

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022424Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

NDA Number:	022424 (Related NDA 022279)
Submissions Date:	11/18/2014
Submission Type:	505(b)(2); Resubmission
Proposed Brand Name:	FLOWTUSS
Generic Name:	Hydrocodone Bitartrate/Guaifenesin
Sponsor:	Mikart, Inc.
Route of Administration:	Oral
Dosage Form:	Immediate Release Solution
Dosage Strength:	2.5 mg Hydrocodone Bitartrate/200 mg Guaifenesin per 5 ml
Proposed Dosing Regimen:	10 mL every 4 to 6 hours, not to exceed 6 doses (60 mL) in 24 hours
Proposed Indication(s):	Symptomatic relief of cough and to loosen mucus associated with the common cold.
Proposed Population(s):	Adults and adolescents 18 years and older
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.

## 1. EXECUTIVE SUMMARY

NDA 022279 (Hydrocodone Bitartrate/Guaifenesin/Pseudoephedrine Hydrochloride) and NDA 022424 (Hydrocodone Bitartrate/Guaifenesin) are related products with the same formulation composition except for the pseudoephedrine component. No separate data were acquired for NDA 022424. Instead, data acquired with the Hydrocodone Bitartrate/Guaifenesin/Pseudoephedrine Hydrochloride was used in support of the Hydrocodone Bitartrate/Guaifenesin product as well.

This product was first submitted to the FDA on November 29, 2010 as an NDA but was given a complete response on September 28, 2011 as there were data integrity issues with the relative bioavailability study (S09-0009) and food effect study (S09-0010) conducted with the triple combination product. The cited deficiency and the recommendations for addressing the deficiency are as follows:

*An audit performed by the Agency for studies S09-0009 and S09-0010 identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies cannot be relied upon to support the clinical pharmacology of hydrocodone, pseudoephedrine, and guaifenesin oral solution.*

*This deficiency may be addressed by doing one of the following:*

- a. If stability data can be provided to show that the study samples are still stable and have no stability problems, reanalyze all subject plasma samples from studies S09-0009 and S09-0010.*

*OR*

- b. Repeat the clinical pharmacology program to evaluate the rate and extent of absorption between your proposed product and the reference products under the fasted state, and repeat the food effect study. Use the bioequivalence goal post of 80 – 125% for the 90% CI for the geometric mean ratio of the AUC and  $C_{max}$  for your proposed product and the reference products.*

*OR*

- c. Conduct clinical efficacy and safety studies to support your combination product.*

Tiber Laboratories chose option *b.* and resubmitted NDA 022279 on 07/18/2011 and included data from a bioavailability study (S11-0028) and food effect study (S11-0029). The BE of hydrocodone and pseudoephedrine were established between the test product and the reference products in study S011-0028. However, BE could not be demonstrated for guaifenesin. A CR was issued on 01/11/2012 with the following Clinical Pharmacology deficiency and recommendations for addressing this deficiency (For details refer to Clinical Pharmacology review by Dr. Arun Agrawal, review dated 11/03/2011).

*The clinical pharmacology studies submitted to support this application (studies S11-028 a single-dose bioavailability study and S11-0029 a single-dose crossover food effect study) show that the guaifenesin component of your oral solution product is not bioequivalent to the reference guaifenesin product* <sup>(b) (4)</sup>

*This deficiency may be addressed by doing one of the following:*

- a. Assess the design of your relative bioavailability study and, if appropriate, correct design deficiencies and repeat the single-dose clinical pharmacology study to evaluate the bioavailability*

*of your proposed hydrocodone 2.5 mg/pseudoephedrine 30 mg/guaifenesin 200 mg per 5 mL oral solution combination product compared to the individual reference products, using the bioequivalence goal post of 80-125%.*

*OR*

*b. Evaluate whether there is a formulation effect with your proposed combination product and reformulate the product if necessary. 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, using the bioequivalence goal post of 80-125%. You may also need to repeat the food effect study if the product is reformulated.*

*OR*

*c. Conduct a clinical development program with clinical efficacy and safety studies to support your combination product.*

A type C meeting was held on December 16, 2011 between the FDA and the current Sponsor, Mikart, Inc. under NDA 022424. FDA's position of requiring demonstration of bioequivalence of their product to the reference products was reiterated as follows:

*Even though the Sponsor's statement that the guaifenesin dosage of the proposed drug is within the dose range of the OTC monograph for guaifenesin is correct, the Sponsor needs to understand that they are not developing a monograph product but a fixed combination drug with the other component (hydrocodone) of the proposed combination drug which is a prescription drug, and which impacts the application of the OTC monograph. as the guaifenesin component in the proposed product was not bioequivalent to the reference product. Bioequivalence to reference drug is a standard in providing a clinical bridge for product quality, safety and efficacy, and the bioequivalence criteria have been applied to all similar cough and cold prescription combination products DPARP reviews.*

