women, including during or immediately prior to labor.
Prolonged use of opioids during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.13), Clinical Considerations].
There are no available data with TRADENAME use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. Published studies with hydrocodone have reported inconsistent findings and have important methodological limitations (see Data).
Reproductive toxicity studies have not been conducted with TRADENAME; however, studies are available with individual active ingredients or related active ingredients (see Data).
In animal reproduction studies, hydrocodone administered by the subcutaneous route to pregnant hamsters during the period of organogenesis produced a teratogenic effect at a dose approximately 45 times the maximum recommended human dose (MRHD) (see Data).
Guaifenesin administered by the oral route to pregnant rats during the period of organogenesis was embryolethal at a dose approximately 1 times the MRHD and produced teratogenic effects at a dose approximately 2 times the MRHD (see Data).
Based on the animal data, advise pregnant women of the potential risk to a fetus.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.
Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.
Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.13)].
Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate.
Opioids, including TRADENAME, can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioids during labor for signs of excess sedation and respiratory depression.
Data

Human Data

Hydrocodone

A limited number of pregnancies have been reported in published observational studies and postmarketing reports describing hydrocodone use during pregnancy. However, these data cannot definitely establish or exclude any drug-associated risk during pregnancy. Methodological limitations of these observational studies include small sample size and lack of details regarding dose, duration and timing of exposure.

Animal Data

Reproductive toxicity studies have not been conducted with TRADENAME; however, studies are available with individual active ingredients or related active ingredients.

Hydrocodone

In an embryofetal development study in pregnant hamsters dosed on gestation day 8 during the period of organogenesis, hydrocodone induced cranioschisis, a malformation, at approximately 45 times the MRHD (on a mg/m2 basis with a maternal subcutaneous dose of 102 mg/kg). Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In an embryofetal development study in pregnant rats dosed throughout the period of organogenesis, codeine increased resorptions and decreased fetal weights at a dose approximately 65 times the MRHD of hydrocodone (on a mg/m2 basis with a maternal oral dose of codeine at 120 mg/kg/day); however, these effects occurred in the presence of maternal toxicity. In embryofetal development studies with pregnant rabbits and mice dosed throughout the period of organogenesis, codeine produced no adverse developmental effects at doses approximately 30 and 160 times, respectively, the MRHD of hydrocodone (on a mg/m2 basis with maternal oral doses of codeine at 30 mg/kg/day in rabbits and 600 mg/kg/day in mice).

Guaifenesin

In an embryofetal development study in pregnant rats dosed throughout the period of organogenesis, guaifenesin resulted in fetal death at doses approximately 1 times the MRHD (on a mg/m2 basis with maternal oral doses of 350 mg/kg/day and higher). Guaifenesin also induced hemorrhagic spots and decreases in fetal weight and lengths of full body, skull, fore- and hind-limbs, and tail at doses 1 times the MRHD (on a mg/m2 basis with maternal oral doses of 250 mg/kg/day and higher). Limb and tail defects, increased intercostal space, and improper development of limbs were observed at doses 2 times the MRHD (on a mg/m2 basis with maternal oral doses of 500 mg/kg/day and higher).

Prenatal and Postnatal Development

Not applicable.
5.5.5. Other Toxicology Studies

Not applicable.

Yu-Mee Kim, PhD
Primary Reviewer

Carol M. Galvis, PhD
Team Leader
6 Clinical Pharmacology

6.1. Executive Summary

ECI Pharmaceuticals, LLC (Applicant) submitted NDA 208085 under Section 505(b)(2) of the FD&C Act on 13 April 2016. This submission relied on the FDA’s previous finding of safety and effectiveness established for the following products:

i. Hycodan NDA 05213 (hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg Tablet, Endo Pharmaceuticals), and used ANDA 088508 Tussigon tablet, one of the Reference Standards for Hycodan (NDA 05213, discontinued), for conducting bioequivalence studies for the hydrocodone component of the proposed combination product.

ii. Over-the-counter (OTC) monograph for guaifenesin (21 CFR 314.18) for the guaifenesin component of the product.

Following a review of the April 2016 NDA submission, the application received a complete response from the Agency on 13 Feb 2017. The reasons cited were that the clinical pharmacology study submitted to support the application (Study 102-13-US) showed that the guaifenesin component of the proposed combination product provided AUC comparable to the reference guaifenesin product, however, the 90% CI of the geometric mean ratio of the Cmax for guaifenesin in the proposed product was lower (76.68%) than what the Agency considers to be acceptable to establish comparative bioavailability. As a result, the application could not rely on the OTC monograph for guaifenesin without additional data or an alternative justification that scientifically bridges the guaifenesin component of the proposed product to that monograph. A bridge was necessary to demonstrate that reliance on the guaifenesin OTC monograph is appropriate.

The applicant was informed that this deficiency may be addressed by performing any of the following:

a. Repeat the single-dose clinical pharmacology study to evaluate the relative bioavailability of your proposed hydrocodone 5 mg/guaifenesin 400 mg immediate release tablet compared to the individual reference products under the fasted state. If you choose to repeat the relative bioavailability study, the study should be designed carefully with considerations of the PK variability observed in your current program,

or

b. Because comparative bioavailability of the proposed combination product was not established, conduct a clinical development program with clinical efficacy and safety studies to support your combination product,

or

c. Evaluate whether there is a need to reformulate your combination product. If you reformulate the product, you must repeat the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the
The applicant responded to the complete response letter on 30 Oct 2017 with a Class 2 resubmission. The resubmission presented the findings of a new relative bioavailability study (Study 11774901). The Applicant is requesting the approval of a combination product of hydrocodone bitartrate 5 mg/guaifenesin 400 mg immediate release tablets. The proposed indications are: “symptomatic relief of cough, to loosen mucus.” The dosing regimen is 1 tablet every 4-6 hours, not to exceed 6 doses in a 24-hour period.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the clinical pharmacology study submitted to address a complete response letter in support of NDA 208085. This NDA is approvable from a clinical pharmacology perspective. A food-effect study for the proposed drug product was submitted as part of the original NDA submission and was reviewed by Dr. Manuela Grimstein (see DARRTS, Document ID: 4039428, dated 09 Jan 2017).

6.2. Summary of Clinical Pharmacology Assessment

Hydrocodone bitartrate is an antitussive, with efficacy established in Drug Efficacy Study Implementation (DESI) Notice No. 5213. Currently, hydrocodone is classified as a Schedule II controlled substance (21 CFR 1308). Guaifenesin is generally recognized as safe and effective (GRASE) as an expectorant in the OTC Drug Monograph, Part 341: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter Human Use.

The Office of Study Integrity and Surveillance (OSIS), Division of New Drug Bioequivalence Evaluation recommended accepting the clinical and bioanalytical data for Study 11774901 without an on-site inspection. The rationale for this decision was that OSIS had recently inspected the sites, for the bioanalytical assays, and Novum Pharmaceutical Research Services for the clinical conduct of the study. The inspectional outcome from the previous inspections was classified as No Action Indicated (NAI) (see memo dated 30 Nov 2017 from Shila S Nkah in DARRTS, Reference ID 4188553).

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1 Evaluation of Primary PK Endpoints

**Hydrocodone**

Bioequivalence was established for the hydrocodone component between the test product, Hydrocodone Bitartrate/Guaifenesin 5 mg/400 mg Tablet from ECI Pharmaceutics, and the reference product, Tussigon® (hydrocodone bitartrate/homatropine methylbromide
Hydrocodone Bitartrate/Guaifenesin 5 mg/400 mg Tablets. The Test/Reference point estimates (90% confidence intervals (CI)) for \( AUC_{(0-\infty)} \), \( AUC_{(0-t)} \), and \( C_{\text{max}} \) were 0.97 (90% CI = 0.94, 1.00), 0.97 (90% CI = 0.94, 1.00) and 0.92 (90% CI = 0.87, 0.96), respectively.

**Guaifenesin**

Bioequivalence was established for the guaifenesin component between the test product, Hydrocodone Bitartrate/Guaifenesin 5 mg/400 mg Tablet from ECI Pharmaceutics, and the reference product, a commercially available OTC Guaifenesin 400 mg immediate release tablet. The Test/Reference point estimates (90% CI) for \( AUC_{(0-\infty)} \), \( AUC_{(0-t)} \), and \( C_{\text{max}} \) were 1.01 (0.96 – 1.06), 1.00 (0.95 – 1.06) and 0.99 (0.89 – 1.10), respectively.

Results of the PK comparison for Hydrocodone Bitartrate/Guaifenesin 5 mg/400 mg Tablet from ECI Pharmaceutics, as compared to Tussigon® (hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg) Tablets and a commercially available OTC Guaifenesin 400 mg immediate release tablet for the hydrocodone and guaifenesin component, respectively, are shown in Figure 1 below.

![Forest Plot](source.png)

**Figure 1. Forest Plot of PK Comparison Between Hydrocodone Bitartrate/Guaifenesin 5 mg/400 mg Tablet, Tussigon (Hydrocodone Bitartrate/Homatropine Methylbromide 5 mg/1.5 mg) Tablet and OTC Guaifenesin 400 mg Immediate Release Tablet**

(Source: Reviewer generated graph)
6.2.1.2 Results from Clinical Pharmacology Trial

6.2.1.2.1 Bioequivalence

Study 11774901 was a pivotal relative bioavailability/bioequivalence (BA/BE), single-dose, cross-over study in 42 healthy male and female subjects under fasted state. The objective of the study was to evaluate the relative bioavailability of the test formulation of hydrocodone bitartrate/guaifenesin tablets compared to the two marketed products, one containing hydrocodone and the other containing guaifenesin.

Test product: Hydrocodone Bitartrate/Guaifenesin CII 5 mg/400 mg Tablet (ECI Pharmaceutics)
Reference product 1: Hycodan NDA 05213 (hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg Tablets), and used ANDA 088508 Tussigon tablets, one of the Reference Standards for Hycodan (NDA 05213, discontinued)
Reference product 2: Commercially available OTC Guaifenesin 400 mg immediate release tablet [CVS Health™ Chest Congestion Relief (guaifenesin), 400 mg tablets (Pharbest)]

The primary endpoints were:

- **AUC$_{0-\infty}$**: area under the plasma hydrocodone or guaifenesin concentration-time curve from 0 to infinity, calculated as: $AUC_{0-\infty} = AUC_{0-t} + C_t/K_{el}$, where $C_t$ is the last measurable drug concentration and $K_{el}$ is the apparent first-order elimination rate constant.
- **AUC$_{0-t}$**: area under the plasma hydrocodone or guaifenesin concentration-time curve from 0 to the time of the last quantifiable concentration over a 24-hour sampling period.
- **C$_{max}$**: maximum observed plasma hydrocodone or guaifenesin concentration over a 24-hour sampling period.

Plasma hydrocodone and guaifenesin concentrations were measured over a period of 24 hours following dosing.

**Hydrocodone:**
Representative mean plasma hydrocodone concentration-time profiles for normal healthy volunteers after a single dose of Hydrocodone Bitartrate/Guaifenesin test product or the reference product, Tussigon are illustrated in Figure 2 below.
Following single-dose oral administration of Hydrocodone Bitarrate/Guaifenesin (5 mg hydrocodone bitartrate/400 mg guaifenesin, test) or Tussigon (5 mg hydrocodone bitartrate, reference), C_{max} of 10.70 ng/mL at a median T_{max} of 1.71 hours for test product and a C_{max} of 11.67 ng/mL at a median T_{max} of 1.25 hours for reference product were observed. The corresponding AUC_{0-t} were 67.12 ng·h/mL and 69.04 ng·h/mL for test and reference, respectively. Corresponding values for area under the curve extrapolated to infinity (AUC_{0-∞}) were 69.94 ng·h/mL and 71.77 ng·h/mL for test and reference, respectively (Table 2).
Table 2. Summary of Statistical Evaluation of PK Parameter Estimates of Hydrocodone Between Test (Hydrocodone Bitartrate/Guaifenesin) and Tussigon

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Test (Hydrocodone Bitartrate/Guaifenesin)</th>
<th>Reference (Tussigon)</th>
<th>Ratio of Test/Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>LS Mean</td>
<td>90% CI</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>40</td>
<td>69.94</td>
<td>(64.72, 75.57)</td>
</tr>
<tr>
<td>(ng·h/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>40</td>
<td>67.12</td>
<td>(62.13, 72.51)</td>
</tr>
<tr>
<td>(ng·h/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>40</td>
<td>10.70</td>
<td>(9.85, 11.63)</td>
</tr>
<tr>
<td>(ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>40</td>
<td>1.71&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(0.50 – 4.00)</td>
</tr>
</tbody>
</table>

CI = Confidence Interval
LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.
*aRatio and CI are based on natural log scale data converted back to the original scale

Statistical evaluation of the pharmacokinetic data by this reviewer using PROC MIXED routine in SAS indicated that the two formulations are comparable. The 90% confidence intervals based on the two-one sided test were (87.13 – 96.50), (94.44 – 100.08), and (94.53 – 100.45) for C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> respectively (Table 2) indicating that there were no differences in terms of rate and extent of systemic exposure for hydrocodone between Hydrocodone Bitartrate/Guaifenesin test product or Tussigon PK following single-dose 5 mg oral administration (Figure 3).
Figure 3. Individual, Mean and Median Plasma Hydrocodone AUC₀-₄ (Top Panel), AUC₀-∞ (Center Panel) and Cmax (Bottom Panel) Values Following a Single-Dose 5 mg Oral Administration for Hydrocodone Bitartrate/Guaifenesin and Tussionex

(Source: Reviewer generated plot; Means represented as red diamonds and median as blue line. Means reported in the graph are arithmetic means and may differ from the least squares means shown in the PK comparison table)
**Guaifenesin:**
Representative mean plasma hydrocodone concentration-time profiles after a single dose of Hydrocodone Bitartrate/Guaifenesin test product or OTC Guaifenesin 400 mg (reference) are illustrated in Figure 4 below for normal healthy volunteers.

![Figure 4. Mean Plasma Concentration-Time Profile of Guaifenesin Following Single-Dose Administration of Hydrocodone Bitartrate/Guaifenesin Test Product or OTC Guaifenesin](Source: Reviewer generated graph)

Following single-dose oral administration of Hydrocodone Bitartrate/Guaifenesin (5 mg hydrocodone bitartrate/400 mg guaifenesin, test) or OTC Guaifenesin 400 mg (Chest Congestion Relief Guaifenesin, 400 mg Tablets, reference), $C_{\text{max}}$ of 1822 ng/mL at a median $T_{\text{max}}$ of 0.5 hours for test product and a $C_{\text{max}}$ of 1844 ng/mL at a median $T_{\text{max}}$ of 0.5 hours for reference product were observed. The corresponding $AUC_{(0-t)}$ were 2644 ng·h/mL and 2632 ng·h/mL for test and reference, respectively. Corresponding values for area under the curve extrapolated to infinity ($AUC_{(0-\infty)}$) were 2668 ng·h/mL and 2650 ng·h/mL for test and reference, respectively (Table 3).
Table 3. Summary of Statistical Evaluation of PK Parameter Estimates of Guaifenesin Between Test (Hydrocodone Bitartrate/Guaifenesin) and Reference (OTC Guaifenesin 400 mg)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Test (Hydrocodone Bitartrate/Guaifenesin)</th>
<th>Reference (OTC Guaifenesin 400 mg)</th>
<th>Ratio of Test/Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>LS Mean</td>
<td>90% CI</td>
</tr>
<tr>
<td>AUC_{inf} (ng·h/mL)</td>
<td>40</td>
<td>2667.84</td>
<td>(2340.26, 3041.28)</td>
</tr>
<tr>
<td>AUC_{(0-t)} (ng·h/mL)</td>
<td>40</td>
<td>2643.98</td>
<td>(2317.45, 3016.51)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>40</td>
<td>1822.04</td>
<td>(1569.23, 2115.58)</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>40</td>
<td>0.50(^b)</td>
<td>(0.33 – 1.50)</td>
</tr>
</tbody>
</table>

CI = Confidence Interval
LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.
\(^a\)Ratio and CI are based on natural log scale data converted back to the original scale
\(^b\)Median (Range)

Statistical evaluation of the pharmacokinetic data by this reviewer using PROC MIXED routine in SAS indicated that the two formulations are comparable for guaifenesin. The 90% confidence intervals based on the two-one sided test were (88.70 – 110.06), (95.45 – 105.72), and (95.63 – 105.96) for C_{max}, AUC_{(0-t)}, and AUC_{inf} respectively (Table 3) indicating that there were no differences in terms of rate and extent of systemic exposure for guaifenesin between Hydrocodone Bitartrate/Guaifenesin test product or OTC Guaifenesin PK following single-dose 400 mg oral administration (Figure 5).
Figure 5. Individual, Mean and Median Plasma Hydrocodone AUC\(_{0\rightarrow t}\) (Top Panel), AUC\(_{0\rightarrow \infty}\) (Center Panel) and C\(_{\text{max}}\) (Bottom Panel) Values Following a Single-Dose 5 mg Oral Administration for Hydrocodone Bitartrate/Guaifenesin and OTC Guaifenesin

(Source: Reviewer generated plot; Means represented as red diamonds and median as blue line. Means reported in the graph are arithmetic means and may differ from the least squares means shown in the PK comparison table)
6.2.1.2.2 Bioanalytical Method Validation

Plasma concentrations of hydrocodone and guaifenesin were determined using validated methods of liquid chromatography with tandem mass spectrometry (LC-MS/MS). The lower limit of quantification (LLOQ) for hydrocodone and guaifenesin were 0.164 ng/mL and 6.412 ng/mL, respectively. The method accuracy and precision were acceptable (<15% Bias or %CV, <20% at the LLOQ) for pre-study and in-study validation. Sample chromatograms provided demonstrated satisfactory specificity. The assay performance was selective and independent from the sample matrix as demonstrated by acceptable recoveries of drug-spiked samples.

The summary of the acceptance criteria for the bioanalytical validation methods of hydrocodone and guaifenesin, used in the PK study 11774901 included in this application are summarized in Table 4.

Table 4. Bioanalytical Method Validation for Hydrocodone and Guaifenesin

<table>
<thead>
<tr>
<th>Hydrocodone</th>
<th>Guaifenesin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Information Requested</strong></td>
<td><strong>Information Requested</strong></td>
</tr>
<tr>
<td>Data</td>
<td>Data</td>
</tr>
<tr>
<td>Bioanalytical method validation report location</td>
<td>Hydrocodone and Guaifenesin Validation Report No.</td>
</tr>
<tr>
<td>Analyte</td>
<td>Guaifenesin</td>
</tr>
<tr>
<td>Internal standard (IS)</td>
<td>Type of Extraction: Liquid-liquid extraction</td>
</tr>
<tr>
<td>Method description</td>
<td>Procedure Analytical Method: LC/MS/MS</td>
</tr>
<tr>
<td>Limit of quantitation (LLOQ)</td>
<td>Limit of quantitation (LLOQ)</td>
</tr>
<tr>
<td>Average recovery of drug (%)</td>
<td>Average recovery of drug (%)</td>
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<tr>
<td>Average recovery of IS (%)</td>
<td>Average recovery of IS (%)</td>
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<tr>
<td>Standard curve concentrations (units/mL)</td>
<td>Standard curve concentrations (units/mL)</td>
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<tr>
<td>QC concentrations (units/mL)</td>
<td>QC concentrations (units/mL)</td>
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<tr>
<td>QC Intraday precision (%)</td>
<td>QC Intraday precision (%)</td>
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<tr>
<td>QC Interday accuracy (%)</td>
<td>QC Interday accuracy (%)</td>
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<tr>
<td>Stock stability (days)</td>
<td>Stock stability (days)</td>
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<tr>
<td>Processed stability (hrs)</td>
<td>Processed stability (hrs)</td>
</tr>
<tr>
<td>Freeze-thaw stability (cycles)</td>
<td>Freeze-thaw stability (cycles)</td>
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<td>Long-term storage stability (days)</td>
<td>Long-term storage stability (days)</td>
</tr>
<tr>
<td>Selectivity</td>
<td>Selectivity</td>
</tr>
</tbody>
</table>

(Source: Module 2, Bioequivalence Tables, Tables 4. And 4.2, pp 7-8)
6.2.2. General Dosing and Therapeutic Individualization

General Dosing

It is recommended that for adults and adolescents 18 years of age and older, the dose should be one tablet orally every 4 to 6 hours, not to exceed 6 tablets in 24 hours. Safety and effectiveness of the proposed product in pediatric patients under 18 years of age has not been established. The use of hydrocodone in children less than 6 years of age is associated with fatal respiratory depression.

Therapeutic Individualization

Under fed conditions hydrocodone median $T_{\text{max}}$ was slightly delayed by approximately 0.5 hour; however, the overall systemic bioavailability of hydrocodone was not affected by food. A decrease in the mean $C_{\text{max}}$ (approximately 35% lower) of guaifenesin was observed when the Test product was administered following a high-fat meal; however, there was no significant effect on exposure with respect to AUC. The effect of food on guaifenesin peak exposure is not considered to be clinically meaningful. Please refer to Dr. Grimstein’s review (DARRTS, Document ID: 4039428, dated 09 Jan 2017) for more details.

The Sponsor has not conducted any studies in population subsets.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Drug Substance

Hydrocodone bitartrate is 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has a chemical formula of C$_{18}$H$_{21}$NO$_3$ C$_4$H$_6$O$_6$·2½H$_2$O and a molecular weight of 494.49 g/mol. It is an odorless, fine white powder, water soluble (1 g per 16 ml of water) with a pKa of 8.3.

Guaifenesin is a racemic mixture of (2R)-3-(2-Methoxyphenoxy)-propoane-1,2-diol and (2S)-3-(2-Methoxyphenoxy)-propoane-1,2-diol. It has a chemical formula of C$_{10}$H$_{14}$O$_4$ and a molecular weight of 198.22.49 g/mol. It is a white free flowing granular powder, soluble in water, and slightly hygroscopic.

Drug Product
The drug product is a white, capsule-shaped tablet, debossed "ECI" on one side and "601" on the other side. Each tablet contains 5 mg of hydrocodone bitartrate and 400 mg of guaifenesin. The quantitative composition and function of ingredients in the Test product formulation is summarized in Table 5.

### Table 5. Quantitative Composition and Function of Drug Product Ingredients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quality Standard</th>
<th>Function</th>
<th>Quantity (mg/tablet)</th>
<th>% w/w</th>
<th>Quantity per batch (kg) [Exhibit Batches]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone Bitartrate</td>
<td>USP</td>
<td>Active Ingredient</td>
<td>5</td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Talc</td>
<td>USP</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td><strong>Total Weight</strong></td>
<td></td>
<td></td>
<td><strong>505</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Source: Module 3.2.P.1, Description and Composition of Drug Product, Table 2)

Hydrocodone (dihydrocodeinone) is a centrally acting opioid agonist with analgesic and antitussive pharmacological properties qualitatively similar to that of codeine. Hydrocodone is believed to act through binding to the μ-opioid receptor of the cough center located in the brain stem. The indication of hydrocodone is for the symptomatic relief of cough.

Guaifenesin is an oral expectorant. It is believed to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi, which may increase the efficiency of the cough reflex and facilitate removal of the secretions. The indication of guaifenesin is to loosen (mucus).

6.3.2. **Clinical Pharmacology Questions**

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Clinical pharmacology information often provides pivotal support for evidence of effectiveness in situations that involve extrapolation of findings (e.g., effectiveness) of an approved product to a new population (e.g., adult to pediatric), or a different dose, dosing regimen, or dosage form.
Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Sponsor submitted this NDA through the 505(b)(2) pathway and is claiming effectiveness of the individual components, hydrocortisone and guaifenesin of the test product to approved products Tussigon and OTC Guaifenesin 400 mg immediate release Tablets, respectively, by establishing bioequivalence.

**Hydrocodone:**

Determination of bioequivalence between hydrocodone bitartrate 5 mg/guaifenesin 400 mg immediate release tablets and Tussigon® (hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg) Tablets for the hydrocodone component provides primary evidence of effectiveness.

**Guaifenesin:**

Determination of bioequivalence between hydrocodone bitartrate 5 mg/guaifenesin 400 mg immediate release tablets and OTC Guaifenesin 400 mg immediate release Tablets for the guaifenesin component provides primary evidence of effectiveness.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

From a Clinical Pharmacology perspective, the proposed dosing regimen of one tablet every 4 to 6 hours, not to exceed 6 doses in 24 hours is acceptable.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Sponsor did not conduct any studies in population subsets. No separate dosing/dosing regimen is recommended in any patient subgroups due to intrinsic (e.g., age and gender) and extrinsic factors.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Under fed conditions hydrocodone median $T_{max}$ was slightly delayed by approximately 0.5 hour; however, the overall systemic bioavailability of hydrocodone was not affected by food. A decrease in the mean $C_{max}$ (approximately 35% lower) of guaifenesin was observed when the Test product was administered following a high-fat meal; however, there was no significant effect on exposure with respect to AUC. The effect of food on guaifenesin peak exposure is not considered to be clinically meaningful. No drug-drug interaction studies were conducted.
Question on clinically relevant specifications (TBD)?

Not applicable.

X  X

Suryanarayana Sista, PhD  Bhawana Saluja, PhD
Primary Clinical Pharmacology Reviewer  Clinical Pharmacology Team Leader
7 Clinical Evaluation

7.1 Sources of Clinical Data and Review Strategy

7.1.1 Table of Clinical Studies

Table 6. Summary of clinical pharmacology study supporting the NDA

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study type</th>
<th>Treatment group</th>
<th>Design</th>
<th>Subject No.</th>
<th>Subjects</th>
<th>BE Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>11774901</td>
<td>BA/BE</td>
<td>A Test drug*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B Reference 1: Tussigon tablet (hydrocodone bitartrate 5 mg/homatropine methylbromide 1.5 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C Reference 2: Guaifenesin tablet 400 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Randomized, open label, single dose, 3-way crossover

42 Healthy adult males and females

Bioequivalence was established for hydrocodone and guaifenesin between test drug and reference drugs

*Test drug: Hydrocodone Bitartrate 5 mg /Guaifenesin 400 mg immediate release tablets

7.1.2 Review Strategy

Data Sources

This is mainly a review of clinical pharmacology study. Detailed review of the clinical pharmacology data can be found in the Clinical Pharmacology Review.

7.2 Review of Relevant Individual Trials Used to Support Efficacy

7.2.1 Study 11774901

This is a clinical pharmacology study entitled: A Relative Bioavailability Study of the Test Formulation of Hydrocodone Bitartrate/ Guaifenesin Tablets CII, 5 mg/400 mg (ECI Pharmaceuticals LLC) compared to Two Marketed Products of TUSSIGON® Tablets (hydrocodone bitartrate and homatropine methylbromide) CII, 5 mg/1.5 mg (Pfizer) and CVS Health™ Chest Congestion Relief (guaifenesin), 400 mg tablets (Pharbest), in Healthy Adult
7.2.2. **Study Results**

**Compliance with Good Clinical Practices**

The clinical pharmacology study in this application was conducted in accordance with Good Clinical Practices. The applicant certified that the clinical contractor complied with all applicable federal, state and local laws, codes, regulations, and orders, including, but not limited to, the Federal Food, Drug, and Cosmetic Act and regulations promulgated there under, and Institutional Review Board requirements relative to clinical studies.

**Financial Disclosure**

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. The Applicant stated that the clinical investigator of the clinical pharmacology study in this application certified that he did not have a proprietary interest in the proposed product or a significant equity in the Applicant. See appendix for Financial Disclosure Checklist.

**Patient Disposition**

Thirty-nine of 40 subjects completed the study. Two subjects were discontinued due to positive drug screens and one subject discontinued due to pregnancy.

**Table of Demographic Characteristics**

**Table 7. Demographic characteristics of the study subjects**

<table>
<thead>
<tr>
<th>Demographic Parameters</th>
<th>Test Group A (N= 40) n (%)</th>
<th>Reference Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference B (N= 40) n (%)</td>
<td>Reference C (N= 39) n (%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (75)</td>
<td>30 (75)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (25)</td>
<td>10 (25)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years (SD)</td>
<td>31.1 ± 6.2</td>
<td>31.1 ± 6.2</td>
</tr>
<tr>
<td>Median (years)</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Min, max (years)</td>
<td>18-45</td>
<td>18-45</td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>
Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects were dosed and monitored at the clinical facility under the direct supervision of an Investigator. A mouth check was performed immediately after dosing to ensure that the tablet was swallowed whole without chewing or biting.

Efficacy Results – Primary Endpoint

This is a clinical pharmacology program. The NDA submission is supported by comparison of the bioavailability of the proposed drug product to reference. No clinical efficacy studies were conducted to support this application.

7.3. Integrated Review of Effectiveness

This is a clinical pharmacology program. No clinical efficacy and safety studies were submitted to support this application. The proposed drug product depends on the bioequivalence to the reference drugs to support its safety and effectiveness. No clinical efficacy and safety studies were submitted to support this application.

7.4. Review of Safety

Overall, the exposure to the study drug product from the clinical pharmacology study is small in terms of assessment of safety. Additionally, the demographics of the study subjects represent a narrow population. Given these limitations, the data from the study serve as an adjunct to what is already available in the monograph and reference drug to determine the safety of the proposed drug product.
7.4.1. Safety Review Approach

Adverse events were collected and tabulated. No formal statistical analyses were performed.

7.4.2. Safety Results

Deaths

No deaths were reported in the study.

Serious Adverse Events

One (1) subject was discontinued from study participation at second period for a positive pregnancy test result. The subject’s physician prescribed Misoprostol 200 mcg tablets to terminate the pregnancy. Fetal demise (no heart beat) was noted during a scheduled appointment with her personal physician. This was reported as a serious adverse event. The Investigator determined this did not affect subject safety.

Dropouts and/or Discontinuations Due to Adverse Effects

A total of 42 subjects were enrolled in the study, and 40 subjects completed at least two periods of the study, one of which included the test treatment. Thirty-nine (39) subjects completed all three periods of the study. Two (2) subjects were discontinued due to positive substance abuse screen result and one subject was discontinued due to a serious adverse event as described above.

Significant Adverse Events

There were no significant adverse events in the clinical pharmacology program.

Treatment Emergent Adverse Events and Adverse Reactions

Twenty-one (21) adverse events were reported by 15 of the 42 subjects who participated in this study. Of the reported adverse events, nine (9) occurred after administration of Test drug (A), nine (9) occurred after administration of Reference hydrocodone (B) and three (3) occurred after administration of Reference guaifenesin (C). Twenty (20) of these adverse events were considered “mild” severity, and one (1) was considered “moderate” severity. All reported adverse events had an outcome of “recovered/resolved”. The adverse events reported in the clinical pharmacology study did not reveal a new safety signal.
Table 8. Frequency of adverse events by body system class

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Test A N(%)</th>
<th>Reference B N(%)</th>
<th>Reference C N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0%)</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Feeling jittery</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin abrasion</td>
<td>1 (2.4%)</td>
<td>3 (7.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate decreased</td>
<td>2 (4.9%)</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (2.4%)</td>
<td>2 (4.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abortion spontaneous</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euphoric mood</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hypervigilance</td>
<td>0 (0.0%)</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>0 (0.0%)</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>TOTAL N(%)</td>
<td>8 (19.5%)</td>
<td>7 (17.1%)</td>
<td>3 (7.7%)</td>
</tr>
</tbody>
</table>

Laboratory Findings

Routine clinical chemistry, hematology, and urinalysis were checked at screening and at the end of study. Laboratory examinations were not safety endpoints in the clinical pharmacology study of this application.

Vital Signs

Vital sign assessments were conducted before and the end of the clinical pharmacology study. No clinically significant changes from baseline data were reported.

Electrocardiograms (ECGs)

ECGs were not safety endpoints in the clinical pharmacology study of this application.

QT

None
Immunogenicity

Not applicable.

7.4.3. Analysis of Submission-Specific Safety Issues

None

7.4.4. Safety Analyses by Demographic Subgroups

None

7.4.5. Specific Safety Studies/Clinical Trials

None

7.4.6. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

None

Pediatrics and Assessment of Effects on Growth

The clinical pharmacology study with the application included no pediatric subjects.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no safety issues related to overdose, drug abuse, withdrawal, or rebound in the clinical pharmacology study. The Applicant relies on the reference product, monograph, literature, and experience with the active ingredient hydrocodone to evaluate these issues. The proposed drug product is a Schedule II controlled product based on the hydrocodone component. The risks of drug abuse potential and overdose are well-recognized for the hydrocodone component.

7.4.7. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

As the proposed drug product has not been marketed, there is no post-marketing experience. However, the active ingredients, hydrocodone and guaifenesin, have a long history of clinical use both separately and in combination. The current understanding of the safety and efficacy of these active ingredients and their clinical acceptability in practice come from post-marketing experience.

Expectations on Safety in the Postmarket Setting

Reference ID: 4252779
The safety profile of the proposed hydrocodone/guaifenesin combination product in the postmarketing setting is expected to be similar to other approved hydrocodone and guaifenesin products for which the safety profile is well characterized.

7.4.8. Integrated Assessment of Safety
This is a clinical pharmacology program. The safety data from the study did not identify a safety signal. A total of 42 subjects received single dose of the proposed drug product in the clinical pharmacology study, and the adverse event data from the study revealed no new safety signals.

The safety of the proposed drug product relies primarily on the Agency’s previous findings of approved hydrocodone product Tussigon (hydrocodone bitartrate and homatropine methylbromide) tablets and the OTC monograph for guaifenesin. Therefore, the safety of the proposed drug product is determined by the bioequivalence to the reference drugs. The clinical pharmacology study demonstrated the bioequivalence between the hydrocodone and guaifenesin of the proposed drug product and the reference drugs. The overall risk-to-benefit profile of this hydrocodone and guaifenesin tablets for symptomatic relief of cough and to loosen mucus associated with the common cold in patients 18 years of age and older is favorable.

SUMMARY AND CONCLUSIONS

7.5. Conclusions and Recommendations
This is a 505(b)(2) application for an immediate release oral tablets fixed dose combination drug product containing hydrocodone bitartrate and guaifenesin (5 and 400 mg, respectively). The Applicant uses Tussigon (hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg) as the reference drug for hydrocodone component of the combination product. The Applicant cites OTC Monograph 21 CFR 341.18 to support guaifenesin component of the combination drug product. The proposed drug product depends on the bioequivalence to the reference drugs to support its safety and effectiveness. No clinical efficacy and safety studies were submitted to support this application.

The clinical pharmacology study demonstrated the bioequivalence between the hydrocodone and guaifenesin of the proposed drug product and the reference drugs. The adverse events in the study were low and revealed no new safety signals. No unexpected adverse events occurred.

The safety and efficacy of the proposed drug product relies primarily on the Agency’s previous findings of approved hydrocodone product Tussigon (hydrocodone bitartrate and homatropine methylbromide) tablets and the OTC monograph for guaifenesin. Therefore, the safety and efficacy of the proposed drug product is determined by the bioequivalence to the reference drugs. The overall risk-to-benefit profile of this hydrocodone and guaifenesin tablets for
symptomatic relief of cough and to loosen mucus associated with the common cold in patients 18 years of age and older is favorable. The pivotal clinical pharmacology study, the OTC monograph, and the reference products all support the safety and efficacy of the hydrocodone and guaifenesin tablets.

The recommended action is Approval.

X       X

Xu Wang, MD       Stacy Chin, MD
Primary Clinical Reviewer       Clinical Team Leader
8 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting is deemed unnecessary for this 505(b)(2) application. The two active ingredients present in this product are well known as individual drug substances, and, based on the current monograph and the Agency’s prior precedent, the combination of products of these classes are acceptable for the proposed indications.

11 Pediatrics

The clinical pharmacology study with the application included no pediatric subjects.

The proposed indication is for patients 18 years of age and older; the Applicant requested a waiver for children under 18 years of age. Historically the safety and effectiveness of hydrocodone have been established in DESI review for the reference drug in pediatric population down to 6 years of age. However, there are safety concerns related to use of this product in pediatric population. On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received long-acting hydrocodone-containing cough product. [http://www.fda.gov/cder/drug/advisory/hydrocodone.htm, http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm] Safety and pharmacokinetic studies were then required in pediatric patients 6-17 years of age to assess the safety and appropriate dose based on PK matching to that of adults. Currently, the safety and efficacy of opioids such as hydrocodone for cough in the pediatric population is ongoing at the Agency including whether to contraindicate such products for the entire pediatric population.

The safety of guaifenesin inpatients down to age 2 is established by OTC monograph. Guaifenesin is available for children down to 2 years old in OTC drug market.

12 Labeling Recommendations

12.1 Prescribing Information

Proposed labeling was submitted in Physician’s Labeling Rule (PLR) format. The Agency has made significant revision based on the Agency’s decision of class labeling for hydrocodone-containing drugs, including the addition of black box warning for Addiction, Abuse, and Misuse; Life-threatening Respiratory Depression; Accidental Ingestion, Medication Errors; Cytochrome P450 3A4 interaction; Concomitant Use with Benzodiazepines or Other CNS Depressants; Interaction with Alcohol; Neonatal Opioid Withdrawal Syndrome. The labeling negotiation is ongoing and the agreed upon labeling will be filed separately.
12.2. Patient Labeling
Patient Labeling has been revised based on the revised Prescribing Information, and has been sent to the Applicant for their agreement.

13 Risk Evaluation and Mitigation Strategies (REMS)

None

14 Post-marketing Requirements and Commitments

Routine post-marketing surveillance is sufficient to monitor adverse events, particularly focusing on respiratory depression and any unexpected adverse events.

15 Appendices

15.1. Financial Disclosure

Covered Clinical Study: 11774901

<table>
<thead>
<tr>
<th>Was a list of clinical investigators provided:</th>
<th>Yes ☑</th>
<th>No ☐ (Request list from Applicant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of investigators identified:</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Number of investigators who are Sponsor employees (including both full-time and part-time employees):</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</td>
<td>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Significant payments of other sorts: _____</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proprietary interest in the product tested held by investigator: _____</td>
<td></td>
</tr>
</tbody>
</table>
This is a 505(b) (2) application for a hydrocodone/guaifenesin combination product for symptomatic relief of cough to loosen mucus associated with the common cold. The Applicant has provided adequate clinical pharmacology data to support the approval of the product without the need for new clinical efficacy and safety data. There are no outstanding product quality or other interdisciplinary or facility inspection issues. I concur with the approval recommendation from the review disciplines and the product.
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
04/24/2018
A memo to file for NDA 208085 was filed on 09 Mar 2018. The memo had noted an incorrect application as the source for FDAs’ reliance on previous finding of safety and effectiveness for the hydrocodone component of the current application. The proper reliance should be as follows:

ECI Pharmaceuticals, LLC (Applicant) submitted NDA 208085 under Section 505(b)(2) of the FD&C Act on 13 April 2016. This submission relied on the FDA’s previous finding of safety and effectiveness established for the following products:

i. Hycodan NDA 05213 (hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg Tablets and Syrup, Endo Pharmaceuticals), and used ANDA 088508 Tussigon tablets, one of the Reference Standards for Hycodan (NDA 05213, discontinued), for conducting bioequivalence studies for the hydrocodone component of the proposed combination product.

ii. Over-the-counter (OTC) monograph for guaifenesin (21 CFR 341.18) for the guaifenesin component of the product.
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/s/

SURYANARAYANA M SISTA
04/05/2018

BHAWANA SALUJA
04/05/2018
The Applicant, ECI Pharmaceuticals, LLC, submitted NDA 208085 under Section 505(b)(2) of the FD&C Act on 13 April 2016. The submission relied on the FDA’s previous finding of safety and effectiveness established for the following products:

- (hydrocodone bitartrate/homatropine methyl bromide 5 mg/1.5 mg) Tablets from King Pharmaceuticals (ANDA 088508) for the hydrocodone component of the proposed combination product.
- Over-the-counter (OTC) monograph for guaifenesin (21 CFR 314.18) for the guaifenesin component of the proposed combination product.

The pharmacology study submitted to support the application (Study 102-13-US) showed that the guaifenesin component of the proposed combination product was not bioequivalent to the reference. The 90% CI of the geometric mean ratio of the Cmax for guaifenesin in the proposed product was lower (76.68%) than what the Agency considers to be acceptable to establish comparative bioavailability. As a result, the application could not rely on the OTC monograph for guaifenesin to support the proposed drug without additional data or an alternative justification that scientifically bridges the guaifenesin component of the proposed product to that monograph.

A Complete Response Letter was issued on 13 Feb 2017. The applicant was informed in the Complete Response Letter that this deficiency may be addressed by performing any of the following:
a. Repeat the single-dose clinical pharmacology study to evaluate the relative bioavailability of your proposed hydrocodone 5 mg/guaifenesin 400 mg immediate release tablet compared to the individual reference products under the fasted state. If you choose to repeat the relative bioavailability study, the study should be designed carefully with considerations of the PK variability observed in your current program;

or

b. Because comparative bioavailability of the proposed combination product was not established, conduct a clinical development program with clinical efficacy and safety studies to support your combination product;

or

c. Evaluate whether there is a need to reformulate your combination product. If you reformulate the product, you must repeat the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the individual reference products under fasted state to demonstrate comparative bioavailability. You may also need to repeat the food effect study if the product is reformulated.

The applicant responded to the Complete Response letter on 30 Oct 2017 with a Class 2 resubmission. The resubmission presented the findings of a new relative bioavailability study (Study 11774901). The Applicant is requesting the approval of a combination product of hydrocodone bitartrate 5 mg/guaifenesin 400 mg immediate release tablets. The proposed indications are: “symptomatic relief of cough, to loosen mucus.” The dosing regimen is one tablet every 4-6 hours, not to exceed 6 doses in a 24-hour period.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology has reviewed the clinical pharmacology study submitted to address the Complete Response Letter in support of the proposed drug, and concluded that this NDA is approvable from a clinical pharmacology perspective because the clinical pharmacology study demonstrated bioequivalence between the hydrocodone and guaifenesin of the proposed drug product and the reference drugs.

The clinical review is mainly for the safety data from the clinical pharmacology study. A total of 42 subjects were enrolled in the single dose study. The adverse events reported in the clinical pharmacology study did not reveal a new safety signal. The single dose exposure to the study drug in the clinical pharmacology study is small in terms of assessment of safety. Also, the demographics of the study subjects represent a narrow population. Given these limitations, the data serve as an adjunct to what is already available in the monograph and with the reference drug to determine the safety of the proposed drug product. The safety and efficacy of the proposed drug product relies primarily on the Agency’s previous findings of approved hydrocodone product (hydrocodone bitartrate and homatropine methyl bromide) tablets and the OTC monograph for guaifenesin. Therefore, the safety and efficacy of the proposed drug product is determined by the bioequivalence to the reference drugs.

The overall risk-to-benefit profile of this hydrocodone and guaifenesin combination product for symptomatic relief of cough and to loosen mucus associated with the common cold in patients 18 years of age and older is favorable. The pivotal clinical pharmacology study, the OTC
monograph, and the reference product all support the safety and efficacy of the proposed hydrocodone and guaifenesin tablets. The recommended action is approval.

Refer to the Multi-Disciplinary Review and Evaluation for additional details.
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/s/

XU WANG
04/03/2018

STACY J CHIN
04/03/2018
I concur.
ECI Pharmaceuticals, LLC (Applicant) submitted NDA 208085 under Section 505(b)(2) of the FD&C Act on 13 April 2016. This submission relied on the FDA’s previous finding of safety and effectiveness established for the following products:

i. Tussigon® (hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg) Tablets from King Pharmaceuticals (ANDA 088508) for the hydrocodone component of the proposed combination product.

ii. Over-the-counter (OTC) monograph for guaifenesin (21 CFR 314.18) for the guaifenesin component of the product.

Following a review of the April 2016 NDA submission, the application received a complete response from the Agency on 13 Feb 2017. The reasons cited were that the clinical pharmacology study submitted to support the application (Study 102-13-US) showed that the guaifenesin component of the proposed combination product provided AUC comparable to the reference guaifenesin product, however, the 90% CI of the geometric mean ratio of the C_{max} for guaifenesin in the proposed product was lower (76.68%) than what the Agency considers to be acceptable to establish comparative bioavailability. As a result, the application could not rely on the OTC monograph for guaifenesin without additional data or an alternative justification that scientifically bridges the guaifenesin component of the proposed product to that monograph. A bridge was necessary to demonstrate that reliance on the guaifenesin OTC monograph is appropriate.

The applicant was informed that this deficiency may be addressed by performing any of the following:

a. Repeat the single-dose clinical pharmacology study to evaluate the relative bioavailability of your proposed hydrocodone 5 mg/guaifenesin 400 mg immediate release tablet compared to the individual reference products under the fasted state. If you choose to repeat the relative bioavailability study, the study should be designed carefully with considerations of the PK variability observed in your current program.
b. Because comparative bioavailability of the proposed combination product was not established, conduct a clinical development program with clinical efficacy and safety studies to support your combination product,

or

c. Evaluate whether there is a need to reformulate your combination product. If you reformulate the product, you must repeat the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the individual reference products under fasted state to demonstrate comparative bioavailability. You may also need to repeat the food effect study if the product is reformulated.

The applicant responded to the complete response letter on 30 Oct 2017 with a Class 2 resubmission. The resubmission presented the findings of a new relative bioavailability study (Study 11774901). The Applicant is requesting the approval of a combination product of hydrocodone bitartrate 5 mg/guaifenesin 400 mg immediate release tablets. The proposed indications are: “symptomatic relief of cough, to loosen (mucus)”. The dosing regimen is 1 tablet every 4-6 hours, not to exceed 6 doses in a 24-hour period.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the clinical pharmacology study submitted to address a complete response letter in support of NDA 208085. This NDA is approvable from a clinical pharmacology perspective. A food-effect study for the proposed drug product was submitted as part of the original NDA submission and was reviewed by Dr. Manuela Grimstein (see DARRTS, Document ID: 4039428, dated 09 Jan 2017).