Mikart has submitted Amendment 0014 on 01/31/2012 under NDA 022424 to provide a study design outline for a new guaifenesin bioequivalence study. The study was proposed to be an open-label, single-dose, randomized, 2-period and 2-treatment crossover study under fasting conditions assessing the bioequivalence of guaifenesin component only as hydrocodone and pseudoephedrine bioequivalence was previously demonstrated. Agency agreed with Mikart's proposal as follows (Clinical Pharmacology review by Dr. Arun Agrawal, Review date 02/22/2012):

*Your proposal to characterize the pharmacokinetic profile of guaifenesin only and determine if guaifenesin bioequivalence can be determined for the test product (hydrocodone, pseudoephedrine and guaifenesin oral solution) when compared to the reference drug is acceptable.*

Subsequently, sponsor conducted five BA/BE studies with the triple combination product with the pivotal PK study 11467601 demonstrating the bioequivalence of guaifenesin from the test product and the reference product (Table 1). A thorough review of these data was undertaken under NDA 022279.

**Table 1 List of Five Phase 1 BE Single-Dose Studies in Healthy Volunteers**

Study ID	Study Design*	# of subjects	Reference drug
11267601	3-way crossover	17	Children’s Mucinex® Chest Congestion Guaifenesin Syrup manufactured (b) (4)
11267602	2-way crossover	30	Guaifenesin Syrup manufactured (b) (4)
11267603	2-way crossover	29	Children’s Mucinex® Chest Congestion
11267604	2-way crossover	36	Children’s Mucinex® Chest Congestion
11467601	2-way crossover	36	Refenesen™ (b) (4)

\* R: Randomized; OL, Open-Labeled. (Source: reviewer’s summary based on 5.2 Tabular listing of clinical reports)

Study 11467601 was an open-label, randomized, single-center, single-dose, two-treatment, two-period, two-sequence, crossover study under fasted conditions comparing equal doses of guaifenesin (400 mg/10 mL) from the test product and the reference product. A washout period of 24 hours was selected for this study. A total of 36 healthy adults enrolled and completed 2-period study. A total of 18 PK samples per subject per period were collected within 5-hour post-dose. 4 mL venous blood was collected for each PK sample. Guaifenesin plasma concentration was quantified via HPLC with MS/MS detection.

The geometric mean ratio (test/reference) of  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  were 0.969 (90% CI = 0.920, 1.020), 0.967 (90% CI = 0.919, 1.019), and 0.925 (90% CI= 0.850, 1.007), respectively (Table 2). The median  $T_{max}$  (range) of guaifenesin in the test and the reference products was 0.42 (0.17 – 1.5) hours and 0.42 (0.25 – 0.83) hour, respectively.

**Table 2 Comparison of PK Parameters of Guaifenesin between the Test product (A) and the Reference Product (B) in Study 11467601 (N=36)**

Parameter	Test product (A)*	Reference product (B)*	Ratio (A/B)	90% Lower Limit of Ratio	90% Upper Limit of Ratio
$AUC_{0-t}$ (ng·h/mL)	2519	2601	0.9687	0.9203	1.0197
$AUC_{0-inf}$ (ng·h/mL)	2603	2690	0.9674	0.9188	1.0186
$C_{max}$ (ng/mL)	2015	2178	0.9253	0.8500	1.0072
$T_{max}$ (hour)	0.42 (0.17 – 1.5)	0.42 (0.25 – 0.83)	-	-	-

\* Least-squares geometric means for areas and peak concentrations.  $T_{max}$  reported as median (range).

Means were adjusted by treatment, sequence and period in a general linear model.

(Source: adapted from CSR report-body-11467601, page 7, Table 2.1)

Office of Study Integrity and Surveillance (OSIS) in their Bioequivalence Establishment Inspection Report Review recommended (Review dated 02/04/2015) accepting data without an on-site inspection because OSIS inspected the relevant site within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

## Food Effect

As stated, the food effect study S011-0029 of the test product was previously submitted and reviewed (review by Dr. Arun Agrawal dated 11/03/2011). Here the results from this study are recapped and compared with the results of NDA 205474, another hydrocodone/guaifenesin product approved on 11/14/2014 (for additional details, see clinical pharmacology review by Dr. Yunzhao Ren dated 09/19/2014).

(b) (4)

As such, similar labeling language related to the food effect is appropriate for this product as well.

## Pediatrics

This product was not studied in pediatric population.

(b) (4)

(b) (4)

## Detailed Labeling Recommendations

Reviewer suggested changes are shown as additions and deletions to the sponsor proposed language.

### 12.3 Pharmacokinetics

Systemic exposure (in terms of peak plasma concentrations and area under plasma concentration versus time curve) of hydrocodone bitartrate and guaifenesin after single dose administration of (b) (4) 5 mg hydrocodone bitartrate and 400 mg guaifenesin are equivalent to respective reference solutions of 5 mL hydrocodone bitartrate (5 mg/5 mL), and 10 mL guaifenesin (200 mg/5 mL).

Hydrocodone: Following a single 10 mL oral dose of 5 mg hydrocodone bitartrate and 400 mg guaifenesin (b) (4) administered to 37 healthy adults, the geometric mean C<sub>max</sub> and AUC<sub>0-inf</sub> for hydrocodone were 9.0 ng/ (b) (4) mL and 61.2 ng·hr/ (b) (4) mL, respectively. The median time to maximum concentration for hydrocodone was about 1. (b) (4) 67 hours. Food has no significant effect on the extent of absorption of hydrocodone. The mean plasma half-life of hydrocodone is approximately 4 (b) (4) hours.