Refer to the Multi-Disciplinary Review and Evaluation for additional details.
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/s/

SURYANARAYANA M SISTA
03/09/2018

BHAWANA SALUJA
03/09/2018
### SUMMARY REVIEW OF REGULATORY ACTION

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<tr>
<td>From</td>
<td>Lydia Gilbert-McClain, M.D., FCCP</td>
</tr>
<tr>
<td>Subject</td>
<td>Summary review of regulatory action</td>
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<tr>
<td>NDA#</td>
<td>NDA 208-085</td>
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<tr>
<td>Applicant</td>
<td>ECI Pharmaceuticals, LLC</td>
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<tr>
<td>Date of Submission</td>
<td>April 13, 2016</td>
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<td>PDUFA Goal Date</td>
<td>February 13, 2017</td>
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<tr>
<th>Proprietary Name/Established (USAN) Names</th>
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<td>Dosage forms/strengths</td>
<td>Oral tablet/hydrocodone bitartrate 5 mg/ guaifenesin 400 mg</td>
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<td>Proposed indication (s)</td>
<td>For symptomatic relief of cough, and to loosen (mucus)</td>
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<th>Action/Recommended action for NME</th>
<th>Complete Response</th>
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<tr>
<td>Material Reviewed/consulted</td>
<td>Names of discipline reviewers</td>
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**Action package including:**
- Medical officer review: Xu Wang
- Cross Discipline Team leader: Anthony Durmowicz
- OSE/DMEPA: Lissan Pringle-Owens/Mishale Mistry
- CMC review team:
  - Craig Bertha, PhD, CMC lead
  - Debasis Ghosh (Drug substance reviewer)
  - Chris Hough (Drug product reviewer)
  - Xiaoying Zhang (process reviewer and microbiology reviewer)
  - Cassandra Abellard (Facility)
  - Angela Lu (Biopharmaceutics)
  - Julia Pinto (Branch Chief)
- Clinical pharmacology: Manuela Grimmstein (primary reviewer); Anshu Marathe (team leader)
- Pharmacology/toxicology: Yu-Mee Kin (primary reviewer); Carol Galvis (team leader [actg.])
- OPDP: Roberta Szydlo
- DPMH: Jane Kiedrka/Denise Pica-Branco

### 1. Introduction

The submission is a 505(b)(2) new drug application and the Applicant is ECI Pharmaceuticals. The application is for a fixed dose combination immediate release tablet...
comprised of hydrocodone bitartrate (an antitussive), and guaifenesin (expectorant) for use in patients 18 years of age and older. There are currently two other FDA approved hydrocodone and guaifenesin combination products being marketed, Obredon (NDA 205474, approved November 14, 2014) and Floutuss (NDA 022424, approved May 14, 2015). Both of these products are formulated as oral solutions. For this NDA for the purposes of (505(b) 2, the applicant will need to rely on the Agency’s prior findings of safety and efficacy for Hycodan® NDA 005213 for the hydrocodone component even though Hycodan is no longer marketed. Although the Applicant claims in the NDA application that they are relying on the generic product Tussigon®, the generic product cannot be relied upon however, because Hycodan® is no longer available in the market the Applicant can use the generic product (ANDA 88508 - Tussigon® (hydrocodone bitartrate 5 mg and homatropine 1.5 mg tablets) as the reference product in the clinical pharmacology studies. For guaifenesin the Agency is relying on the accepted safety and efficacy of the monograph (21 CFR 341.18). The NDA was originally submitted on April 13, 2016 and relies on two clinical pharmacology studies to evaluate bioequivalence and to assess for the effect of food on the formulation. The PDUFA date for this application is February 13, 2017. This summary review provides an overview of the application and the justification for the regulatory decision.

2. Background

FDA published a final Federal Register (FR) notice of its intention to take enforcement action against illegally marketed cough/cold drug products containing hydrocodone on October 1, 2007 [Docket No. 2007N-0353]. To date several hydrocodone-containing cough/cold products have been approved and two hydrocodone and guaifenesin oral solution combination products are currently in the market. This combination of hydrocodone and guaifenesin is for an immediate release oral tablet – hence the product could not be submitted under the 505(j) pathway.

3. CMC

The proposed product in this NDA is for an immediate release tablet containing hydrocodone bitartrate 5 mg, and guaifenesin 400 mg. Inactive ingredients include crospovidone, microcrystalline cellulose, stearic acid, talc, and magnesium stearate. The immediate release tablets are white, capsule-shaped debossed with “ECT” and “601” on either side.

The drug substance hydrocodone bitartrate, USP, is manufactured by . The drug substance guaifenesin is manufactured by . The drug product hydrocodone bitartrate and guaifenesin tablets is manufactured, processed, and packaged by ECI Pharmaceuticals, LLC, Fort Lauderdale, Florida. The CMC reviewers noted that the drug product is manufactured by .

Therefore, the CMC review team is recommending that the Applicant provide such data prior to approval of the application and have recommended a
complete response action from the drug product process perspective. I concur with the CMC recommendation.

**Facilities Inspection**

Inspection of the hydrocodone and guaifenesin drug substance manufacturing sites yielded acceptable outcomes. However, inspection of the drug product manufacturing and packaging site ECI Pharmaceuticals LLC, Fort Lauderdale, FL, resulted in a withhold recommendation based on multiple deficiencies among which was a lack of written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

4. **Nonclinical Pharmacology/Toxicology**

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

5. **Clinical Pharmacology/Biopharmaceutics**

The hydrocodone component of the product showed comparative bioavailability to the reference product. The 90% CI for the ratios of the geometric means of the test/reference products for the AUC and $C_{\text{max}}$ were within 80–125% in the clinical pharmacology study ECI 102-13-US. However, the guaifenesin component of the combination product did not show comparative bioavailability to the reference product because the 90% CI for $C_{\text{max}}$ was below the range accepted by the Agency for demonstrative of comparative bioavailability (76.68%). In the food effect study – Study ECI 099-13-US the systemic exposure of hydrocodone was comparable between fed and fasted conditions for both the test and reference products. However for guaifenesin, both the $AUC_{\text{inf}}$ and $C_{\text{max}}$ results suggest that food decreases the systemic bioavailability compared to the fasted state. (CI for the ratio of the $AUC_{\text{inf}}$ and $AUC_{0-t}$ of fed vs. fasted state for test/reference = 0.77, 1.06; CI for the $C_{\text{max}}$ =0.52, 0.80).

6. **Clinical Microbiology**

This is a non-sterile solution and clinical microbiology is 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 Tussigon® and the OTC monograph product guaifenesin. No clinical studies were required to support the application.

8. **Safety**

The safety of the product is based on establishing bioequivalence of the product compared to approved reference products. There were no safety concerns in the clinical pharmacology studies.
9. Advisory Committee Meeting
An advisory committee meeting was not convened for this application. The active ingredients present in this product are not new molecules and there are no issues that need to be discussed at an advisory committee meeting.

10. Pediatrics
The proposed indication is for adults 18 years of age and older. Similar applications for hydrocodone-containing combination cough/cold products have ongoing post marketing required studies under the Pediatric Research Equity Act (Act) to evaluate the PK and safety in pediatric patients 6 to 17 years of age. This issue is being revisited internally. The product is contraindicated in children less than 6 years because of the risk of respiratory depression with hydrocodone and therefore, studies in this age group are waived under PREA. An oral solution product Obredon (hydrocodone and guaifenesin) with the same active ingredients (hydrocodone and guaifenesin) was approved on November 14, 2014 and has an open PREA commitment. The issue of risk/benefit of opioids for cough suppression in children and the overarching issue of whether cough in children should be pharmaceutically treated at all is undergoing discussions within the Agency. No decision has been reached at this time. This product is going to be given a complete response action and so PREA will be revisited.

11. Other Relevant Regulatory Issues
Data Quality, Integrity, and Financial Disclosure
The study site for the pivotal clinical pharmacology study was inspected. The Office of Study Integrity and Surveillance (OSIS) in their Bioequivalence Establishment Inspection report review concluded that the clinical data were reliable and could be used for regulatory decision making. The Applicant certified that the clinical pharmacology study was conducted in accordance with Good Clinical Practices. Regarding financial disclosures the Applicant certified that there was no financial arrangement with the investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The Applicant certified that the clinical investigator for the clinical pharmacology study did not have a proprietary interest in the proposed product or a significant equity in the applicant.

12. Labeling
The Applicant submitted a label in Physician’s Labeling Rule (PLR) format. The label was not reviewed because the application is not going to be approved in this cycle. The Applicant submitted the proposed trade name [REDACTED] which was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA). The DMEPA provided the Applicant with a Denied letter on August 3, 2016 and the applicant did not propose an alternate trade name during the review cycle. Because of the deficiencies in the Application, further evaluation of the trade name has not occurred.
13. Action and Risk Benefit Assessment

Regulatory action
The regulatory action on the application will be a complete response for a number of reasons. The clinical pharmacology study did not demonstrate that both active ingredients are bioequivalent to the reference product and therefore the Applicant cannot rely on the Agency’s previous findings of safety and efficacy of the individual ingredients to support the efficacy and safety of the proposed combination product without the Applicant conducting clinical efficacy and safety studies. In addition, there are drug product manufacturing process issues that need to be addressed before the application can be recommended for approval. Finally, one the manufacturing facility failed inspection.

- Risk Benefit Assessment
While the overall risk and benefit assessment of the individual ingredients hydrocodone and guaifenesin does not suggest an unfavorable risk benefit, for this combination product a risk benefit assessment cannot be made because the applicant has not established bioequivalence of the combination product to the individual reference products (guaifenesin specifically) and therefore cannot rely on the Agency’s previous determination of safety and efficacy.

- Recommendations for Postmarketing Risk Management Activities
Not applicable

- Recommendations for other Postmarketing Study Commitments
Not applicable

- Deficiencies for the Complete Response letter

CLINICAL PHARMACOLOGY
1. The development program for this application was based on demonstration of comparative bioavailability to the listed drug relied upon for the hydrocodone bitartrate aspect of the combination product and a guaifenesin product that complies with the over-the-counter (OTC) monograph (the reference guaifenesin product). The clinical pharmacology study submitted to support this application (study 102-13-US) showed that the guaifenesin component of the proposed combination product provided AUC comparable to the reference guaifenesin product, but the 90% CI of the geometric mean ratio of the Cmax for guaifenesin in the proposed product was lower (76.68%) than what the Agency considers to be acceptable to establish comparative bioavailability. As a result, this application cannot rely on the OTC monograph for guaifenesin without additional data or an alternative justification that scientifically bridges the guaifenesin component of the proposed product to that monograph. A bridge is necessary to demonstrate that reliance on the guaifenesin OTC monograph is appropriate.

This deficiency may be addressed by performing the following:
a. Repeat the single-dose clinical pharmacology study to evaluate the relative bioavailability of your proposed hydrocodone 5 mg/guaifenesin 400 mg immediate release tablet compared to the individual reference products under the fasted state. If you choose to repeat the relative bioavailability study, the study should be designed carefully with considerations of the PK variability observed in your current program.

Or

b. Because comparative bioavailability of the proposed combination product was not established, conduct a clinical development program with clinical efficacy and safety trials to support your combination product.

Or

c. Evaluate whether there is a need to reformulate your combination product. If you reformulate the product, you must repeat the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the individual reference products under fasted state to demonstrate comparative bioavailability. You may also need to repeat the food effect study if the product is reformulated.

PRODUCT QUALITY

2. Provide the following data to the NDA for at least one commercial scale drug product batch:

- Data from the per your submission Sections 3.2.P.3.4 and 3.2.P.5.2 (Version 09).

- Drug product certificate of analysis against the current release specification.

- Certificate of analysis for the APIs [used for that drug product batch (es)] per your current specification for drug substance.

3. During a recent inspection of the ECI Pharmaceuticals LLC, FEI 3008798439, in Fort Lauderdale, Florida manufacturing facility for this NDA, the FDA field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved. Please list communications submitted to, or held with, the agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.
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/s/

LYDIA I GILBERT MCCLAIN
02/13/2017
# Cross-Discipline Team Leader Review

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<td>PDUFA Goal Date</td>
<td>February 13, 2017</td>
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<td>Proprietary Name / Established (USAN) names</td>
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<td>Proposed Indication(s)</td>
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## 1. Introduction

This NDA submission by the Applicant, ECI Pharmaceuticals, LLC, received April 13, 2016, is a 505(b)(2) new drug application based on a clinical pharmacology program for a hydrocodone bitartrate and guaifenesin combination immediate release oral tablet (proposed name [4], with a proposed indication “for the symptomatic relief of cough and to loosen [4] (mucus)”.

There are currently two other FDA approved hydrocodone and guaifenesin combination products being marketed, Obreton (NDA 205474, approved November 14, 2014) and Flowtuss (NDA 022424, approved May 14, 2015), both formulated as oral solutions.

For this submission, the Applicant submitted a set of two studies in to support the bioequivalence of the hydrocodone bitartrate and guaifenesin components to their proposed product to that of the respective reference products (Tussigon, hydrocodone bitartrate 5 mg and homatropine 1.5 mg tablets and guaifenesin 400 mg tablets) and to assess for food effect.

This CDTL review will provide an overview of the application, with a focus on the clinical pharmacology studies submitted to support bioequivalence of the hydrocodone and guaifenesin components of the hydrocodone/guaifenesin combination product to the respective reference products. The PDUFA date for this application is February 13, 2017.
2. Background

This application is to market a combination product containing hydrocodone bitartrate and guaifenesin, as an immediate release oral tablet containing 5 mg and 400 mg of hydrocodone and guaifenesin, respectively. Guaifenesin is a well known expectorant found in many cough and cold products and is listed in the OTC monograph (21 CFR 341.40). The proposed dosage is one tablet every 4-6 hours, not to exceed 6 doses in 24 hours for adults 18 years of age and older.

The Applicant submitted a pre-IND meeting request on June 23, 2010. The Division’s written responses confirmed that for the proposed immediate release hydrocodone and guaifenesin tablets, a 505 (b)(2) application would be an appropriate pathway and that a single dose bioequivalence study comparing the proposed drug product against each of the active individual components administered separately under fasted state and a food effect study to evaluate the effect of food on the proposed drug product would be required. Subsequent discussion occurred at a Type B meeting on February 25, 2011 during which with the Division advised that additional studies might be necessary to support efficacy and safety of the combination product. ECI opened an IND on November 11, 2013, and submitted this 505(b)(2) application on April 13, 2016.

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 (the combination of hydrocodone and chlorpheniramine) with clinical pharmacology data only, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combinations can 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. However, lack of such a program (lack of bioequivalence) would not allow the Applicant to rely on the Agency’s previous determination of safety and efficacy for the reference products and therefore require the Applicant to support any differences with clinical studies or evaluate and correct the reason(s) for lack of bioequivalence and repeat the bioequivalence studies.

3. CMC/Device

Hydrocodone bitartrate and guaifenesin immediate release tablets are white, capsule-shaped tablets, debossed "ECI" on one side and "601" on the other side. Each tablet contains 5 mg of hydrocodone bitartrate and 400 mg of guaifenesin. Inactive ingredients (excipients) include crospovidone, microcrystalline cellulose, stearic acid, talc, and magnesium stearate.

The drug substance hydrocodone bitartrate, USP, is manufactured by . The drug substance guaifenesin is manufactured by .
The drug product hydrocodone bitartrate and guaifenesin tablets is manufactured, processed, and packaged by ECI Pharmaceuticals, LLC, Fort Lauderdale, Florida.

Inspection of the hydrocodone and guaifenesin drug substance manufacturing sites yielded acceptable outcomes. However, inspection of the drug product manufacturing and packaging site ECI Pharmaceuticals LLC, Fort Lauderdale, FL, resulted in a “Withold” recommendation based on multiple deficiencies among which was a lack of written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted 2 clinical pharmacology studies; one to support the bioequivalence of hydrocodone bitartrate and guaifenesin to their listed reference products (ECI 102-13-US) and the other to assess for food effect (Study ECI 099-13-US). Following is an overview and results for the two studies.

Pivotal bioequivalence study

Study ECI 102-13-US:

Design

Study ECI 102-13-US was the pivotal study conducted by ECI to assess for bioequivalence of their proposed combination tablet to the hydrocodone and guaifenesin reference products. It was an open-label, randomized, single-center, single-dose, three-treatment, three-period, three-sequence, crossover study under fasted conditions comparing equal doses of ECI’s hydrocodone bitartrate 5 mg/guaifenesin 400 mg immediate release tablets to the respective reference products, Tussigon (hydrocodone bitartrate 5 mg and homatropine 1.5 mg) tablets and guaifenesin 400 mg tablets in 14 healthy adult human subjects under fasting conditions. Subjects were randomized to receive 1) Test drug, hydrocodone bitartrate 5 mg / guaifenesin 400 mg immediate release tablet; 2) Reference 1, Tussigon (hydrocodone bitartrate 5 mg and homatropine 1.5 mg) tablet; or 3) Reference 2, guaifenesin 400 mg tablet. After a washout period of 7 days, the subjects crossed over to receive another treatment until each subject received all 3 treatments. After study drug administration, serial blood samples were collected over a period of 24 hours. Plasma concentrations of hydrocodone and guaifenesin were measured by the LC-MS/MS method. Pharmacokinetic (PK) parameters $C_{\text{max}}$, AUC0-t, and AUCinf were determined for hydrocodone and guaifenesin, respectively.

Results

The results showed that Applicant’s test guaifenesin product was not bioequivalent to the listed product based on the $C_{\text{max}}$ geometric mean ratio 90% CI being out of the 0.80-1.25 range. The geometric mean ratio (test/listed) of AUC0–t, AUCinf, and $C_{\text{max}}$ were 0.96 (90% CI = 0.89, 1.04), 0.96 (90% CI = 0.89, 1.04), and 0.92 (90% CI= 0.77, 1.10), respectively (Table 1).
Table 1: Geometric Mean, Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameters of Hydrocodone and Guaifenesin Following Single Dose Administration of Test and Reference Product under Fasted Conditions. (Study ECI 102-13-US)

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<th>Parameter</th>
<th>Hydrocodone</th>
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<td>Ratio b</td>
<td>Geometric Mean a</td>
<td>Ratio b</td>
</tr>
<tr>
<td>AUC(_{0-t}) (mcg∙h/mL)</td>
<td>69.49</td>
<td>70.30</td>
<td>0.99</td>
</tr>
<tr>
<td>AUC(_{inf}) (mcg∙h/mL)</td>
<td>74.14</td>
<td>75.00</td>
<td>0.99</td>
</tr>
<tr>
<td>C(_{max}) (mcg/mL)</td>
<td>10.74</td>
<td>10.70</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Food effect

Study ECI 099-13-US:

Design

This was a single-dose food effect cross-over study to assess the impact of food on the bioavailability of ECI’s hydrocodone and guaifenesin oral tablet. Fourteen healthy male and female subjects 18 to 64 years of age were randomized to receive a single open-label dose of the proposed hydrocodone and guaifenesin oral tablet under fed and fasting conditions with 13 subjects completing the study. At least a 7-day washout period was observed between the doses.

Results

The systemic exposure of hydrocodone was comparable between fed condition and fasted condition for both products. For guaifenesin the point estimates and their 90% CIs for AUC\(_{0-t}\), AUC\(_{inf}\), and C\(_{max}\) were not contained within the acceptance range of 80.00 - 125.00%, demonstrating that food had an overall significant impact on the systemic bioavailability of guaifenesin as compared to the fasting state (Table 2).

Table 2: Food effect assessment; Geometric Mean, Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameters of Hydrocodone and Guaifenesin Following Single Dose Administration Under Fed and Fasted Conditions (Study ECI 099-13-US)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hydrocodone</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric Mean a</td>
<td>Ratio b</td>
<td>Geometric Mean a</td>
</tr>
<tr>
<td>AUC(_{0-t}) (mcg∙h/mL)</td>
<td>72.69</td>
<td>67.40</td>
</tr>
<tr>
<td>AUC(_{inf}) (mcg∙h/mL)</td>
<td>76.87</td>
<td>71.21</td>
</tr>
</tbody>
</table>

Source: NDA 208-085, 2.7.1 Summary of Biopharmaceutical studies and Associated Analytical Methods

a Geometric Mean for Test Formulation-Fasted and Reference Product-Fasted based on Least Squares Mean of log-transformed parameter values

b Ratio = Geometric Mean (Test)/Geometric Mean (Ref)
Anthony Durmowicz M.D.
Cross Discipline Team Leader Review
NDA 208085, [hydrocodone bitartrate (5 mg) and guaifenesin (400 mg) tablets]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Guaifenesin</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric Mean a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fed</td>
<td>2276</td>
<td>2521</td>
</tr>
<tr>
<td>Fasted</td>
<td>2317</td>
<td>2536</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>890.5</td>
<td>1375</td>
</tr>
</tbody>
</table>

Source: NDA 208-085, 2.7.1 Summary of Biopharmaceutical studies and Associated Analytical Methods

a Geometric Mean for Test Formulation-Fasted based on Least Squares Mean of log-transformed parameter values

b Ratio = Geometric Mean (Fed)/Geometric Mean (Fasted)

### 6. Clinical Microbiology

Not applicable.

### 7. Clinical/Statistical- Efficacy

The efficacy of the product relies on establishing bioequivalence of the proposed combination product compared to the approved reference product, Tussigon (hydrocodone bitartrate and homatropine methylbromide) tablets and the OTC monograph for guaifenesin. No clinical efficacy studies were conducted to support this application. While the hydrocodone component of the combination met bioequivalence criteria based on $AUC_{inf}$ and $C_{max}$, the guaifenesin component failed bioequivalence criteria based on the $C_{max}$ geometric mean ratio 90% CI being out of the 0.80-1.25 range (0.77). As the failure of $C_{max}$ criteria was on the lower side of the CI range (0.77), efficacy could not be established.

### 8. Safety

The safety of the product is also based on establishing bioequivalence of the proposed combination product compared to the approved reference product, Tussigon (hydrocodone bitartrate and homatropine methylbromide) tablets and the OTC monograph for guaifenesin. As noted above, the hydrocodone component of the combination met bioequivalence criteria based on $AUC_{inf}$ and $C_{max}$ while the guaifenesin component failed bioequivalence criteria based on the $C_{max}$ geometric mean ratio 90% CI being out of the 0.80-1.25 range. However, as the failure of $C_{max}$ criteria was on the lower side of the CI range (0.77), safety would not be an issue.

The Applicant also submitted a Clinical Summary including the safety data from the clinical pharmacology studies ECI 102-13-US and ECI 099-13-US. A total of 28 subjects received single dose of the proposed drug product in the 2 studies, and the adverse event data from the 2 studies reveal no new safety signals.

### 9. Advisory Committee Meeting

An advisory committee meeting is not necessary for this application. 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

The proposed indication is for patients 18 years of age and older; the Applicant requested a waiver for children under 18 years of age. Historically the Agency has waived studies of all hydrocodone-containing products in children under 6 years of age based on the fact that the extended release hydrocodone cough and cold product, Tussionex, is contraindicated for use in children less than 6 years of age (because of the risk of fatal respiratory depression) as well as the risk of respiratory depression in young children caused by immediate release hydrocodone containing cough and cold products. Safety and pharmacokinetic studies were then required in pediatric patients 6-17 years of age to assess the safety and appropriate dose based on PK matching to that of adults. That being said, the safety and efficacy of opioids such as hydrocodone for cough in the pediatric population is ongoing at the Agency including whether to contraindicate such products for the entire pediatric population.

The safety of guaifenesin inpatients down to age 2 is established by OTC monograph.

11. Other Relevant Regulatory Issues

Inspections

The review team requested the inspection for the clinical and analytical sites of the clinical pharmacology studies. The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) observed no significant deficiencies and concluded that the clinical data from the audited study to be reliable.

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 complied with all applicable federal, state and local laws, codes, regulations, and orders, including, but not limited to, the Federal Food, Drug, and Cosmetic Act and regulations promulgated there under, and Institutional Review Board requirements relative to clinical studies.

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 Applicant stated that the clinical investigator of the clinical pharmacology studies in this application certified that he did not have a proprietary interest in the proposed product or a significant equity in the Applicant.

12. Labeling

Proprietary Name

The proposed trade name was reviewed and deemed to be provisionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

Physician Labeling
13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is for a Complete Response as ECI Pharmaceuticals, LLC has not submitted adequate data to support approval of hydrocodone and guaifenesin oral tablets for use as an antitussive and expectorant in patients 18 years of age and older. The submitted open-label bioavailability study failed to demonstrate bioequivalence for the guaifenesin drug component and, as a result, cannot rely on the Agency’s previous determinations of safety and efficacy. While the failure of guaifenesin on the lower side of the 0.80-1.25 side of the 90% confidence interval would not necessarily be a safety issue, failure to meet the same bioequivalence criteria as generic products are required is a product quality deficiency.

- **Risk Benefit Assessment**

While the overall risk and benefit assessment of the individual ingredients hydrocodone and guaifenesin does not suggest an unfavorable risk benefit, for this combination product a risk benefit assessment cannot be made because the applicant has not established bioequivalence of the combination product to the individual reference products (guaifenesin specifically) and therefore cannot rely on the Agency’s previous determination of safety and efficacy.

- **Recommendation for Postmarketing Risk Management Activities**

Not Applicable

- **Deficiencies for the Complete Response Letter**

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form for the following reasons:

1. Your clinical pharmacology 505(b)(2) application is based on being able to demonstrate bioequivalency of the test drugs to the reference drugs and the guaifenesin component in the test oral solution is not bioequivalent to the reference product with the 90% CI for the geometric mean ratio of $C_{\text{max}}$ falling outside of the 80.00% to 125.00% acceptance range.

To address this deficiency you should do the following:

- If you believe the failure to demonstrate bioequivalency is because of study design issues, repeat the single dose bioavailability study between your product and the reference products under fasted state by appropriately redesigning the study. To gain approval based on bioequivalency criteria, bioequivalence must be established between your proposed product and the reference products under a fasted state.
Or

- If you believe the failure to demonstrate bioequivalency is due to formulation issues, reformulate the product and repeat the clinical pharmacology program to demonstrate bioequivalence between the reformulated product and the reference products under a fasted state, and repeat the food effect study if necessary.

Or

- Develop your combination product by conducting clinical trials to support its safety and efficacy.

2. During a recent inspection of the ECI Pharmaceuticals LLC, FEI 3008798439, in Fort Lauderdale, Florida manufacturing facility for this NDA, the FDA field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

List communications submitted to, or held with, the agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

- Recommendation for other Postmarketing Study Commitments
  Not applicable.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY G DURMOWICZ
01/27/2017
Pharmacology and Toxicology Secondary Review for NDA 208085

Date: January 12, 2017

To: NDA 208085
Hydrocodone bitartrate and guaifenesin (5mg/400mg) Tablets
ECI Pharmaceuticals, LLC

From: Carol M. Galvis, PhD
Acting Pharmacology and Toxicology Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Recommendation
I concur with Dr. Kim’s review dated January 4, 2017 that recommended approval of NDA 208085 from the nonclinical pharmacology and toxicology perspective. There are no outstanding nonclinical issues at this time, except for labeling.

Background
The proposed product is for a tablet formulation containing hydrocodone bitartrate (5 mg) and guaifenesin (400 mg), and is proposed as a prescription product under the 505(b)(2) pathway. No nonclinical studies were submitted for review. Hydrocodone bitartrate is an opioid that is generally recognized as antitussive (DESI Notice #5213) and guaifenesin is an accepted expectorant in the OTC monograph. ECI Pharmaceuticals relied on the existing safety data available for both ingredients; including current literature, data from approved drug products, and the OTC monograph. Both active ingredients are widely used in the US and are generally recognized as safe and effective at the proposed doses.

Labeling
Pharmacology and toxicology review of labeling will be conducted at a later time.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL M GALVIS
01/12/2017
<table>
<thead>
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<th><strong>CLINICAL PHARMACOLOGY REVIEW</strong></th>
</tr>
</thead>
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<tr>
<td>NDA Number: 208085</td>
</tr>
<tr>
<td>Submissions Date: 04/13/2016</td>
</tr>
<tr>
<td>Submission Type: 505(b)(2)</td>
</tr>
<tr>
<td>Proposed Brand Name:</td>
</tr>
<tr>
<td>Generic Name: Hydrocodone Bitartrate/Guaifenesin</td>
</tr>
<tr>
<td>Sponsor: ECI Pharmaceuticals, LLC.</td>
</tr>
<tr>
<td>Route of Administration: Oral</td>
</tr>
<tr>
<td>Dosage Form: Immediate Release Tablet</td>
</tr>
<tr>
<td>Dosage Strength: 5 mg Hydrocodone Bitartrate /400 mg Guaifenesin</td>
</tr>
<tr>
<td>Proposed Dosing Regimen: 1 tablet every 4 to 6 hours, not to exceed 6 tablets in 24 hours</td>
</tr>
<tr>
<td>Proposed Indication(s): For use in symptomatic relief of cough, to loosen mucus</td>
</tr>
<tr>
<td>Proposed Population(s): Adults and adolescents 18 years of age and older</td>
</tr>
<tr>
<td>OND Divisions: Division of Pulmonary, Allergy, and Rheumatology Products</td>
</tr>
<tr>
<td>OCP Division: Clinical Pharmacology II</td>
</tr>
<tr>
<td>Reviewer: Manuela Grimstein, M.Sc., Ph.D.</td>
</tr>
<tr>
<td>Team Leader: Anshu Marathe, Ph.D.</td>
</tr>
</tbody>
</table>
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<th>Page number</th>
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<td>1.2 Phase 4 Commitments</td>
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<td>4 APPENDICES</td>
<td></td>
</tr>
<tr>
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<td>11</td>
</tr>
</tbody>
</table>

1 EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the clinical pharmacology studies submitted to support NDA 208085, and recommends a complete response action.

The guaifenesin component of the proposed combination product is not bioequivalent to the reference guaifenesin product: the 90% CI of the geometric mean ratio of the Cmax for guaifenesin in the proposed product was lower (76.68%) than the bioequivalence acceptance range of 80.00-125.00%.

This deficiency may be addressed by doing the following:

- Repeat the single-dose clinical pharmacology study to evaluate the relative bioavailability of your proposed hydrocodone 5 mg/guaifenesin 400 mg immediate release tablet compared to the individual reference products under the fasted state, using the bioequivalence acceptance range of 80.00-125.00%. The study should be designed carefully with considerations of the PK variability observed in your current program, or

- Because the proposed combination product did not meet the BE criteria, conduct a clinical development program with clinical efficacy and safety studies to support your combination product, or

- Evaluate whether there is a need to reformulate your combination product. If you reformulate the product, you must repeat the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the individual reference products under fasted state, using the bioequivalence acceptance range of
80.00-125.00%. You may also need to repeat the food effect study if the product is reformulated.

1.2 Phase 4 Commitments

Not Applicable.

1.3 Summary of Clinical Pharmacology Findings

1.3.1 Background

ECI Pharmaceuticals, LLC (Applicant) is requesting the approval of a combination product of hydrocodone bitartrate 5 mg/guaifenesin 400 mg immediate release tablets under the proposed trade name of Tablets. The proposed indications are symptomatic relief of cough, to loosen (mucus). The dosage is 1 tablet every 4-6 hours, not to exceed 6 doses in a 24-hour period.

The applicant has submitted NDA 208085 under Section 505(b)(2) of the FD&C Act. This submission relies on the FDA’s previous finding of safety and effectiveness established for the following:

i. Tussigon® (hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg) Tablets from King Pharmaceuticals (ANDA088508) for the hydrocodone component of the proposed combination product.

ii. Over-the-counter (OTC) monograph for guaifenesin (21 CFR 314.18) for the guaifenesin component of the product.

Hydrocodone bitartrate is an antitussive, with efficacy established in Drug Efficacy Study Implementation (DESI) Notice No. 5213. Currently, hydrocodone is classified as a Schedule II controlled substance (21 CFR 1308). Guaifenesin is generally recognized as safe and effective (GRASE) as an expectorant in the OTC Drug Monograph, Part 341: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter Human Use.

The clinical development program of this NDA application consists of a relative bioavailability/bioequivalence (BA/BE) study (102-13-US) and a comparative bioavailability food effect study (099-13-US) to establish a clinical bridge between hydrocodone/guaifenesin IR tablets and the reference products, Tussigon®(hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg tablet) and a currently marketed OTC immediate-release guaifenesin product.

The Office of Study Integrity and Surveillance (OSIS), Division of New Drug Bioequivalence Evaluation inspected the clinical site of the relative The inspectional findings were classified as No Action Indicated (NAI). The clinical data from the audited study was considered reliable and acceptable (Establishment Inspection Report Review, dated ). The OSIS also conducted an analytical inspection at . The audit examined selected records
1.3.2 Results from Clinical Pharmacology Trials

1.3.2.1 Bioequivalence

Study 102-13-US was a pivotal relative BA/BE, single-dose, cross-over study in 14 healthy subjects under the fasted state.

Test product: Hydrocodone Bitartrate/Guaifenesin 5 mg/400 mg Tablet from ECI Pharmaceutics

Reference product 1: Tussigon® (hydrocodone bitartrate/homatropine methylbromide 5 mg/1.5 mg) Tablets distributed by King Pharmaceuticals

Reference product 2: Commercially available OTC Guaifenesin 400- mg immediate release product

Following oral administration of single-dose of the Test product or the Reference product 1, the hydrocodone geometric mean ratios (test/reference, N=13) for $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\text{inf}}$, and the associated 90% confidence intervals were within the bioequivalence range of 80.00-125.00% (Table 1). The bioequivalence of guaifenesin was not established between the Test product and the Reference product 2. The 90% CI of the geometric mean ratio of the Cmax for guaifenesin was lower (76.68%) than the acceptance range of 80.00-125.00% for bioequivalence (Table 1). See Individual Study Review in Section 4.1.1 for details.

Table 1. Comparison of PK parameters of hydrocodone and guaifenesin between the Test product and the Reference products in Study 102-13-US (n=13)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PK Parameter</th>
<th>LSMean Ratio Test/Reference (%)</th>
<th>90% Lower Limit of Ratio</th>
<th>90% Upper Limit of Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocodone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test vs Reference Product 1</td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>100.40</td>
<td>93.52</td>
<td>107.79</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-t}$ (ng.h/mL)</td>
<td>98.86</td>
<td>95.18</td>
<td>102.68</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-\text{inf}}$ (ng.h/mL)</td>
<td>98.84</td>
<td>94.39</td>
<td>103.51</td>
</tr>
<tr>
<td><strong>Guaifenesin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test vs Reference Product 2</td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>91.85</td>
<td>76.68</td>
<td>110.01</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-t}$ (ng.h/mL)</td>
<td>96.20</td>
<td>89.17</td>
<td>103.77</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-\text{inf}}$ (ng.h/mL)</td>
<td>96.39</td>
<td>89.29</td>
<td>104.05</td>
</tr>
</tbody>
</table>

(Source: Adapted from BE Effect Study SAS Output Codes 0003 module 5.3.1.2, and CSR 102-13-US 0003 Tables 15 and 18)
1.3.2.2 Food Effect

Study 099-13-US was a randomized, open-label, two-period, two sequence, 2-way crossover, comparative bioavailability food effect study in 14 healthy subjects.

A single dose of hydrocodone bitartrate/guaifenesin 5 mg/400 mg Tablet was administered either under fasting or fed conditions in each study period.

The systemic exposure of hydrocodone (AUC and Cmax) from 13 subjects was comparable between fed and fasted condition (Table 2). The median Tmax of hydrocodone was delayed by 0.5 hour under the fed condition compared to the fasted condition. This delay in Tmax with food is consistent with the observations from previously approved hydrocodone/guaifenesin immediate-release products.

Conversely, food reduced guaifenesin exposure with respect to Cmax. The mean Cmax of guaifenesin were approximately 35% lower under fed condition compared to fasted condition (Table 2). The same trend was observed in previous hydrocodone/guaifenesin immediate-release products. The time to reach maximum guaifenesin concentration (Tmax) was not affected by food. See Individual Study Review in Section 4.1.2 for details.

Table 2. Comparison of PK parameters of hydrocodone and guaifenesin between the fed and fasted status in Study 099-13-US (n=13)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Fed</th>
<th>Fasted</th>
<th>LSMean Ratio Fed/Fasted (%)</th>
<th>90% CI of Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocodone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>10.43</td>
<td>9.83</td>
<td>106.14</td>
<td>97.68-115.32</td>
</tr>
<tr>
<td>AUC₀-₉₀ (ng.h/mL)</td>
<td>72.69</td>
<td>67.40</td>
<td>107.85</td>
<td>101.62-114.46</td>
</tr>
<tr>
<td>AUC₀-∞ (ng.h/mL)</td>
<td>76.87</td>
<td>71.21</td>
<td>107.95</td>
<td>100.83-115.56</td>
</tr>
<tr>
<td>Median Tmax (h)</td>
<td>2.00</td>
<td>1.50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Guaifenesin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>890.5</td>
<td>1375</td>
<td>64.76</td>
<td>52.41-80.01</td>
</tr>
<tr>
<td>AUC₀-₉₀ (ng.h/mL)</td>
<td>2276</td>
<td>2521</td>
<td>90.29</td>
<td>76.86-106.05</td>
</tr>
<tr>
<td>AUC₀-∞ (ng.h/mL)</td>
<td>2317</td>
<td>2536</td>
<td>91.35</td>
<td>77.27-107.99</td>
</tr>
<tr>
<td>Median Tmax (h)</td>
<td>1.00</td>
<td>0.66</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(Source: Adapted from Food Effect Study SAS Output Codes 0003 module 5.3.1.2, and CSR 099-13-US 0003 Tables 14 and 16)
2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug and Drug Product

2.1.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Drug Substance
Hydrocodone bitartrate is 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has a chemical formula of \( C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O \) and a molecular weight of 494.49 g/mol. It is an odorless, fine white powder, water soluble (1 g per 16 ml of water) with a pKa of 8.3.

Guaifenesin is a racemic mixture of (2R)-3-(2-Methoxyphenoxy)-propoane-1,2-diol and (2S)-3-(2-Methoxyphenoxy)-propoane-1,2-diol. It has a chemical formula of \( C_{10}H_{14}O_4 \) and a molecular weight of 198.22.49 g/mol. It is a white free flowing granular powder, soluble in water, and slightly hygroscopic.

Drug Product
The drug product is a white, capsule-shaped tablet, debossed "ECI" on one side and "601" on the other side. Each tablet contains 5 mg of hydrocodone bitartrate and 400 mg of guaifenesin. The quantitative composition and function of ingredients in the Test product formulation is summarized in Table 3.

Table 3. Quantitative composition and function of drug product ingredients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quality Standard</th>
<th>Function</th>
<th>Quantity (mg/tablet)</th>
<th>% w/w</th>
<th>Quantity per batch (kg) [Exhibit Batches]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone Bitartrate</td>
<td>USP</td>
<td>Active Ingredient</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crespovidone</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>USP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Weight</strong></td>
<td></td>
<td></td>
<td><strong>505</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Source: Module 3.2.P.1, Description and Composition of Drug Product, Table 2)

2.1.2 What are the proposed mechanism of action, therapeutic indication and dosage recommendation for the proposed product?)
Hydrocodone (dihydrocodeinone) is a centrally acting opioid agonist with analgesic and antitussive pharmacological properties qualitatively similar to that of codeine. Hydrocodone is believed to act through binding to the μ-opioid receptor of the cough center located in the brain stem. The indication of hydrocodone is for the symptomatic relief of cough.

Guaifenesin is an oral expectorant. It is believed to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi, which may increase the efficiency of the cough reflex and facilitate removal of the secretions. The indication of guaifenesin is to loosen (mucus).

Dosage and Administration
Adults and adolescents 18 years of age and older: One tablet (5 mg hydrocodone bitartrate and 400 mg guaifenesin) every 4 to 6 hours, not to exceed 6 doses in 24 hours.

2.2 General Clinical Pharmacology

2.2.1 Was hydrocodone and guaifenesin tablet bioequivalent to the reference products?
Pharmacokinetic results of relative BA/BE study 102-13-US demonstrated that hydrocodone met the BE criteria, however, guaifenesin failed the BE criteria as the upper end of 90% CI for Cmax was below (76.68%) the acceptance range of 80.00% to 125.00%.

2.2.2 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?
Since approval of this product was based on successful demonstration of bioequivalence to the reference products, no clinical efficacy and safety studies were conducted.

2.3 General Biopharmaceutics

2.3.1 What is the effect of food on the bioavailability
A dedicated food-effect study investigated the effect of food on the PK of hydrocodone and guaifenesin. Under fed conditions hydrocodone median Tmax was slightly delayed by approximately 0.5 hour; however, the overall systemic bioavailability of hydrocodone was not affected by food. A decrease in the mean Cmax (approximately 35% lower) of guaifenesin was observed when the Test product was administered following a high-fat meal; however, no significant effect on exposure with respect to AUC. See section 1.3.2.2 for details.

2.3.2 Was the to-be-marketed formulation used in the PK/Clinical trials?
The to-be marketed formulation was used in the relative BA/BE and food effect studies.
2.3.3 Is there a potential for dose dumping in the presence of alcohol?

Not applicable as this is an immediate release oral solution.

2.4 Analytical Section

2.4.1 Were the analytical methods used to determine hydrocodone and guaifenesin in plasma adequately validated?

Plasma concentrations of hydrocodone and guaifenesin were determined using validated methods of liquid chromatography with tandem mass spectrometry (LC-MS/MS). The lower limit of quantification (LLOQ) for hydrocodone and guaifenesin were 0.05 ng/mL and 5.00 ng/mL, respectively. The method accuracy and precision were acceptable (<15% Bias or %CV, <20% at the LLOQ) for pre-study and in-study validation. Sample chromatograms provided demonstrated satisfactory specificity. The assay performance was selective and independent from the sample matrix as demonstrated by acceptable recoveries of drug-spiked samples.

The summary of the acceptance criteria for the bioanalytical validation methods used in the PK studies 102-13-US and 099-13-US included in this application is summarized in Table 4.

Table 4. Bioanalytical assay performance of pre-study validation for hydrocodone and guaifenesin

<table>
<thead>
<tr>
<th></th>
<th>Hydrocodone</th>
<th>Guaifenesin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linearity</strong></td>
<td>Satisfactory: Standard curve ranged from 0.05 to 30.0 ng/mL, ( r^2 \geq 0.9983 ).</td>
<td>Standard curve ranged from 5.00 to 5000 ng/mL, ( r^2 \geq 0.9991 ).</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Inter-run bias ranged from -12.0 to -0.600%. Intra-run bias ranged from -13.4 to -0.900% at three QC levels and LLOQ QC.</td>
<td>Inter-run bias ranged from 8.67 to -1.13%. Intra-run bias ranged from -10.6 to 12.8% at three QC levels and LLOQ QC.</td>
</tr>
<tr>
<td>Precision</td>
<td>Inter-run ( \leq 7.05 % ) CV and intra-run ( \leq 7.91 % ) CV at three QC levels and LLOQ QC.</td>
<td>Inter-run ( \leq 11.8 % ) CV and intra-run ( \leq 8.26 % ) CV at three QC levels and LLOQ QC.</td>
</tr>
</tbody>
</table>

(Source: Bioanalytical Method Validation Report (Hydrocodone) and Bioanalytical Method Validation Report (Guaifenesin) module 5.3.1.2).

The performance of the bioanalytical method during PK sample analysis from the pivotal BE study (102-13-US) is listed in Table 5.

Table 5. Bioanalytical assay performance of in-study validation for hydrocodone and guaifenesin

<table>
<thead>
<tr>
<th></th>
<th>Hydrocodone</th>
<th>Guaifenesin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linearity</strong></td>
<td>Satisfactory: Standard curve ranged from 0.05 to 30.0 ng/mL, ( r^2 \geq 0.9977 ).</td>
<td>Satisfactory: standard curve ranged from 5.00 to 5000 ng/mL, ( r^2 \geq 0.9974 ).</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Inter-run bias ranged from 0.889 to 7.33% at three QC levels.</td>
<td>Inter-run bias ranged from -7.78 to 3.33% at three QC levels.</td>
</tr>
</tbody>
</table>
2.4.2 How are parent drug and relevant metabolites identified?

Only parent drugs, hydrocodone or guaifenesin, were measured in the PK studies 102-13-US and 099-13-US.

2.4.3 For all moieties measured, is free, bound, or total measured?

Total amount of hydrocodone and guaifenesin were measured.

2.4.4 What is the sample stability under conditions used in the study?

Hydrocodone solution was stable for 74 days at 4°C. The frozen matrix was stable for 396 days at -70 °C. The matrix could sustain three cycles thawed at room temperature. The thawed matrix was stable for 18.25 hours at room temperature. The batch run stability was 97 hours at 4°C.

Guaifenesin solution was stable for 30 days at 4°C. The frozen matrix was stable for 140 days at -70 °C. The matrix could sustain four cycles thawed at room temperature. The thawed matrix was stable for 7.5 hours at room temperature. The batch run storage integrity was 68 hours at 4°C.

Samples from PK studies 102-13-US and 99-13-US were stored and analyzed within the determined storage stability period and conditions for both hydrocodone and guaifenesin.

2.4.5 How does the range of standard curve relate to the requirements for clinical studies? What curve fitting techniques were used?

Quantitation of both hydrocodone and guaifenesin was performed using analyte to IS peak area ratio and linear regression with a weighting factor of 1/concentration². The linear range of the standard curves for hydrocodone and guaifenesin were 0.05-30 ng/ml and 5-5000 ng/mL, respectively.

There were no samples requiring dilution due to concentrations that were above the upper limit of quantification (ULOQ) for both hydrocodone and guaifenesin. Similarly, none of the sample concentrations were below the lower limit of quantification (LLOQ) at the first sampling time point after three mean elimination half-lives (15 hours for hydrocodone and 3 hours for guaifenesin).

2.4.6 What is the result for the re-analysis of the incurred samples?

Hydrocodone and guaifenesin samples from each PK study (102-13-US and 099-13-US) were re-analyzed as part of the incurred sample reanalysis. The acceptance criterion was met demonstrating satisfactory performance of the method throughout the sample analysis period.
3 LABELING RECOMMENDATIONS

Label is not being reviewed because a complete response is considered appropriate from a clinical pharmacology perspective for this submission.

4 APPENDICES

4.1 Individual Study Review

4.1.1 Study 102-13-US

Study Type: Phase 1 single-dose bioequivalence study in healthy volunteers

Title: A randomized, open-label, balanced, three-treatment, three-period, three-sequence, single-dose, crossover comparative oral bioavailability study of a Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg immediate release tablets of ECI Pharmaceuticals versus a Tussigon® (Hydrocodone bitartrate 5 mg and Homatropine 1.5 mg) Tablets of King Pharmaceuticals versus Guaifenesin 400 mg tablets in 14 healthy, adult, human subjects under fasting conditions yielding a total evaluable population of 42

Objective: to evaluate the rate and extent of absorption of equal dose of hydrocodone bitartrate 5 mg and guaifenesin 400 mg from a test formulation of immediate release tablets of hydrocodone bitartrate 5 mg/guaifenesin 400 mg (ECI Pharmaceuticals) compared with two marketed reference products: Tussigon® (hydrocodone bitartrate 5 mg and homatropine methyl bromide1.5 mg) Tablets and OTC Guaifenesin 400 mg Tablets in healthy adults under fasting conditions.

Study Population: Healthy, adult subjects aged 18 to 65 years of age with normal vital signs, BMI range from to 18 to 30 kg/m², normal medical and surgical history.

The Applicant states no formal sample size determination was conducted based on current guidelines that a minimum of 12 volunteers is recommended to evaluate bioequivalence. Fourteen subjects were dosed in Period 1, and 13 subjects completed all three study periods. One subject withdrew consent in Period 1 due to repeated cannulas clotting and the need for additional venipunctures. The subject population included 8 males and 5 females, with averaged 32.0 ± 12.7 years of age.

Key Exclusion Criteria

- Use of any prescribed medication or OTC medicines or herbal medicinal products during the 21 days preceding the first period check-in until completion of the study.
- Treatment currently or within 21 days prior to check-in with any weak, moderate, and strong inhibitors of CYP2D6, CYP3A4, or P-gp transporter and or weak, moderate, and strong inducers of CYP3A4 and P-gp.
- Use of any investigational drug within 30 days prior to dosing.
- Refusal to abstain from the following foods from 14 days prior to first study drug administration until study completion: grapefruit, pomegranate, pomelo, and star fruit.
juice/products, as well as foods containing poppy seeds, Seville oranges, and/or drinks or foods containing quinine (i.e., tonic water).

**Study Design and Treatments:** This is an open-label, randomized, single-dose, three-treatment, three-period, crossover study conducted in healthy adults under fasting conditions. The washout period was seven days. Subjects received the treatment from one of the following products in each period:

- **Period 1 (Test product):** Single dose of hydrocodone bitartrate 5 mg / guaifenesin 400mg tablet from ECI Pharmaceuticals, LLC
- **Period 2 (Reference product 1):** Single dose of hydrocodone bitartrate 5 mg/homatropine methyl bromide1.5 mg tablet (Tussigon®, King Pharmaceuticals)
- **Period 3 (Reference product 2):** Single dose of OTC Guaifenesin 400 mg immediate-release tablet

During the three study periods, Test product or Reference products 1 and 2 were received in one of the sequences: Test, Reference 1, Reference 2; Reference 2, Test, Reference1; or Reference1, Reference 2, Test.

**PK Sampling:** Twenty-one (21) blood samples were collected from each subject during each period at pre-dose [within 1.00 hour prior to dosing] and at 0.16, 0.33, 0.5, 0.66, 0.83, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 20.0 and 24.0 hours post-dose.

The following PK parameters were determined from the plasma concentration-time curve: maximum plasma concentration (Cmax), time to reach Cmax (Tmax), area under the plasma concentration time curve from 0 hour to last measurable concentration (AUC<sub>0-t</sub>), area under the plasma concentration time curve from 0 hour to infinity (AUC<sub>0-inf</sub>), slope of the terminal portion of the plasma concentration versus time curve (K<sub>el</sub>), and elimination half-life (t<sub>1/2</sub>).

An intensive sampling collection for the first two-hours was adequate to capture peak plasma concentrations of both hydrocodone and guaifenesin. The 24-hour collection period was also adequate to capture more than 90% of the relevant AUC and characterize the elimination half-life for both components.

**Data Analysis and Criteria for Evaluation:** ANOVA was performed on ln-transformed AUCs and Cmax. The 90% confidence intervals (CI) were generated for the ratio of Test/Reference. 90% CI for the geometric mean ratio were obtained for AUCs and Cmax by taking the antilog of the 90% CI for the difference between means on the log scale.

To allow for comparison of the rate and extent of absorption of each active drug ingredient in the proposed hydrocodone/guaifenesin combination product to the rate and extent of absorption of each active drug ingredient administered concurrently in separate single-ingredient preparations, the ratios (Test/Reference) of geometric means and their corresponding 90% CIs were to be within 80.00-125.00% goal post for Cmax, AUC<sub>0-t</sub>, and AUC<sub>0-inf</sub>.
PK Analytical Method: Plasma samples were assayed for hydrocodone and guaifenesin using a validated LC-MS/MS method, as described in section 2.4. The results from calibration curve standards, quality control samples, and incurred sample met the regulatory criterion for acceptable performance during sample analysis. The study samples were stored and analyzed within the validated conditions.

Results
A total of 13 healthy adults completed the 3-period study. A total of 20 post-dose blood samples per subject per period were collected for measuring plasma concentrations of hydrocodone and guaifenesin.

Following a single oral dose of hydrocodone (5 mg), the ratios (Test/Reference 1, N=13) of least-squares geometric means (point estimate) for all pivotal PK parameters, Cmax, AUC0-t, AUC0-inf were closed to 100%, and their corresponding 90% CIs were all contained within the acceptance range of 80.00-125.00% (Table 6). Therefore, the hydrocodone component of the proposed combination product met the BE criteria.

Table 6. Geometric means, ratio (Test/Reference) of means and 90% confidence intervals for hydrocodone and guaifenesin PK parameters

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PK Parameter</th>
<th>Test (n=13)</th>
<th>Reference (n=13)</th>
<th>LSMean Ratio Test/Reference (%)</th>
<th>90% CI of Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test vs Reference Product 1</td>
<td>Cmax (ng/mL)</td>
<td>10.74</td>
<td>10.70</td>
<td>100.40</td>
<td>93.52-107.79</td>
</tr>
<tr>
<td></td>
<td>AUC0-t (ng.h/mL)</td>
<td>69.49</td>
<td>70.30</td>
<td>98.86</td>
<td>95.18-102.68</td>
</tr>
<tr>
<td></td>
<td>AUC0-inf (ng.h/mL)</td>
<td>74.14</td>
<td>75.00</td>
<td>98.84</td>
<td>94.39-103.51</td>
</tr>
<tr>
<td>Test vs Reference Product 2</td>
<td>Cmax (ng/mL)</td>
<td>1629</td>
<td>1773</td>
<td>91.85</td>
<td>76.68-110.01</td>
</tr>
<tr>
<td></td>
<td>AUC0-t (ng.h/mL)</td>
<td>2651</td>
<td>2756</td>
<td>96.20</td>
<td>89.17-103.77</td>
</tr>
<tr>
<td></td>
<td>AUC0-inf (ng.h/mL)</td>
<td>2666</td>
<td>2766</td>
<td>96.39</td>
<td>89.29-104.05</td>
</tr>
</tbody>
</table>

Test product: Hydrocodone bitartrate 5 mg/guaifenesin 400 mg tablet (ECI Pharmaceuticals)
Reference product 1: Hydrocodone bitartrate 5 mg/homatropine methyl bromide1.5 mg tablet (Tussigon®, King Pharmaceuticals)
Reference product 2: OTC Guaifenesin 400 mg Tablet
(Source: Adapted from BE Effect Study SAS output codes 0003 module 5.3.1.2, and CSR 102-13-US Tables 15 and 18)

Following a single oral dose of guaifenesin (400 mg), the point estimates (Ratio Test/Reference 2, N=13) and the 90% CIs for AUC0-t and AUC0-inf were contained within the acceptance range of 80.00-125.00% (Table 6). However, the 90% CI for Cmax was not, as the lower end of 90% CI was 76.68%. Therefore, the guaifenesin component of the proposed combination product did not met the BE criteria.
Conclusions: The PK results of this study demonstrated that the rate and extent of absorption of hydrocodone were comparable between the test product and the reference product 1 (Tussigon®) as the ratios (test/reference) and associated 90% CIs for C\text{max}, AUC\text{0-t}, and AUC\text{0-inf} were within the bioequivalence range of 80.00-125.00%. However, bioequivalence was not established for guaifenesin between the test product and the reference product 2 (OTC Guaifenesin 400 mg Tablets) as the lower boundary of 90% CI of Guaifenesin C\text{max} ratio was numerically lower (76.68) than the acceptance range of 80.00-125.00%.

Reviewer’s comments: Reviewer’s independent PK analysis showed similar results compared to Applicant’s analysis for both hydrocodone and guaifenesin.

4.1.2 Study 099-13-US

Study Type: Phase 1 single-dose food effect bioavailability study in healthy subjects

Title: A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two-way crossover oral food effect study comparing Hydrocodone Bitartrate 5 mg/Guaifenesin 400 mg immediate release tablets of ECI Pharmaceuticals LLC in 14 healthy, adult, human subjects under fed (high fat high calorie breakfast) versus fasting conditions yielding a total evaluable population of 28.

Objectives
Primary objective: to evaluate the effect of food (high fat high calorie breakfast) on the rate and extent of absorption of a single oral dose of hydrocodone bitartrate 5 mg/guaifenesin 400 mg immediate-release tablet formulation.

Secondary objective: to monitor clinical status, adverse events, laboratory investigations and assess relative safety and tolerability of hydrocodone bitartrate 5 mg/guaifenesin 400 mg tablet when administered under fasted and fed conditions to healthy adults.

Study population: Healthy, adult subjects aged 18 to 65 years of age with normal vital signs, BMI range from to 18 to 30 kg/m\textsuperscript{2}, normal medical and surgical histories.

The Applicant states that no formal sample size determination was conducted based on the current guidelines that a minimum of 12 subjects is recommended for assessment of food effects on bioavailability. Fourteen (14) subjects were screened, and 13 completed both study Period 1 and 2. One subject withdrew prior to the start of the study in Period 1 and did not receive the study drug. The population included 7 males and 6 females, with averaged 27.2 ± 8.2 years of age.

Key Exclusion Criteria
- Use of any prescribed medication or OTC medicines or herbal medicinal products during the 21 days preceding the first period check-in until completion of the study.
- Treatment currently or within 21 days prior to check-in with any weak, moderate, and strong inhibitors of CYP2D6, CYP3A4, or P-gp transporter and or weak, moderate, and strong inducers of CYP3A4 and P-gp.
- Use of any investigational drug within 30 days prior to dosing.
- Refusal to abstain from the following foods from 14 days prior to first study drug administration until study completion: grapefruit, pomegranate, pomelo, and star fruit juice/products, as well as foods containing poppy seeds, Seville oranges, and/or drinks or foods containing quinine (i.e., tonic water).

**Study Design and Treatments:** This was an open-label, randomized, single-dose, two-periods, two-treatments crossover study conducted under fasting and fed conditions in healthy subjects. Subjects were randomized into Treatment A (fed conditions, high fat high calorie breakfast 30 minutes prior to dosing) and Treatment B (fasted conditions) during two study periods (Period 1 and Period 2). The washout period was seven days. Subjects received one tablet of the test product of hydrocodone bitartrate 5 mg/guaifenesin 400 mg (ECI Pharmaceuticals, LLC) in both periods.

**PK Sampling:** Twenty-one (21) blood samples were collected from each subject during each period, at pre-dose [within 1.00 hour prior to dosing] and at 0.16, 0.33, 0.5, 0.66, 0.83, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 20.0 and 24.0 hours post-dose.

The following PK parameters were determined from the plasma concentration-time curve: Cmax, Tmax, AUC_{0-t}, AUC_{0-inf}, Ke, and t_{1/2}.

**Analytical Method:** Plasma samples were assayed for hydrocodone and guaifenesin using a validated LC-MS/MS method, as described in section 2.4. The results from calibration curve standards, quality control samples, and incurred sample met the regulatory criterion for acceptable performance during sample analysis. The study samples were stored and analyzed within the validated conditions.

**Results**
A total of 13 healthy adults completed both periods of the study. A total of 20 post-dose blood samples per subject per period were collected for measuring plasma concentrations of hydrocodone and guaifenesin.

The systemic exposure of hydrocodone was comparable between fed condition and fasted condition. The median Tmax was delayed approximately 0.5 hour under fed conditions (Table 7).

Food affected the peak concentration of guaifenesin, approximately 35% lower Cmax; however, food did not affect the overall exposure (AUC_{0-t} and AUC_{0-inf}). The median Tmax was delayed approximately 0.33 hour under fed conditions (Table 7).
Table 7. Geometric means, ratio (fed/fasted) of means for hydrocodone and guaifenesin PK parameters comparing fed and fasted conditions

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Fed (n=13)</th>
<th>Fasted (n=13)</th>
<th>LSMean Ratio Fed/Fasted (%)</th>
<th>90% CI of Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocodone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>10.43</td>
<td>9.83</td>
<td>106.14</td>
<td>97.68-115.32</td>
</tr>
<tr>
<td>AUCₜₐₒ (ng.h/mL)</td>
<td>72.69</td>
<td>67.40</td>
<td>107.85</td>
<td>101.62-114.46</td>
</tr>
<tr>
<td>AUCₜₐ₋ₖ (ng.h/mL)</td>
<td>76.87</td>
<td>71.21</td>
<td>107.95</td>
<td>100.83-115.56</td>
</tr>
<tr>
<td>Median Tmax (h)</td>
<td>2.00</td>
<td>1.50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Guaifenesin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>890.5</td>
<td>1375</td>
<td>64.76</td>
<td>52.41-80.01</td>
</tr>
<tr>
<td>AUCₜₐₒ (ng.h/mL)</td>
<td>2276</td>
<td>2521</td>
<td>90.29</td>
<td>76.86-106.05</td>
</tr>
<tr>
<td>AUCₜₐ₋ₖ (ng.h/mL)</td>
<td>2317</td>
<td>2536</td>
<td>91.35</td>
<td>77.27-107.99</td>
</tr>
<tr>
<td>Median Tmax (h)</td>
<td>1.00</td>
<td>0.66</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Test product: Hydrocodone bitartrate 5 mg/guaifenesin 400 mg tablet (ECI Pharmaceuticals)
(Source: Adapted from Food Effect Study SAS Output Codes 0003 module 5.3.1.2, and CSR 099-13-US 0003 Tables 14 and 16)

Conclusions: The pharmacokinetic results of the food-effect study demonstrated that the overall systemic bioavailability of hydrocodone was not affected by food; although median Tmax was slightly delayed (around 0.5 hour) under fed conditions. A decrease in guaifenesin mean Cmax (around 35% lower) was observed when the proposed product was administered under fed conditions; however, no significant effect on exposure with respect to AUC.

Reviewer’s comments:

Reviewer’s independent PK analysis showed similar results compared to Applicant’s analysis for both hydrocodone and guaifenesin.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MANUELA GRIMSTEIN
01/09/2017

ANSHU MARATHE
01/09/2017

CHANDRAHAS G SAHAJWALLA
01/09/2017

Reference ID: 4039428
CLINICAL REVIEW

Application Type: NDA
Application Number(s): 208-085
Priority or Standard: S
Submit Date(s): 04/13/2016
Received Date(s): 04/13/2016
PDUFA Goal Date: 02/13/2017
Division / Office: DPARP/ODE II/OND
Reviewer Name(s): Xu Wang, M.D.
Review Completion Date: 01/09/2017

Established Name: Hydrocodone Bitartrate and Guaifenesin (5 mg/400 mg) tablets
(Proposed) Trade Name: [Redacted] tablets
Therapeutic Class: Antitussive and expectorant
Applicant: ECI Pharmaceuticals, LLC

Formulation(s): Tablet
Dosing Regimen: One tablet every 4 to 6 hours, not to exceed 6 doses in 24 hours
Indication(s): For symptomatic relief of cough, to loosen (mucus)

Intended Population(s): Adults 18 years of age and older

Template Version: March 6, 2009
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends a Complete Response action for the Hydrocodone Bitartrate and Guaifenesin tablets for symptomatic relief of cough, to loosen mucus in patients 18 years of age and older, because the guaifenesin component of the proposed drug product was not bioequivalent to the reference drug.

1.2 Risk Benefit Assessment

This is a 505(b)(2) application for an immediate release oral tablets fixed dose combination drug product containing hydrocodone bitartrate and guaifenesin (5 and 400 mg, respectively). The development program for the proposed drug product is a clinical pharmacology program. As a basis for the 505(b)(2) submission pathway, the Applicant uses Tussion (hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg) as the reference drug for hydrocodone component of the combination product. The Applicant cites OTC Monograph 21 CFR 341.18 to support guaifenesin component of the combination drug product. The proposed drug product depends on the bioequivalence to the reference drugs to support its safety and effectiveness. No clinical efficacy and safety studies were submitted to support this application.

The clinical pharmacology studies demonstrated the bioequivalence between the hydrocodone component of the proposed drug product and the reference drug. However, the guaifenesin component of the proposed drug product was not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of Cmax is outside of the 80 -125% goal post for bioequivalence). Because the proposed drug product was not bioequivalent to the reference drug, clinical efficacy and safety studies are required for risk benefit assessment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No special postmarket risk evaluation and mitigation strategies are recommended at this time since the recommended regulatory action is Complete Response.

1.4 Recommendations for Postmarket Requirements and Commitments

No special Phase 4 commitments are recommended at this time since the recommended regulatory action is Complete Response.
2 Introduction and Regulatory Background

2.1 Product Information

The Applicant has developed an immediate release oral tablet formulation of hydrocodone and guaifenesin. The drug product contains 5 mg hydrocodone bitartrate and 400 mg guaifenesin per tablet. It is proposed as a prescription fixed dose combination of antitussive and expectorant. The labeled indication is for symptomatic relief of cough and to loosen mucus associated with the common cold.

Hydrocodone (HC) is a commonly used antitussive. The safety and effectiveness of HC as a prescription drug for the symptomatic relief of cough are supported by DESI review and by the FDA approved product Hycodan (NDA 5-213). HC is an opioid, a schedule II controlled substance as a single ingredient (21 CFR 1308.12). Also, according to 21 CFR 1308 published on February 27, 2014 in Federal Register Volume 79, Number 39, all HC combination products (analgesic and antitussive) are placed into schedule II controlled substance as well.

Hycodan Tablets and Syrup (HC 5 mg plus homatropine methylbromide (HTM) 1.5 mg, and HC 5 mg plus HTM 1.5 mg per 5 mL, NDA 5-213) were classified in the DESI review as safe and effective for prescription drug for the symptomatic relief of cough (DESI Notice #5123). The approved dosages are:

- Adults: One tablet or one teaspoonful of the syrup (5 mg HC) every 4 to 6 hours as needed; not to exceed (NTE) 6 tablets or 6 teaspoonfuls (30 mg HC) in 24 hours
- Children 6 to 12 years of age: One-half (1/2) tablet or one-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 tablets or 3 teaspoonfuls (15 mg HC) in 24 hours
- Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age is contraindicated due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic product labeling].

Guaifenesin (GU) is considered to be generally recognized as safe and effective (GRASE) as an expectorant [21 CFR 341.18] in the following age groups at the following oral doses [21 CFR 341.78]:

- Adults and children 12 years of age and older: 200 to 400 mg every 4 hours, NTE 2400 mg in 24 hours
- Children 6 to under 12 years of age: 100 to 200 mg every 4 hours, NTE 1200 mg in 24 hours
- Children 2 to under 6 years of age: 50 to 100 mg every 4 hours, NTE 600 mg in 24 hours
- Children under 2 years of age: consult a doctor
The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

**Reviewer’s comments:**

Hydrocodone, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50).

However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product, which can be found in detail in Medical Officer Review, IND M-001, MR, Charles E. Lee, M.D., 9/25/2006. Briefly, during the FDA deliberations on the approvability of Tussionex Pennkinetic extended release suspension (NDA 19-111) at the Center Level the FDA determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. The development program for Tussionex Pennkinetic was comprised of 3 bioavailability studies and no clinical studies. Based on this prior precedent, the Division has accepted the conclusion that for a HC combination product containing monograph active ingredients, a drug development plan does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the efficacy and safety of the combination product, and that approval can be based on establishment of bioequivalence.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

Hydrocodone is currently approved in the United States in tablet and syrup as an immediate release antitussive drug (Hycodan, NDA 5-213). The owner of NDA 5-213, Endo Pharmaceuticals, had withdrawn the products voluntarily not because of reasons of safety or efficacy. The company keeps the NDA 5-213 current, but stopped manufacturing and marketing the Hycodan Tablets and Solution on January 4 and May 14, 2008, respectively. Hydrocodone is also approved in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111). Also, hydrocodone is approved as immediate release formulations in combination with guaifenesin (Guaifenesin and Hydrocodone Bitartrate Oral Solution, Obredon, NDA 205-474), chlorpheniramine maleate (Vituz, NDA 204-307), pseudoephedrine HCl (Rezira, NDA 22-442), and chlorpheniramine maleate and pseudoephedrine HCl (Zutripro, NDA 22-439).

There are other generic hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussigon (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). Guaifenesin is a readily
available immediate release OTC monograph drug, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph doses to loosen (mucus).

2.3 Availability of Proposed Active Ingredient in the United States

Hydrocodone is currently available in combination with guaifenesin, chlorpheniramine maleate, and pseudoephedrine HCl in NDAs and multiple generic antitussive drugs. In addition, hydrocodone is available in the United States in tablet and capsule formulations as analgesic medications at higher doses than antitussives, such as Vicoprofen (NDA 20716), Vicodin and Vicodin HP (ANDA 88058, ANDA 40117), Lortab (ANDA 40100, ANDA 87722), and Anexsia (ANDA 40405, ANDA 40409, ANDA 40686, ANDA 89160).

Guaifenesin is currently approved in the United States in tablet (Mucinex ER, NDA 21-282), in combination with dextromethorphan (Mucinex™ DM, NDA 21-620), hydrocodone bitartrate (NDA 205-474), and pseudoephedrine HCl (NDA 21-585). These products are extended release formulations. Guaifenesin is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

2.4 Important Safety Issues With Consideration to Related Drugs

Hydrocodone is a semi-synthetic opioid that has the potential for abuse. Dependence and tolerance may develop upon repeated administration. Hydrocodone is a schedule II controlled substance as a single ingredient (21 CFR 1308.12). Also, according to 21 CFR 1308 published on February 27, 2014 in Federal Register Volume 79, Number 39, all hydrocodone combination products (analgesic and antitussive) are placed into schedule II controlled substance as well.

The Controlled Substances Staff (CSS) was consulted to advise on the abuse potential for the related triple combination product (NDA 22-279) during its review cycle. The CSS concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies (Memorandum, Consult on NDA 22-279, N000, Controlled Substance Staff, March 27, 2009). On June 12, 2009, a CDER regulatory briefing was held to discuss the need for abuse potential studies for these products. The consensus from the panel was that abuse potential assessment was not required for these combination products. These types of combinations have been on the market for years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The panel recommended that a post-marketing signal could trigger the need for abuse potential studies for these products.
2.5 Summary of Presubmission Regulatory Activity Related to Submission

- 6/23/2010: ECI submitted a pre-IND meeting request (pre0IND 109,251). Upon review of the briefing document submitted on 8/21/2010, the Division cancelled the meeting, but provided comments on the drug development program in a facsimile dated 9/21/2010. The Division’s comments stated that for the proposed immediate release hydrocodone and guaifenesin tablets 505 (b)(2) would be an appropriate pathway, and a single dose bioequivalence (BE) study comparing the proposed drug product against each of the active individual components administered separately under fasted state and a food effect study to evaluate the effect of food ion the proposed drug product would be required.
- 2/25/2011: ECI had a Type B meeting with the Division further discuss the drug development program for the proposed drug product. In addition to comments on issues of product quality and stability for the proposed drug product and reference drugs for the pharmacology studies, the Division advised that additional studies might be necessary to support efficacy and safety of the proposed product in pediatric population.
- 11/11/2013: ECI submitted an opening IND (IND 109,251) including protocols for 2 clinical pharmacology studies (a single dose BE study and a food effect study).
- 4/13/2016: NDA 208-085 N000 was filed for the proposed drug product.

2.6 Other Relevant Background Information

On 05/07/2016 the Applicant submitted a Request for Proprietary Name Review for the proposed drug product for the name [(b)(4)] The Agency concluded that the proposed proprietary name was not acceptable. Proprietary Name Request Unacceptable Letter was conveyed to the Applicant on 08/04/2016.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The review team requested the inspection for the clinical and analytical sites of the clinical pharmacology studies. The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) concluded that the clinical data from the audited study to be reliable and no significant deficiencies were observed. OSIS recommends that the data for the clinical portion of study submitted to NDA 208085 be accepted. [NDA 208-085, MEMORANDUM, Arindam Dasgupta, PhD, Division of New Drug Bioequivalence Evaluation Office of Study Integrity and Surveillance (OSIS), 12/6/2016]
However, OASIS inspection of the manufacture site found some issues that need to be verified at the time of completion of this review.

3.2 Compliance with Good Clinical Practices

The clinical pharmacology studies in this application were conducted in accordance with Good Clinical Practices. The applicant certified that the clinical contractor complied with all applicable federal, state and local laws, codes, regulations, and orders, including, but not limited to, the Federal Food, Drug, and Cosmetic Act and regulations promulgated there under, and Institutional Review Board requirements relative to clinical studies.

3.3 Financial Disclosures

The applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The Applicant stated that the clinical investigator of the clinical pharmacology studies in this application certified that he did not have a proprietary interest in the proposed product or a significant equity in the Applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Hydrocodone Bitartrate and Guaifenesin tablets are white, capsule-shaped tablets, debossed "ECI" on one side and "601" on the other side. Each tablet contains 5 mg of Hydrocodone Bitartrate and 400 mg of Guaifenesin. Table 1 below lists the composition and function of the drug product ingredients. The drug product Hydrocodone Bitartrate and Guaifenesin tablets is manufactured, processed, and packaged by ECI Pharmaceuticals, LLC. At Fort Lauderdale, Florida.

The drug substance hydrocodone bitartrate, USP, is manufactured by[2]. The drug substance guaifenesin is manufactured by[2].
Table 1 Composition of drug product ingredients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quality Standard</th>
<th>Function</th>
<th>Quantity (mg/tablet)</th>
<th>% w/w</th>
<th>Quantity per batch (kg) [Exhibit Batches]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone Bitartrate</td>
<td>USP</td>
<td>Active Ingredient</td>
<td>5</td>
<td></td>
<td>(0) (4)</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td>(0) (4)</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>USP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Weight</strong></td>
<td></td>
<td></td>
<td><strong>505</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: NDA 2080085, 3.2.P.1 Description and Composition of the Drug Product.

CMC review team has some concerns about the manufacture process of the proposed drug product to ensure the content uniformity of hydrocodone component, because the drug content of hydrocodone is *(0)(4)*% (w/w). Detailed review of the CMC portion of the application can be found in the ONDQA drug product (DP) and drug substance (DS) reviews by Drs. Christopher Hough and Debasis Ghosh.

4.2 Clinical Microbiology

There are no clinical microbiology issues for the proposed Hydrocodone Bitartrate and Guaifenesin tablets.

4.3 Preclinical Pharmacology/Toxicology

No preclinical pharmacology or toxicology studies were conducted with the proposed Hydrocodone Bitartrate and Guaifenesin tablets.

4.4 Clinical Pharmacology

The clinical development program in this application was comprised of 2 clinical pharmacology studies. Table 1 summarizes the studies that make up the clinical program. The 2 clinical pharmacology studies are discussed in Section 5 Sources of Clinical Data below.
4.4.1 Mechanism of Action

Hydrocodone is a semisynthetic narcotic 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.

4.4.2 Pharmacodynamics

As described above, the clinical development program was comprised of 2 clinical pharmacology studies. No PD studies were performed.

4.4.3 Pharmacokinetics

The PK results from the 2 clinical pharmacology studies are discussed in Section 5 Sources of Clinical Data below. The detailed PK data and review can be found in the Clinical Pharmacology Review by Manuela Grimstein, Ph.D.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant included 2 clinical pharmacology studies in this submission (Table 2).

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study type</th>
<th>Treatment group</th>
<th>Design</th>
<th>Subject No.</th>
<th>Subjects</th>
<th>BE Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECI 102-13-US</td>
<td>BA/BE</td>
<td><strong>A Test drug</strong></td>
<td>Randomized, open label, single dose, 3-way crossover</td>
<td>14</td>
<td>Healthy adult males and females</td>
<td>Hydrocodone was BE to reference; Cmax of guaifenesin failed to meet BE criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>B Reference 1: Tussigon tablet (hydrocodone bitartrate 5 mg/ homatropine 1.5 mg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>C Reference 2: Guaifenesin 400 mg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**5.2 Review Strategy**

This is mainly a review of clinical pharmacology studies. Detailed review of the clinical pharmacology data can be found in the Clinical Pharmacology Review. [NDA 208-085, Clinical Pharmacology Review, Manuela Grimstein, Ph.D.]

**5.3 Discussion of Individual Studies/Clinical Trials**

Study ECI 102-13-US is entitled “A randomized, open-label, balanced, three-treatment, three-period, three-sequence, single-dose, crossover comparative oral bioavailability study of a Hydrocodone Bitartrate 5 mg/Guaifenesin 400 mg immediate release tablets of ECI Pharmaceuticals LLC versus Tussigon (Hydrocodone bitartrate 5 mg and Homatropine 1.5 mg) Tablets of King Pharmaceuticals and Guaifenesin 400 mg tablets in 14 healthy adult human subjects under fasting conditions”. Fourteen (14) subjects were randomized to receive 1) Test drug, Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg immediate release tablet; 2) Reference 1, Tussigon (Hydrocodone bitartrate 5 mg and Homatropine 1.5 mg) tablet; or 3) Reference 2, Guaifenesin 400 mg tablet. After a washout period of 7 days, the subjects crossed over to receive another treatment until each subject received all 3 treatments. After study drug administration, serial blood samples were collected over a period of 24 hours. Plasma concentrations of hydrocodone and guaifenesin were measured by LC-MS/MS method. Pharmacokinetic (PK) parameters Cmax, AUC0-t, AUC0-∞, and kel were determined for the Hydrocodone and Guaifenesin, respectively (Table 3). One subject withdrew consent in the first period due to the difficulty in obtaining blood sample. A total of 13 subjects completed the study and provided PK data for analysis. The data showed that hydrocodone in test drug and references are bioequivalent. The ratios between test drug and references in Cmax, AUC0-t, and AUC0-∞ for hydrocodone are within the bioequivalence range of 80% to 125%. The guaifenesin in the test drug, however, was not bioequivalent to that of the reference drug. The 90% confidence interval of the ratio between test drug and reference in Cmax fell outside of the bioequivalence range of 80% to 125%.

One subject reported 2 adverse events (nausea and vomiting) after taking the test drug. There were no death or serious adverse events reported during the study.
Table 3 PK profile of hydrocodone and guaifenesin in test drug and references (ECI 102-13-US)

<table>
<thead>
<tr>
<th></th>
<th>Test drug</th>
<th>Reference 1</th>
<th>Reference 2</th>
<th>Test/Ref ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocodone (mean)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>10.74</td>
<td>10.70</td>
<td></td>
<td>1.00 (0.94 – 1.08)</td>
</tr>
<tr>
<td>AUC_{0-t} (µg·h/mL)</td>
<td>69.49</td>
<td>70.30</td>
<td></td>
<td>0.99 (0.95 – 1.03)</td>
</tr>
<tr>
<td>AUC_{0-inf} (µg·h/mL)</td>
<td>74.14</td>
<td>75.00</td>
<td></td>
<td>0.99 (0.94 – 1.04)</td>
</tr>
<tr>
<td><strong>Guaifenesin (mean)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>1629</td>
<td>1773</td>
<td></td>
<td>0.92 (0.77 – 1.10)</td>
</tr>
<tr>
<td>AUC_{0-t} (µg·h/mL)</td>
<td>2651</td>
<td>2756</td>
<td></td>
<td>0.96 (0.89 – 1.04)</td>
</tr>
<tr>
<td>AUC_{0-inf} (µg·h/mL)</td>
<td>2666</td>
<td>2766</td>
<td></td>
<td>0.96 (0.89 – 1.04)</td>
</tr>
</tbody>
</table>

Source: NDA 208-085, 2.7.1 Summary of Biopharmaceutical studies and Associated Analytical Methods

Study ECI 099-13-US is entitled “A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two-way crossover oral food effect study comparing Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg immediate release tablets of ECI Pharmaceuticals LLC in 14 healthy adult human subjects under fed (high fat high calorie breakfast) versus fasting conditions”. Fourteen (14) subjects were randomized to receive 1) Test drug, Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg immediate release tablet, after a standard overnight (10 hours) fast; 2) Test drug, Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg immediate release tablet, after consuming a standard high fat high calorie breakfast. After a washout period of 7 days, the subjects crossed over to receive another treatment. Plasma concentrations of Hydrocodone and Guaifenesin were measured by LC-MS/MS method. Pharmacokinetic (PK) parameters Cmax, Tmax, t\textsubscript{1/2}, AUC_{0-t}, AUC_{0-∞}, and kel were determined for the Hydrocodone and Guaifenesin, respectively. One subject withdrew consent prior to the start of the study. A total of 13 subjects completed the study and provided PK data for analysis.

Hydrocodone under the fast and fed conditions had similar PK characteristics among these healthy adult human subjects. The ratios between fed and fast in Cmax, AUC_{0-t}, and AUC_{0-inf} for hydrocodone were within the bioequivalence range of 80% to 125%. However, the gauifenesin component of the test drug showed a significant food effect on Cmax and AUC. The ratio of Cmax between fed and fast was 0.65 with a 90% CI of 0.52 – 0.80. The ratios of AUC_{0-t} and AUC_{0-inf} between fed and fast were 0.90 (90% CI 0.77 – 1.06) and 0.91 (90% CI 0.77 – 1.08), respectively (Table 4). Both hydrocodone and gauifenesin reach the maximum blood concentration at a shorter time at fast than at fed condition. The maximum blood concentrations of hydrocodone were at 2.0 and 1.5 hours after dosing at fast and fed condition, respectively. The maximum blood concentrations of gauifenesin were at 1.0 and 0.66 hours after dosing at fed and fast condition, respectively. The time to reach the maximum blood concentration (Tmax) would be expected shorter at fast than at fed condition, because the absorption of the test drug would be quicker after dosing at fast condition.

The test drug was well tolerated under both fast and fed conditions. There was no adverse event reported during the study.
Table 4 PK profiles of hydrocodone and guaifenesin at fed and fast conditions (ECI 099-13-US)

<table>
<thead>
<tr>
<th></th>
<th>Fed</th>
<th>Fast</th>
<th>Fed/Fast ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocodone (mean)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>10.43</td>
<td>9.83</td>
<td>1.06 (0.98 – 1.05)</td>
</tr>
<tr>
<td>AUC(_{0-t}) (µg·h/mL)</td>
<td>72.69</td>
<td>67.40</td>
<td>1.08 (1.02 – 1.14)</td>
</tr>
<tr>
<td>AUC(_{0-inf}) (µg·h/mL)</td>
<td>76.87</td>
<td>71.21</td>
<td>1.01 (1.01 – 1.16)</td>
</tr>
<tr>
<td>Tmax (hour)</td>
<td>2.0</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td><strong>Guaifenesin (mean)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>890.5</td>
<td>1375</td>
<td>0.65 (0.52 – 0.80)</td>
</tr>
<tr>
<td>AUC(_{0-t}) (µg·h/mL)</td>
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<td>2521</td>
<td>0.90 (0.77 – 1.06)</td>
</tr>
<tr>
<td>AUC(_{0-inf}) (µg·h/mL)</td>
<td>2317</td>
<td>2536</td>
<td>0.91 (0.77 – 1.08)</td>
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<tr>
<td>Tmax (hour)</td>
<td>1.0</td>
<td>0.66</td>
<td></td>
</tr>
</tbody>
</table>

Source: NDA 208-085, 2.7.1 Summary of Biopharmaceutical studies and Associated Analytical Methods

### 6 Review of Efficacy

**Efficacy Summary**

This is a clinical pharmacology program. The NDA submission is supported by comparison of the bioavailability of the proposed drug product to reference. No clinical efficacy studies were conducted to support this application.

#### 6.1 Indication

Hydrocodone Bitartrate and Guaifenesin tablet is indicated for symptomatic relief of cough and to loosen mucus associated with the common cold in patients 18 years of age and older.

### 7 Review of Safety

**Safety Summary**

The safety of the proposed drug product relies primarily on the Agency’s previous findings of approved hydrocodone product Tussigon (hydrocodone bitartrate and homatropine methylbromide) tablets and the OTC monograph for guaifenesin. Therefore the safety of the proposed drug product is determined by the bioequivalence to the reference drugs. Since the guaifenesin component of the proposed drug product failed to meet the BE criterion, the safety of the proposed drug product cannot be supported by the Agency’s previous findings. The Applicant needs to provide data to
demonstrate the bioequivalence of the proposed drug product to reference drugs or conduct clinical studies to support its safety and efficacy.

The Applicant submitted a Clinical Summary including the safety data from the clinical pharmacology studies ECI 102-13-US and ECI 099-13-US. The safety data did not identify a safety signal. A total of 28 subjects received single dose of the proposed drug product in the 2 studies, and the adverse event data from the 2 studies revealed no new safety signals.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical pharmacology studies ECI 102-13-US and ECI 099-13-US are used in this review to evaluate the safety of the proposed drug product. Note that the 2 clinical pharmacology studies are single dose studies in healthy subjects, and the safety data did not identify a safety signal.

7.1.2 Categorization of Adverse Events

The investigational staff recorded all adverse events (AEs), queried or spontaneously volunteered by the subjects. Subjects were instructed to inform the study physician and/or research personnel of any AEs that occurred at any time during the study. Subjects were monitored for AEs from the beginning of confinement through the end of study visit. Reported or observed AE, as well as the treatment administered, were documented in the source documents and on the case report form (CRF).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data from 2 clinical pharmacology studies were not pooled.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, the exposure to the study drug product from these 2 clinical pharmacology studies is small in terms of assessment of safety. Additionally, the demographics of the study subjects, although similar in both studies, represent a narrow population. Given these limitations, the data from these studies serve as an adjunct to what is already
available in the monograph and reference drug to determine the safety of the proposed drug product.

7.2.2 Explorations for Dose Response

There was no exploration for dose response.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was performed with the proposed drug product.

7.2.4 Routine Clinical Testing

Routine clinical chemistry, hematology, and urinalysis were checked at screening and at the end of study. Laboratory examinations were not safety endpoints in the clinical pharmacology studies of this application.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific metabolic, clearance, or interaction studies were performed with the proposed drug product.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

7.3.1 Deaths

There was no death in the 2 clinical pharmacology studies.

7.3.2 Nonfatal Serious Adverse Events

There was no nonfatal serious adverse event in the 2 clinical pharmacology studies.

7.3.3 Dropouts and/or Discontinuations

There were 2 dropouts in the clinical pharmacology program. The 2 dropouts were not related to any adverse events. One subject withdrew consent in study ECI 102-13-US after received the test drug due to repeated cannulas clotting and the need for additional venipunctures to collect blood sample. One subject in study ECI 099-13-US withdrew consent prior to taking the test drug for unknown reason.
7.3.4 Significant Adverse Events

There were no significant adverse events in the clinical pharmacology program.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the 2 clinical pharmacology studies, only one subject in study ECI 102-13-US reported nausea one hour after administration of single dose of proposed drug product Hydrocodone Bitartrate and Guaifenesin tablet. Then the same subject reported vomiting once 7 hours post dosing. No adverse event reported in study ECI 099-13-US.

The adverse events reported in the clinical pharmacology studies did not reveal a new safety signal.

7.4.2 Laboratory Findings

Laboratory examinations were not safety endpoints in the clinical pharmacology studies of this application.

7.4.3 Vital Signs

Vital sign assessments were conducted before and the end of the clinical pharmacology studies. No clinically significant changes from baseline data were reported.

7.4.4 Electrocardiograms (ECGs)

ECGs were not safety endpoints in the clinical pharmacology studies of this application.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or trials were conducted with this application.

7.4.6 Immunogenicity

Not applicable.
7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

No specific drug-drug interaction studies were conducted with this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed with this application.

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected in the clinical pharmacological studies with this application. Further, no adequate and well-controlled studies with hydrocodone and guaifenesin were performed in pregnant women, and no reproductive studies were conducted. The proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women.

There was a literature report of 2 cases of hydrocodone excretion in breast milk\(^1\). The infants of the mothers who were taking hydrocodone received an estimated 3.1% and 3.7% of the maternal weight-adjusted dosage. The absolute hydrocodone doses the infants received were 8.58 mcg/kg and 3.07 mcg/kg per day. One infant (18-day-old)

became groggy and slept for most of the day while the mother was taking 20 mg hydrocodone every 4 hours. The infant’s symptoms improved when mother decreased her hydrocodone dose by half. Another infant (5-week-old) became cyanotic and required intubation while the mother was taking hydrocodone and methadone for migraine headache. The infant was positive for opioids in urinary test and responded well to naloxone treatment. There are no reports of hydrocodone in breast milk while a mother takes hydrocodone at a much lower antitussive dosage. The prescribers and patients should be aware of the potential hydrocodone excretion into breast milk and use Hydrocodone Bitartrate and Guaifenesin tablets with caution.

7.6.3 Pediatrics and Assessment of Effects on Growth

The clinical pharmacology studies with the application included no pediatric subjects.

The safety and effectiveness of hydrocodone have been established in DESI review for the reference drug in pediatric population down to 6 years of age. However, there are safety concerns related to use of this product in pediatric population. On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received long-acting hydrocodone-containing cough product. [http://www.fda.gov/cder/drug/advisory/hydrocodone.htm, http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm] Currently, the safety of hydrocodone in pediatric population is still an issue under discussion in the Agency.

The safety of guaifenesin inpatients down to age 2 is established by OTC monograph. Guaifenesin is available for children down to 2 years old in OTC drug market.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no safety issues related to overdose, drug abuse, withdrawal, or rebound in the clinical pharmacology studies. The Applicant relies on the reference product, monograph, literature, and experience with the active ingredient hydrocodone to evaluate these issues. The proposed drug product is a Schedule II controlled product based on the hydrocodone component. The risks of drug abuse potential and overdose are well-recognized for the hydrocodone component.

7.7 Additional Submissions / Safety Issues

No additional submissions were provided, and no other safety issues were addressed.
8 Postmarket Experience

As the proposed drug product has not been marketed, there is no post-marketing experience. However, the active ingredients, hydrocodone and guaifenesin, have a long history of clinical use both separately and in combination. The current understanding of the safety and efficacy of these active ingredients and their clinical acceptability in practice come from post-marketing experience. Routine post-marketing surveillance would be beneficial for the product under review to monitor adverse events, particularly focusing on respiratory depression and any unexpected adverse events.

9 Appendices

9.1 Literature Review/References

The OTC monograph and the reference drug were the references used in this application. In the review process relevant literatures are referenced as noted in the review.

9.2 Labeling Recommendations

Proposed labeling was submitted in Physician’s Labeling Rule (PLR) format. Detailed labeling review is not conducted because the proposed drug product is not ready for approval in the present NDA application.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting is deemed unnecessary for this 505(b)(2) application. The two active ingredients present in this product are well known as individual drug substances, and, based on the current monograph and the Agency’s prior precedent, the combination of products of these classes are acceptable for the proposed indications.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XU WANG
01/09/2017

ANTHONY G DURMOWICZ
01/09/2017
PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 208085
Supporting document/s: SDN 1
Applicant's letter date: 4/13/2016
CDER stamp date: 4/13/2016
Product: Hydrocodone bitartrate and guaifenesin, 5 mg/400 mg, Tablets
Indication: For symptomatic relief of cough and to loosen mucus
Applicant: ECI Pharmaceuticals, LLC
Review Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer: Yu-Mee Kim, Ph.D., DABT
Acting Team Leader: Carol M. Galvis, Ph.D.
Division Director: Badrul A. Chowdhury, M.D., Ph.D.
Project Manager: LeAnn D. Brodhead

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208085 are owned by ECI Pharmaceuticals, LLC or are data for which ECI Pharmaceuticals, LLC has obtained a written right of reference.

Any information or data necessary for approval of NDA 208085 that ECI Pharmaceuticals, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208085.
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1 Executive Summary

1.1 Introduction

The proposed product in this NDA is for a tablet containing hydrocodone bitartrate and guaifenesin, and this combination drug product is proposed as a prescription product. Hydrocodone bitartrate is a generally recognized antitussive, with efficacy established in DESI Notice #5213, dated June 1, 1982; whereas guaifenesin is an accepted expectorant in the OTC Drug Monograph (21 CFR 341.18).

In accordance with 505(b)(2), ECI Pharmaceuticals, LLC, submitted a New Drug Application (NDA) on April 13, 2016 for hydrocodone bitartrate and guaifenesin, 5 mg/400 mg, tablets. The proposed indication is for the symptomatic relief of cough to loosen mucus in adult patients 18 years of age and older.

This nonclinical pharmacology and toxicology review includes evaluation of the proposed doses for each of the components from the nonclinical perspective.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical pharmacology or toxicology studies were conducted with the Hydrocodone Bitartrate and Guaifenesin tablets. The applicant (ECI pharmaceuticals, LLC) relied on the previously approved products and OTC monograph review and labeling for the individual products. Hydrocodone has been shown to be teratogenic in hamsters 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).

The acute and chronic toxicity studies in animals demonstrated no adverse pathological findings for guaifenesin based on OTC monograph review. Animal studies to assess carcinogenicity, genotoxicity, and effects on fertility have not been conducted with guaifenesin. Guaifenesin has been shown to be teratogenic in rats when given in doses greater than or equivalent to the MRHDD of 2400 mg/day.

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

Pharmacology and toxicology review of labeling for this drug product will be issued later in a separate document.
2 Drug Information

2.1 Drug

**Generic Name:** Hydrocodone and Guaifenesin tablets

Two active pharmaceutical ingredients (API) in the following:

**Hydrocodone Bitartrate**

**CAS Registry Number:** 34195-34-1

**Generic Name:** Hydrocodone bitartrate

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

Or
4,5α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

**Molecular Formula/Molecular Weight**
\[ C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O / 494.490 \]

**Structure**

![Structure](image)

Figure 1 Biochemical structure of hydrocodone bitartrate

**Pharmacologic Class:** Analgesic and antitussive
GUAIFENESIN

**CAS Registry Number:** 93-14-1
**Generic Name:** Guaifenesin

**Chemical Name**
1,2-Propanediol, 3-(2-methoxyphenoxy)-(±)-
(±)-3-(o-Methoxyphenoxy)-1,2-propanediol
(RS)-3-(2-methoxyphenoxy) propane-1,2-diol

**Molecular Formula/Molecular Weight**
$\text{C}_{10}\text{H}_{14}\text{O}_4$ / 198.22

**Structure**

Figure 2 Biochemical structure of guaifenesin

**Pharmacologic Class:** Expectorant

2.2 **Relevant INDs, NDAs, BLAs and DMFs**
- IND 109251 Hydrocodone and Guaifenesin Immediate Release Solid Oral Dose for Symptomatic relief of cough (ECI Pharmaceuticals, LLC)
- DMF
- DMF
- DMF

Reference ID: 4036856
2.3 Drug Formulation

Details of the drug product formulation are included in Dr. Patel’s IND 109251 review dated December 11, 2013.

The drug product consists of white capsule-shaped tablets, each containing 5 mg hydrocodone bitartrate and 400 mg guaifenesin. The formulation is summarized in the table below.

Table 1 Quantitative and Qualitative Composition and Function of Drug Product Ingredients (excerpted from the Sponsor’s submission)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talc</td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Magnesi</td>
<td>(b)(4)</td>
</tr>
</tbody>
</table>

None of the ingredients contain (b)(4) except Talc, USP. The specification of (b)(4) for Talc, USP was reported to be set at NMT (b)(4)%. The maximum amount of (b)(4) is approximately (b)(4) which is within the FDA limit for (b)(4).

2.4 Comments on Novel Excipients

The drug product contains no novel excipients. All excipient levels are within the levels found in approved oral products.

2.5 Comments on Impurities/Degradants of Concern

There is no safety concern for impurities.

2.6 Proposed Clinical Population and Dosing Regimen

Hydrocodone bitartrate and guaifenesin tablets were developed for symptomatic relief of cough, to (b)(4) loosen (b)(4) (mucus) (b)(4). The proposed dosing regimen is one tablet every 4 to 6 hours, not to exceed 6 tablets in 24 hours for
adult patients 18 years of age and older. Each tablet contains 5 mg hydrocodone bitartrate, 400 mg guaifenesin, crospovidone, maltodextrin, magnesium stearate, microcrystalline cellulose, povidone K 30, silicon dioxide, stearic acid, and talc. The maximum daily dose is 30 mg hydrocodone bitartrate and 2400 mg guaifenesin. This product is not indicated for pediatric patients under 18 years of age.

2.7 Regulatory Background
This drug product was developed under IND 109251. This 505(b)(2) NDA was originally submitted on April 13, 2016, by ECI pharmaceuticals, LLC.

3 Studies Submitted
None

4 Pharmacology
No study submitted

5 Pharmacokinetics/ADME/Toxicokinetics
No study submitted

6 General Toxicology
Nonclinical studies were not conducted with the drug product or any of the components individually under this NDA. Each active ingredient has a long history of clinical use in the US. Refer to Dr. Patel’s IND 109251 review dated December 11, 2013, for additional information (Appendix 1).

7 Genetic Toxicology
No study submitted

8 Carcinogenicity
No study submitted

9 Reproductive and Developmental Toxicology
No study submitted

10 Special Toxicology Studies
No study submitted

11 Integrated Summary and Safety Evaluation
The proposed product in this NDA is for a tablet containing hydrocodone bitartrate and guaifenesin. Hydrocodone is an opioid derived from codeine that has antitussive and
analgesic effects, whereas guaifenesin is a recognized expectorant. The combination drug product is proposed as a prescription product, which was submitted under the 505(b)(2) process. No nonclinical pharmacology and toxicology studies were conducted with Hydrocodone Bitartrate and Guaifenesin tablets; however, reference was made to existing safety data available for hydrocodone and guaifenesin, including current literature, the approved label for Tussigon® (ANDA # 088508), and the guaifenesin OTC monograph. Each active ingredient is widely used in the US and is generally recognized as safe and effective.

Hydrocodone is a semi-synthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. Although the precise mechanism of action of hydrocodone and other opiates is not known, hydrocodone is believed to act directly on the cough center. Hydrocodone bitartrate is a recognized antitussive, with efficacy established in Drug Efficacy Study Implementation (DESI) Notice 5213, dated June 1, 1982. Hydrocodone bitartrate is not included in any OTC monograph and is available on a prescription (Rx only) basis. There are several approved formulations containing hydrocodone including Hycodan® (NDA 05-213, 1943), Flowtuss (NDA 022424, 2014), Tussigon® (ANDA088508, 1985) and Zohydro ER (NDA 202880, 2013). Hydrocodone has been shown to be teratogenic in hamsters in a dose approximately 27 times the maximum recommended human daily dose (MRHDD) (on a mg/m^2 basis at a single subcutaneous dose of 102 mg/kg on gestation day 8) (Label of Flowtuss Oral Solution, 2014). In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and psychological dependence.

Guaifenesin has been used widely in the US as a recognized monograph drug (21 CFR 341.18). It is a recognized expectorant that promotes or facilitates the evacuation of secretions from the bronchial airways to provide for the temporary relief of cough due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion. The OTC monograph review for guaifenesin in Advanced Notice of Proposed Rulemaking, FR, Vol 41, No 176, 9/9/76, pp 38362 referenced that acute and chronic toxicity studies in animals demonstrated no adverse pathological findings for glyceryl guaiacolate (guaifenesin). Animal studies to assess carcinogenicity, genotoxicity, or effects on fertility have not been conducted with guaifenesin. Guaifenesin has been shown to be teratogenic in rats when given in doses greater than or equivalent to the maximum recommended human daily dose (MRHDD) of 2400 mg/day (on a mg/m^2 basis). Guaifenesin administered orally to female rats during the period of organogenesis resulted in fetal death at doses greater than or equal to 350 mg/kg/day (1.4 times the MRHDD). In this study, hemorrhagic spots and decreases in fetal weight and lengths of full body, skull, fore- and hind-limbs, and tail were observed in all treated groups at doses greater than or equivalent to 250 mg/kg/day (equivalent to the MRHDD). Limb and tail defects, increased intercostal space and improper development of limbs were observed at 500 or 600 mg/kg/day, equivalent to 2 or 2.4 times the MRHDD (Shabbir A, Shamsi S, Shahzad M, Butt HI, Aamir K, and Iqbal J. 2016. Evaluation of developmental toxicity of guaifenesin using pregnant female rats. Indian Journal of Pharmacology. 48 (3): 264-9).
Hydrocodone Bitartrate and Guaifenesin tablet is intended to provide symptomatic relief of cough and to loosen (mucus) in adult patients 18 years of age and older. This product is not indicated for pediatric patients under 18 years of age. The recommended dosage of each active ingredient for this NDA is within the dose ranges recommended in OTC monograph (21CFR 341.78 for guaifenesin) and the approved products (see Table 2).

Table 2 Recommended dosage in the approved product and OTC monograph for hydrocodone and guaifenesin, respectively

<table>
<thead>
<tr>
<th>Active ingredient administered by age group</th>
<th>Adults and children 12 years of age and over</th>
<th>Children 6 to 11 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone (Hycodan® Syrup by Endo)</td>
<td>q 4-6 hr 5 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td></td>
<td>NTE in 24 hr 30 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>Guaifenesin (21CFR341.78)</td>
<td>q 4 hr 200-400 mg</td>
<td>100-200 mg</td>
</tr>
<tr>
<td></td>
<td>NTE in 24 hr 2400 mg</td>
<td>1200 mg</td>
</tr>
</tbody>
</table>

The OTC monograph 21 CFR 341.40 recognizes the combination of any single monograph oral antitussive drug (such as codeine phosphate) 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 product containing monograph active ingredients has been accepted based on the prior regulatory precedent of approving Flowtuss (the combination of hydrocodone bitartrate and guaifenesin; NDA 22424), for which approval was based on establishment of bioequivalence only.

12 Appendix

Appendix 1: IND 109251 pharmacology/toxicology review dated December 11, 2013
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number: 109,251
Supporting document/s: SDN6
Sponsor’s letter date: November 11, 2013
CDER stamp date: November 12, 2013
Product: Hydrocodone and Guaifenesin Immediate Release Solid Oral Dose
Indication: Symptomatic relief of cough
Sponsor: ECI Pharmaceuticals LLC
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, M.D., Ph.D.
Project Manager: Laura Musse, R.N., M.S., C.R.N.P

Template Version: September 1, 2010

Reference ID: 3420253
Reference ID: 4036856
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1 Executive Summary

1.1 Introduction

The subject of the current investigator-sponsored IND is the use of hydrocodone 5 mg and guaifenesin 400 mg immediate-release (IR) combination oral tablets for the symptomatic relief of cough and to loosen mucus. Hydrocodone is believed to suppress cough by acting centrally on the cough center and guaifenesin is believed to work by stimulating receptors that cause increased respiratory tract fluid secretion, thereby reducing viscosity of the mucus in the lungs. In this opening IND, the sponsor proposes to conduct 2 clinical studies to evaluate the comparative bioavailability and bioequivalence of the proposed combination drug product.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were submitted with the current IND; however, reference is made to existing safety data available for hydrocodone and guaifenesin, including current literature, the approved label for Tussigon® (ANDA #.88508, most recent label from Monarch Pharmaceuticals, 2010), and the guaifenesin OTC monograph.

From the Tussigon® approved combination product label (see section 2.2 below for a summary of approved hydrocodone combination products), studies of Tussigon® in animals to evaluate the carcinogenic and mutagenic potential and the effect on fertility have not been conducted. Tussigon® is a Pregnancy Category C drug. Animal reproduction studies have not been conducted with Tussigon®. From the Lortab® label (hydrocodone 7.5 mg/acetaminophen 500 mg) hydrocodone has not demonstrated mutagenic potential in the Ames assay, the Basc test on Drosophila germ cells, and the mouse bone marrow Micronucleus test. Data summarized from published studies indicates that hydrocodone has adverse effects on reproduction and fertility in rats (reduced body weight gains and feed consumption in males and females, and reduced seminal vesicle weights in males). Hydrocodone had no reproductive effects in EFD studies in rats and rabbits, but it was found to have teratogenic potential in hamsters.

From approved product labels for guaifenesin, no studies have been conducted to assess the mutagenicity and carcinogenicity of guaifenesin. In addition there are no studies to assess the effects of guaifenesin on fertility and reproduction, teratogenic potential, or perinatal/postnatal events. Guaifenesin is classified as a Pregnancy Category C drug.

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: The proposed clinical study is reasonably safe to proceed from the nonclinical perspective.
2 Drug Information

2.1 Drug

CAS Registry Number: Hydrocodone: 34195-34-1; Guaifenesin: 93-14-1

Code Name: Hydrocodone bitartrate / Dihydrocodeinone Bitartrate and Guaifenesin

Chemical Name:
**Hydrocodone bitartrate / Dihydrocodeinone Bitartrate**: Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5α), [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5) / 4,5-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5).

**Guaifenesin**: 1, 2-Propanediol, 3-(2-methoxyphenoxy)-,(-)-,(-)-3-(α-Methoxyphenoxy)-1,2-propanediol.

Molecular Formula/Molecular Weight: **Hydrocodone**: 494.490 Da; **Guaifenesin**: 198.22

Structure or Biochemical Description:
**Hydrocodone**:

![Dihydrocodeinone Bitartrate structure](image)

**Guaifenesin**:

![Guaifenesin structure](image)

Pharmacologic Class: **Hydrocodone**: antitussive; **Guaifenesin**: expectorant.

2.2 Relevant INDs, NDAs, BLAs and DMFs

The sponsor provided the following Drug Master Files (DMFs): # [Drug Master File](#) (drug substance of guaifenesin USP) and # [general properties of hydrocodone bitartrate](#).

Prescription drug products containing a combination of hydrocodone bitartrate and guaifenesin had been previously marketed in the US. However, the majority of these products were withdrawn as of December 31, 2007 as they were considered
unapproved prescription drug products by the Agency. There are no currently approved prescription fixed-dose combination drug products that contain hydrocodone bitartrate plus guaifenesin. The table below summarizes current FDA approved products containing hydrocodone in combination with a decongestant. The sponsor proposes to use Tussigon® (hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg), approved July 30, 1985 (ANDA 088508) as the RLD for comparison to the proposed drug product.

Table 1: Approved hydrocodone-decongestant combination NDAs and ANDAs

<table>
<thead>
<tr>
<th>Product</th>
<th>Trade Name / Generic Name</th>
<th>Year(s)</th>
<th>US Approvals (NDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone bitartrate 5 mg + pseudoephedrine hydrochloride 60 mg</td>
<td>Rezira</td>
<td>2011</td>
<td>NDA 22442</td>
</tr>
<tr>
<td>Hydrocodone bitartrate 5 mg + chlorpheniramine polistirex 4 mg</td>
<td>Tussicaps</td>
<td>2007</td>
<td>NDA 77273</td>
</tr>
<tr>
<td>Hydrocodone bitartrate 10 mg + chlorpheniramine polistirex 8 mg</td>
<td>homatropine methylbromide + hydrocodone bitartrate</td>
<td>1983, 2008, 2011</td>
<td>ANDAs 88008, 88017, 40613, 91528</td>
</tr>
<tr>
<td>Hydrocodone polistirex 10 mg + chlorpheniramine polistirex 8 mg</td>
<td>chlorpheniramine polistirex + hydrocodone polistirex</td>
<td>2010</td>
<td>ANDA 91632</td>
</tr>
<tr>
<td>Hydrocodone bitartrate 10 mg + chlorpheniramine polistirex 8 mg</td>
<td>Tussionex Pennkinetic</td>
<td>1987</td>
<td>NDA 19111</td>
</tr>
<tr>
<td>Hydrocodone bitartrate 5 mg + homatropine methylbromide 1.5 mg</td>
<td>Tussigon</td>
<td>1985</td>
<td>ANDA 88508</td>
</tr>
<tr>
<td>Hydrocodone bitartrate 5 mg + chlorpheniramine polistirex 4 mg + pseudoephedrine hydrochloride 60 mg</td>
<td>Zutripro</td>
<td>2011</td>
<td>NDA 22439</td>
</tr>
</tbody>
</table>

Guaifenesin is an OTC monograph drug which is approved under the NDAs and ANDAs listed in the table below.

Table 2: Approved guaifenesin NDAs and ANDAs

<table>
<thead>
<tr>
<th>Product</th>
<th>Trade Name / Generic Name</th>
<th>Year(s)</th>
<th>US Approvals (NDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guaifenesin 600 and 1200 mg</td>
<td>Mucinex®</td>
<td>2002</td>
<td>NDA 021282</td>
</tr>
<tr>
<td>Guaifenesin 600 and 1200 mg; Pseudoephedrine hydrochloride 60 and 120 mg</td>
<td>Mucinex D®</td>
<td>2004</td>
<td>NDA 021585</td>
</tr>
<tr>
<td>Guaifenesin 600 and 1200 mg; Dextromethorphan hydrobromide 30 and 60 mg</td>
<td>Mucinex DM®</td>
<td>2004</td>
<td>NDA 021620</td>
</tr>
<tr>
<td>Guaifenesin 600 mg</td>
<td>Guaifenesin</td>
<td>2011</td>
<td>ANDA 078912</td>
</tr>
</tbody>
</table>
2.3 Drug Formulation

The drug product consists of white capsule-shaped tablets, each containing 5 mg Hydrocodone bitartrate and 400 mg guaifenesin. The formulation is summarized in the table below. All excipients are present in approved oral products at comparable or higher concentrations.

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Quantity (mg/tablet)</th>
<th>Function</th>
<th>Reference to Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone Bitartrate, USP</td>
<td>5</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Crospovidone, NF</td>
<td></td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Microcrystalline Cellulose, NF</td>
<td>(b)(4)</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Steanic Acid, NF</td>
<td>(b)(4)</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Talc, USP</td>
<td>(b)(4)</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Magnesium Stearate, NF</td>
<td>(b)(4)</td>
<td></td>
<td>(b)(4)</td>
</tr>
</tbody>
</table>

2.4 Comments on Novel Excipients

The drug product contains no novel excipients.

2.6 Proposed Clinical Protocol

The sponsor proposes two clinical protocols to demonstrate bioavailability and bioequivalence between the proposed combination drug product and reference single ingredient products, hydrocodone and guaifenesin.

The first clinical protocol (protocol # 099-13-US) is a randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two-way crossover oral food effect study comparing the proposed drug product (hydrocodone Bitartrate 5 mg / guaifenesin 400 mg immediate release tablets) in 28 healthy adults, under fed (high fat high calorie breakfast consumed no more than 5 minutes before dosing) versus fasting conditions (10 hours fasting before dosing). There will be a 7 day washout period between treatments.

The second clinical protocol (protocol # 102-13-US) is a randomized, open-label, balanced, three-treatment, three-period, three-sequence, single-dose, crossover comparative oral bioavailability study comparing the proposed drug product (hydrocodone bitartrate 5 mg / guaifenesin 400 mg immediate release tablets) versus Tussigon® (hydrocodone bitartrate 5 mg and homatropine methyl bromide 1.5 mg tablets) and OTC guaifenesin tablets (400 mg guaifenesin) distributed by CVS...
pharmacy, in 28 healthy adult subjects under fasting conditions. There will be a 7 day washout period between treatments.

In both studies males and females of child bearing potential must use adequate contraception throughout the study period. Exclusion criteria include females with a positive pregnancy test, and females who are breast feeding, lactating, or plan to become pregnant within 60 days after the last administration of study drug.

2.7 Previous Clinical Experience

Hydrocodone bitartrate is an antitussive present in a number of approved products including Tussigon® (ANDA 088508, approved July 30, 1985) which the sponsor plans to use as a reference listed drug (RLD) in the proposed clinical trials. From the approved label, the recommended doses of Tussigon® for the symptomatic relief of cough in adults is 1 tablet (hydrocodone bitartrate, 5 mg and homatropine methyl bromide, 1.5 mg) every 4 to 6 hours, not to exceed 6 tablets in 24 hours.

Guaifenesin is an OTC monograph expectorant (21CFR 341.18 for “Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Use”). From the guaifenesin OTC monograph (21CFR 341.78 for “Labeling of expectorant drug products” part (d), in adults and children 12 years and over oral dosage is 200 to 400 mg every 4 hours, not to exceed 2,400 mg in 24 hours.

2.8 Regulatory Background

The sponsor submitted a pre-IND meeting request dated June 23, 2010 and a briefing package on August 21, 2010. Upon review of the briefing package, the Division cancelled the meeting and instead provided the sponsor preliminary meeting comments via facsimile dated September 21, 2010. The sponsor submitted another meeting request and package on December 16, 2010, and a pre-IND meeting was held on February 25, 2011. The Division agreed that no additional nonclinical studies are required, provided that the total intake, with the exception of for impurities and degradants with structural alerts, does not exceed (b)(4) µg/day and the levels of impurities and degradants do not exceed the ICH qualification thresholds for drug substances. On November 12, 2013, the sponsor submitted IND 109251.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical studies were submitted with this application.

11 Integrated Summary and Safety Evaluation

The opening IND is for 2 proposed clinical trials to demonstrate bioequivalence and bioavailability of hydrocodone bitartrate 5 mg / guaifenesin 400 mg IR combination tablets in healthy adult subjects. The first study will compare the bioavailability of the proposed drug product in healthy adults, under fed versus fasting conditions. The
second study will evaluate the comparative bioavailability and bioequivalence of the proposed drug product with the RLD, Tussigon® (hydrocodone bitartrate 5 mg and Homatropine methyl bromide 1.5 mg tablets) in healthy adults under fasting conditions.

Hydrocodone bitartrate is approved under numerous NDAs and ANDAs (see Table 1). Hydrocodone was first approved on March 23, 1943 (NDA 05-213 for Hycodan Syrup and Tablets). Hycodan was subsequently withdrawn; however, an approved, marketed generic -Tussigon® (ANDA # 88508) will be used in the proposed clinical study.

Guaifenesin is an OTC monograph expectorant drug (21CFR 341.18 for “Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Use”). In addition, guaifenesin is approved as Mucinex® under a number of NDAs (NDAs 021282, 021585 and 021620; see Table 2).

No new nonclinical studies were submitted with the current IND; however, reference is made to existing safety data available for hydrocodone and guaifenesin, including current literature, the approved label for Tussigon® (ANDA # 088508, most recent label date 2010), and the guaifenesin OTC monograph.

Single-dose toxicity studies of hydrocodone administered SC in mice produced a Straub tail reaction (contraction of the sacrococcygeus muscle, resulting in erection of the tail commonly observed with μ-opioids), circling behavior, depression, muscle weakness, and muscle twitching. Convulsions were noted at 47.1 mg/kg and mortality at 85.7 mg/kg. In rats, hydrocodone produced depression at 4.2 mg/kg, but in cats, excitation (restlessness) occurred at ≥ 1 mg/kg (Eddy and Reid, J Pharmacology and Experimental Therapeutics. 1934 Dec;52(4):468 – 493).

From the Tussigon® approved combination product label, studies of Tussigon® in animals to evaluate the carcinogenic and mutagenic potential and the effect on fertility have not been conducted. Tussigon® is a Pregnancy Category C drug. Animal reproduction studies have not been conducted with Tussigon®.

Data that the sponsor summarized from published studies indicates that hydrocodone has adverse effects on reproduction and fertility in rats (reduced body weight gains and feed consumption in males and females, and reduced seminal vesicle weights in males) (Hoberman et al., Reproductive Toxicology, 2003; 17:495). Hydrocodone had no effects in EFD studies in rats and rabbits (York at al., Reproductive Toxicology, 2003, 17:507) but was found to have teratogenic potential in hamsters (Geber et al., Am J Obstet Gynecol. 1975 Dec 1;123(7):705-13).

No studies have been conducted to assess the mutagenic and carcinogenic potential of guaifenesin. In addition there are no studies to assess the effects of guaifenesin on fertility and reproduction, teratogenic potential, or perinatal/postnatal events.

The active ingredients in the proposed combination product each have a significant history of clinical use in the US. The proposed clinical doses of hydrocodone bitartrate
and guaifenesin are also within currently approved doses of each individual product. Therefore, from a nonclinical standpoint, the proposed IND clinical studies appear reasonably safe to proceed.
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/s/

NIKUNJ S PATEL
12/11/2013

MARCIE L WOOD
12/11/2013
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YU-MEE KIM
01/04/2017

CAROL M GALVIS
01/04/2017

I concur.
# MEDICAL OFFICER REVIEW

## Division Of Pulmonary and Allergy Products (HFD-570)

**APPLICATION:** NDA 208-085  
**TRADE NAME:** Hydrocodone bitartrate and guaifenesin  
**APPLICANT/SPONSOR:** ECI Pharmaceuticals, LLC  
**MEDICAL OFFICER:** Xu Wang, M.D., Ph.D.  
**TEAM LEADER:** Anthony G. Durnowiec, M.D.  
**DATE:** 06/08/2016  
**ROUTE:** Oral

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## SUBMISSIONS REVIEWED IN THIS DOCUMENT

<table>
<thead>
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<th>Comments</th>
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<td>NDA 208-085</td>
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## RELATED APPLICATIONS

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<th>Comments</th>
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<tr>
<td>11/11/2013</td>
<td>IND 109,251</td>
<td>IND for Hydrocodone Bitartrate and Guaifenesin Tablets</td>
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</table>

### REVIEW SUMMARY:

This is a 505(b)(2) application for a cough and cold combination drug Hydrocodone Bitartrate and Guaifenesin Tablets, 5 mg/400 mg. The proposed proprietary name is [proprietary name](#) Tablets. The proposed indication is for symptomatic relief of cough, to loosen (mucus) for hours, not to exceed 6 doses in 24 hours for adults and adolescents 18 years of age and older. As a basis for the 505(b)(2) submission route, the applicant cites Tussin (hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg) Tablets (ANDA 88508) and OTC drug Guaifenesin (21 CFR 314.18) to support the proposed combination drug.

The drug development program consists of 2 clinical pharmacology studies to demonstrate that the proposed drug is bioequivalent to the reference drugs. Study ECI 102-13-US is a bioavailability/bioequivalence study to compare the PK profile of a single dose of the proposed drug with that of the reference drugs in 14 healthy volunteers. The data showed that both hydrocodone and guaifenesin in test drug and references are bioequivalent. The 90% CI for ratios between test drug and references in Cmax, AUC0-t, and AUC0-inf for both hydrocodone and guaifenesin are within the bioequivalence range of 80% to 125%. Study ECI 099-13-US assesses the effect of food on the proposed drug. Fourteen (14) healthy volunteers receive a single dose of the proposed drug on fed and fast conditions. The ratios between fed and fast of PK parameters Cmax, AUC0-t, and AUC0-inf for both hydrocodone and guaifenesin are within the bioequivalence range of 80% to 125%. Tmax for both hydrocodone and guaifenesin was significantly smaller at fast than at fed condition, suggesting that the administration of the test drug with food resulted in slower absorption. There was one subject reported 2 adverse events (nausea and vomiting) after taking the test drug in the 2 studies. There were no new safety signals identified in the 2 clinical pharmacology studies.

The submission did not contain an integrated summary of safety (ISS) as required per regulation (21 CFR 314.50 (d)(5)(vi)). Lack of an ISS in an application can be an issue leading to an action of refuse to file. However, this application is a relatively small clinical pharmacology program, which reveals no new safety signal. Also the safety profiles of the proposed drug (hydrocodone and guaifenesin) are well understood, and an ISS is not expected to provide any new safety information for the proposed drug. The sponsor will be requested to submit an ISS and a safety update report 4 months after the initial submission to fulfill the regulatory requirements. The application is considered filable.

### OUTSTANDING ISSUES:

The sponsor will be requested to submit an integrated summary of safety (ISS) and a safety update report.

---

## RECOMMENDED REGULATORY ACTION

<table>
<thead>
<tr>
<th>NDA/SUPPLEMENTS</th>
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<tbody>
<tr>
<td>APPROVAL</td>
<td>APPROVABLE</td>
<td>NOT APPROVABLE</td>
</tr>
</tbody>
</table>

**OTHER ACTION:** COMMENTS FOR SPONSOR

---

Reference ID: 3937331
1. GENERAL INFORMATION

This is a 505(b)(2) application for a cough and cold combination drug Hydrocodone Bitartrate and Guaifenesin Tablets, 5 mg/400 mg. The sponsor is ECI Pharmaceuticals, LLC, and the proposed proprietary name is Tablets. The proposed indication is for symptomatic relief of cough, to loosen mucus. The dose regimen is one tablet every 4 to 6 hours, not to exceed 6 doses in 24 hours for adults and adolescents 18 years of age and older. The application is provided electronically.

As a basis for the 505(b)(2) submission route, the applicant cites the following reference listed drugs (RLDs): 1) Tussionex (hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg) Tablets of King Pharmaceuticals (ANDA 88508) for the hydrocodone component of Tablets; 2) Guaifenesin OTC monograph (21 CFR 314.18) for the guaifenesin component of Tablets.

2. FOREIGN MARKETING AND REGULATORY HISTORY

The proposed drug has not been marked in domestic or foreign markets.

Prior to submit the opening IND on November 11, 2013 (IND 109,251), ECI had a pre-IND meeting with the Division to discuss the drug development program on February 25, 2011. The Division’s comments in the pre-IND meeting which relate to this application are summarized below:

- A 505(b)(2) pathway would be an acceptable approach for the proposed combination drug.
- No additional efficacy and safety studies would be required for the proposed drug to support efficacy and safety in the adult (18 years of age and older population), provided that the proposed drug demonstrates bioequivalence to the RLDs in clinical pharmacology studies.
- Although hydrocodone is currently labeled in the RLD for use in children down to 6 years of age, safety concerns regarding dose-related respiratory depression identified by the Agency raises the question regarding the most appropriate dose for the pediatric population. Pharmacokinetic studies would be needed to determine the exposure of hydrocodone in the pediatric population (i.e. patients under 18 years of age) to provide data to guide dose selection, and safety studies would be needed to support the use of the proposed combination drug in patients under 18 years of age.

Reviewer’s comment: The Agency’s DESI review determined that hydrocodone is safe and effective for symptomatic relief of cough. Hydrocodone is not an OTC monograph drug. Normally clinical studies would be required to demonstrate that a combination drug containing hydrocodone is safe and effective per regulation (21 CFR 300.50(a)). However, there is a regulatory precedent regarding the combination of hydrocodone with a monograph cold, cough,
allergy, bronchodilator, and antiasthmatic drug. The precedent was established in response to
the NDA for Tussionex Pennkinetic Extended-Release Suspension (NDA 19-111), equivalent to
10 mg hydrocodone plus 8 mg chlorpheniramine maleate/5 ml. The NDA, which included three
bioavailability studies and no clinical studies, was approved on December 31, 1987. The
decision was made at the Center level. Given this regulatory background, and recognizing that
the Agency has determined that both single ingredients are safe and effective for their respective
indications, the pK program as the Division recommended is sufficient to support the proposed
combination drug products, provided bioequivalence is demonstrated.

3. ITEMS REQUIRED FOR FILING (21 CFR 314.50)

The following items pertinent to a clinical review are included in the submission:

- Application form (FDA 356h) [m1\1.1-forms\1.1.2-fda-form-356h]
- Summary [m2\2.7-Clinical Summary]
- Clinical technical section
  - Clinical study reports
    - Study Reports (ECI 099-13-US and ECI 102-13-US) [m5-Clinical Study
      Reports\5.3.1-Reports of Biopharmaceutic Studies\5.3.1.2-Comparative BA and BE
      Study Reports]
    - Case Report Forms [m5\5.3.1-Reports of Biopharmaceutic Studies\5.3.1.2-
      Comparative BA and BE Study Reports\crfs]
    - Good Clinical Practice certification [m5-Clinical Study Reports\5.3.1-Reports of
      Biopharmaceutic Studies\5.3.1.2-Comparative BA and BE Study Reports\Ethical
      Conduct]
    - Case Report Forms [m5\5.3.1-Reports of Biopharmaceutic Studies\5.3.1.2-
      Comparative BA and BE Study Reports\crfs]
    - Integrated summary of safety (ISS): not provided
  - Other pertinent data
    - none
    - Debarment Certification [m1\1.3-Administrative Information\1.3.3-Debarment
      Certification]
    - Pediatric Use [m1\1.9-Pediatric Administrative Information\1.9.1-Request for Waiver of
      Pediatric Studies (Initial Pediatric Study Plan)]
- Labeling [m1\1.14-Labeling\1.14.1-Draft Labeling]
- Financial Disclosure [m1\1.3-Administrative Information\1.3.4-Financial Certification and
  Disclosure]

Reviewer’s comment: The submission did not contain an integrated summary of safety (ISS) as
required per regulation (21 CFR 314.50 (d)(5)(vi)). Lack of an ISS in an application can be an
issue leading to an action of refuse to file. However, this application is a relatively small clinical pharmacology program, which reveals no new safety signal. Also the safety profiles of the proposed drug (hydrocodone and guaifenesin) are well understood, and an ISS is not expected to provide any new safety information for the proposed drug. The sponsor will be requested to submit an ISS and a safety update report 4 months after the initial submission, including new safety information learned about the proposed drug to fulfill the regulatory requirements. The application is considered filable.

4. CLINICAL PROGRAM

The drug development program is a clinical pharmacology program, consisting of 2 pharmacokinetic studies.

Study ECI 102-13-US is entitled “A randomized, open-label, balanced, three-treatment, three-period, three-sequence, single-dose, crossover comparative oral bioavailability study of a Hydrocodone Bitartrate 5 mg/Guaifenesin 400 mg immediate release tablets of ECI Pharmaceuticals LLC versus Tussigon (Hydrocodone bitartrate 5 mg and Homatropine 1.5 mg) Tablets of King Pharmaceuticals and Guaifenesin 400 mg tablets in 14 healthy adult human subjects under fasting conditions”. Fourteen (14) subjects were randomized to receive 1) Test drug, Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg immediate release tablet; 2) Reference 1, Tussigon (Hydrocodone bitartrate 5 mg and Homatropine 1.5 mg) tablet; or 3) Reference 2, Guaifenesin 400 mg tablet. After a washout period of 7 days, the subjects crossed over to receive another treatment until each subject received all 3 treatments. After study drug administration, serial blood samples were collected over a period of 24 hours. Plasma concentrations of Hydrocodone and Guaifenesin were measured by LC-MS/MS method. Pharmacokinetic (PK) parameters $C_{\text{max}}$, $AUC_{0-t}$, $AUC_{0-\infty}$, and kel were determined for the Hydrocodone and Guaifenesin, respectively. One subject withdrew consent in the first period due to the difficulty in obtaining blood sample. A total of 13 subjects completed the study and provided PK data for analysis. The data showed that both hydrocodone and guaifenesin in test drug and references are bioequivalent (Table 1). The ratios between test drug and references in $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ for both hydrocodone and guaifenesin are within the bioequivalence range of 80% to 125%. One subject reported 2 adverse events (nausea and vomiting) after taking the test drug. There were no death or serious adverse events reported during the study.

Table 1. PK profile of hydrocodone and guaifenesin in test drug and references (ECI 102-13-US)

<table>
<thead>
<tr>
<th></th>
<th>Test drug</th>
<th>Reference 1</th>
<th>Reference 2</th>
<th>Test/Ref ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone (mean)</td>
<td></td>
<td></td>
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<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>2.38</td>
<td>2.37</td>
<td>1 (0.97 – 1.03)</td>
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<tr>
<td>$AUC_{0-t}$ (µg·h/mL)</td>
<td>4.24</td>
<td>4.26</td>
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<td>$AUC_{0-\infty}$ (µg·h/mL)</td>
<td>4.31</td>
<td>4.32</td>
<td>1 (0.99 – 1.01)</td>
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<tr>
<td>Guaifenesin (mean)</td>
<td></td>
<td></td>
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<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>7.41</td>
<td>7.51</td>
<td>0.99 (0.97 – 1.01)</td>
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<td>$AUC_{0-t}$ (µg·h/mL)</td>
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<td>7.96</td>
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<td>$AUC_{0-\infty}$ (µg·h/mL)</td>
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<td>7.97</td>
<td>1 (0.99 – 1.01)</td>
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</tbody>
</table>
Study ECI 099-13-US is entitled “A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two-way crossover oral food effect study comparing Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg immediate release tablets of ECI Pharmaceuticals LLC in 14 healthy adult human subjects under fed (high fat high calorie breakfast) versus fasting conditions”. Fourteen (14) subjects were randomized to receive 1) Test drug, Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg immediate release tablet, after a standard overnight (10 hours) fast; 2) Test drug, Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg immediate release tablet, after consuming a standard high fat high calorie breakfast. After a washout period of 7 days, the subjects crossed over to receive another treatment. Plasma concentrations of Hydrocodone and Guaifenesin were measured by LC-MS/MS method. Pharmacokinetic (PK) parameters C\text{max}, T\text{max}, t_{1/2}, \text{AUC}_{0-t}, \text{AUC}_{0-\infty}, \text{and} \text{kel} \text{ were determined for the Hydrocodone and Guaifenesin, respectively. One subject withdrew consent prior to the start of the study. A total of 13 subjects completed the study and provided PK data for analysis. Hydrocodone and Guaifenesin under the fast and fed conditions are similar in PK characteristics among these healthy adult human subjects. The ratios between fed and fast in C\text{max}, \text{AUC}_{0-t}, \text{and} \text{AUC}_{0-\infty} \text{ for both hydrocodone and guaifenesin are within the bioequivalence range of 80% to 125% (Table 2). Both hydrocodone and guaifenesin reach the maximum blood concentration at a shorter time at fast than at fed condition. The maximum blood concentrations of hydrocodone were at 1.61 hours and 2.08 hours after dosing at fast and fed condition, respectively. The maximum blood concentrations of guaifenesin were at 0.64 hours and 1.18 hours after dosing at fast and fed condition, respectively. The time to reach the maximum blood concentration (T\text{max}) would be expected shorter at fast than at fed condition, because the absorption of the test drug would be quicker after dosing at fast condition. The test drug was well tolerated under both fast and fed conditions. There was no adverse event reported during the study.

<table>
<thead>
<tr>
<th></th>
<th>Fed</th>
<th>Fast</th>
<th>Fed/Fast ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocodone (mean)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C\text{max} (µg/mL)</td>
<td>2.35</td>
<td>2.29</td>
<td>1.03 (0.97 – 1.06)</td>
</tr>
<tr>
<td>AUC\text{0-t} (µg·h/mL)</td>
<td>4.29</td>
<td>4.21</td>
<td>1.02 (1 – 1.03)</td>
</tr>
<tr>
<td>AUC\text{0-\infty} (µg·h/mL)</td>
<td>4.34</td>
<td>4.27</td>
<td>1.02 (1 – 1.03)</td>
</tr>
<tr>
<td><strong>Guaifenesin (mean)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C\text{max} (µg/mL)</td>
<td>6.81</td>
<td>7.23</td>
<td>0.94 (0.97 – 1.01)</td>
</tr>
<tr>
<td>AUC\text{0-t} (µg·h/mL)</td>
<td>7.75</td>
<td>7.84</td>
<td>0.99 (0.99 – 1.01)</td>
</tr>
<tr>
<td>AUC\text{0-\infty} (µg·h/mL)</td>
<td>7.76</td>
<td>7.84</td>
<td>0.99 (0.99 – 1.01)</td>
</tr>
</tbody>
</table>

Reviewer’s comment: The BA/BE data from both studies are almost identical for the proposed drug and the references. Clinical pharmacology review team is requesting DSI review and audit for the PK study and the bioanalytic sites to assess the quality of the studies and the integrity of the data.
5. BRIEF REVIEW OF PROPOSED LABELING

The proposed label is based on the approved product labels for hydrocodone and guaifenesin containing cough and cold drugs. The preliminary review did not identify any major deficiencies.

6. DSI REVIEW AND AUDIT

Clinical pharmacology review team is requesting DSI review and audit for the PK study and the bioanalytic sites.

7. REVIEW TIMELINE

The PDUFA action date is February 13, 2016. The schedule for review is provided in Table 3. Write-up will be concomitant with the review process. The review will culminate with the proposed label, which will include comparison to the referenced listed drug and OTC monograph. The initial draft review will be complete by November 13, 2016, and the final draft review will be completed by December 13, 2016.

Table 3. Review timeline for NDA 208-085

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Target date for completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filing and planning meeting</td>
<td>May 23, 2016</td>
</tr>
<tr>
<td>Filing action date</td>
<td>June 10, 2016</td>
</tr>
<tr>
<td>74 day letter</td>
<td>June 24, 2016</td>
</tr>
<tr>
<td>Mid-cycle review meeting</td>
<td>Sept. 12, 2016</td>
</tr>
<tr>
<td>Initial draft review complete</td>
<td>November 13, 2016</td>
</tr>
<tr>
<td>Final draft review complete</td>
<td>December 13, 2016</td>
</tr>
<tr>
<td>Wrap-up meeting/Label</td>
<td>January 9, 2017</td>
</tr>
<tr>
<td>PDUFA Action date (10 months)</td>
<td>February 13, 2017</td>
</tr>
</tbody>
</table>

8. COMMENTS FOR THE SPONSOR

The comment below will be conveyed to the applicant:

*Per regulation (21 CFR 314.50 (d)(5)(vi)), submit an integrated summary of safety (ISS), including pertinent information and data for potential adverse effects of the proposed drug. Include a discussion of potentially clinically significant drug/drug interactions from clinical studies and literature surveys, and other safety considerations such as data from epidemiological studies of related drugs. The safety data shall be presented by gender, age, and racial subgroups.*
Submit a safety update report 4 months after the initial submission, including new safety information learned about the proposed drug. The safety update is required to include the same kinds of information as originally submitted in ISS. If no new safety information is available, the safety update may consist of a statement to that effect.

Reviewed by:

____________________________________
Xu Wang, M.D., Ph.D.
Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products

____________________________________
Anthony G. Durmowicz, M.D.
Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

cc:  NDA 208-085
     HFD-570/Division File
     HFD-570/ Durmowicz/Medical Team Leader
     HFD-570/Wang/Medical Reviewer
     HFD-715/Li/Biometrics Reviewer
     HFD-570/Kim/Pharmacology-Toxicology Reviewer
     ONDQA/Bertha/CMC Reviewer
     OCP/Grimstein/Clinical Pharmacology Reviewer
     OSE/Owens/DMEPA Reviewer
     HFD-570/Brodhead/CSO
**Clinical Filing Checklist**

**NDA/BLA Number: 208-085**  
**Applicant: ECI Pharmaceuticals, LLC**  
**Stamp Date: April 13, 2016**

**Drug Name:** Tablets  
**NDA/BLA Type: 505(b)(2)**

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

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FORMAT/ORGANIZATION/LEGIBILITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Identify the general format that has been used for this application, e.g. electronic CTD.</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2. On its face, is the clinical section organized in a manner to allow substantive review to begin?</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3. Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5. Are all documents submitted in English or are English translations provided when necessary?</td>
<td>X</td>
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<tr>
<td>6. Is the clinical section legible so that substantive review can begin?</td>
<td>X</td>
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</tr>
<tr>
<td><strong>LABELING</strong></td>
<td></td>
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</tr>
<tr>
<td>7. Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>SUMMARIES</strong></td>
<td></td>
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<tr>
<td>8. Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>9. Has the applicant submitted the integrated summary of safety (ISS)?</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>10. Has the applicant submitted the integrated summary of efficacy (ISE)?</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11. Has the applicant submitted a benefit-risk analysis for the product?</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>DOSE</strong></td>
<td></td>
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<tr>
<td>13. If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?</td>
<td>X</td>
<td></td>
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</tbody>
</table>

Reference ID: 3937331
<table>
<thead>
<tr>
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<th>No</th>
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<th>Comment</th>
</tr>
</thead>
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<tr>
<td><strong>Arms:</strong> Location in submission:</td>
<td></td>
<td></td>
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<tr>
<td><strong>EFFICACY</strong></td>
<td></td>
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<tr>
<td>14. Do there appear to be the requisite number of adequate and well-controlled studies in the application?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pivotal Study #1 Indication:</td>
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<td></td>
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<tr>
<td>Pivotal Study #2 Indication:</td>
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</tr>
<tr>
<td>15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>SAFETY</strong></td>
<td></td>
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</tr>
<tr>
<td>18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>19. Has the applicant submitted adequate information to assess the arythmogenic potential of the product (e.g., QT interval studies, if needed)?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>20. Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>21. For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure(^1)) been exposed at the dose (or dose range) believed to be efficacious?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>22. For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>23. Has the applicant submitted the coding dictionary(^2) used for mapping investigator verbatim terms to preferred terms?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>24. Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>25. Have narrative summaries been submitted for all deaths and</td>
<td></td>
<td>No deaths or</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\(^1\) For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

\(^2\) The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).
<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>adverse dropouts (and serious adverse events if requested by the Division)?</td>
<td></td>
<td></td>
<td></td>
<td>discontinuations due to AEs</td>
</tr>
<tr>
<td>OTHER STUDIES</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>26. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?</td>
<td>X</td>
<td></td>
<td></td>
<td>No special studies/data requested</td>
</tr>
<tr>
<td>27. For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?</td>
<td>X</td>
<td></td>
<td></td>
<td>Not a Rx-to-OTC switch</td>
</tr>
<tr>
<td>PEDIATRIC USE</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>28. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABUSE LIABILITY</td>
<td></td>
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</tr>
<tr>
<td>29. If relevant, has the applicant submitted information to assess the abuse liability of the product?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOREIGN STUDIES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?</td>
<td>X</td>
<td></td>
<td></td>
<td>No foreign data</td>
</tr>
<tr>
<td>DATASETS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>31. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32. Has the applicant submitted datasets in the format agreed to previously by the Division?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33. Are all datasets for pivotal efficacy studies available and complete for all indications requested?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34. Are all datasets to support the critical safety analyses available and complete?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CASE REPORT FORMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36. Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?</td>
<td>X</td>
<td></td>
<td></td>
<td>No additional CRFs</td>
</tr>
<tr>
<td>FINANCIAL DISCLOSURE</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>38. Has the applicant submitted the required Financial Disclosure information?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOOD CLINICAL PRACTICE</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>39. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES__**

If the Application is not filable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XU WANG
05/26/2016

ANTHONY G DURMOWICZ
05/27/2016