Guaifenesin: Following a single 10 mL oral dose of 5 mg hydrocodone bitartrate and 400 mg (b) (4) administered to 36 healthy adults, the geometric mean C<sub>max</sub> and AUC<sub>0-inf</sub> for guaifenesin were 2.0 mcg/ (b) (4) mL and 2.6 mcg·hr/ (b) (4) mL, respectively. The median time to maximum concentration was about (b) (4) 25 minutes. The effect of food on guaifenesin systemic exposure is not considered to be clinically meaningful. The mean plasma half-life of guaifenesin is approximately 1 hour.

#### Drug interactions

When guaifenesin and hydrocodone were administered in combination, the pharmacokinetics for each component (b) (4) was similar to those observed when each component was administered separately.

### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the NDA 022424 resubmitted on November 18, 2014 and has found the application Acceptable from a clinical pharmacology perspective.

### 1.2 Phase 4 Commitments

None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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YUNZHAO REN  
04/24/2015

SURESH DODDAPANENI  
04/24/2015

<b>CLINICAL PHARMACOLOGY REVIEW</b>	
NDA Number:	22-424
Submission Type:	505(b)(2)
Brand Name:	TRADENAME
Generic Name:	Hydrocodone and Guaifenesin Oral Solution
Sponsor:	Tiber Laboratories
Indication:	(b) (4)
Route of Administration:	Oral
Dosage Form:	Solution
Dosage Strength:	2.5 mg hydrocodone/200 mg guaifenesin per 5 mL
Dosage Administration:	(b) (4)
Submissions Dates:	11/29/2010 (SDN 1), 06/24/2011 (SDN 8)
OND Division:	Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Division of Clinical Pharmacology II
Reviewer:	Arun Agrawal, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.

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## 1. EXECUTIVE SUMMARY

This NDA review is for hydrocodone (HC) and guaifenesin (GUA) oral solution submitted under 505(b)(2) of the FDC Act. Both HC and GUA are widely used in the US and are generally recognized as safe and effective. This dual combination product, proposed as a prescription product, is an immediate release oral solution that contains HC bitartrate (antitussive) and GUA (expectorant) at the concentration of 2.5 mg and 200 mg per 5 mL, respectively. Sponsor is seeking approval of this product (b) (4)

The two clinical pharmacology studies [a drug-drug interaction and relative bioavailability study (S09-0009) and a food effect study (S09-0010)] submitted for NDA 22-424 on 11/29/2010 (SDN 1) were previously submitted for NDA 22-279 for HC, pseudoephedrine (PSE) HCl, and GUA triple combination product which was given a CR on 01/25/2011. For NDA 22-279, an audit performed by the Agency for studies S09-0009 and S09-0010 identified deficiencies relating to (i) documentation irregularities, and (ii) integrity of the bioanalytical data (b) (4)

Because of these deficiencies, these studies were not relied upon to support the clinical pharmacology program of HC, PSE, and GUA oral solution for NDA 22-279. Therefore, sponsor was informed at the time of filing of NDA 22-424 (02/11/2011) that those two studies (S09-0009 and S09-0010) may not be used to support NDA 22-424 submission unless the deficiencies stated above have been addressed. In response to this, sponsor repeated those two studies for their triple combination (HC, PSE and GUA) product and submitted data (Study #S11-0028 and S11-0029) to the Agency on 06/24/2011 as "Clinical Pharmacology/Response to Information Request" (SDN 8). Bioanalytical data for these studies was generated (b) (4)

Although, submitted studies included data for their triple combination (HC, PSE, and GUA) product, since NDA 22-424 is seeking approval for HC and GUA dual combination oral solution, only data pertaining to HC and GUA components is reviewed here. The pharmacokinetic results of drug-drug interaction study (S11-0028) demonstrated that HC met the bioequivalence (BE) criteria, however, GUA did not meet the BE criteria (b) (4)

The pharmacokinetic results of food-effect study (S11-0029) indicated that both HC and GUA did not meet the BE criteria (b) (4)

### 1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, NDA 22-424 is Not Acceptable. The GUA component of the proposed product is not bioequivalent to the reference drug Robitussin Chest Congestion (GUA) oral solution at 400 mg dose. A DSI audit for the two pivotal studies was not conducted because GUA failed BE and therefore, this application would get a Complete Response (CR).

The NDA is deficient as the approval of this product was based on demonstration of BE of the test drugs to the reference drugs and the GUA component in the test oral solution is not bioequivalent to the reference product (b) (4)

This deficiency may be addressed by doing the following:

- If the failure to demonstrate BE 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, BE must be established between your proposed product and the reference products under fasted state, or
- Conduct clinical efficacy and safety studies to support your proposed combination product, or
- If it is determined that failure to demonstrate BE is due to formulation issues, reformulate the product and repeat the clinical pharmacology program to demonstrate BE between the reformulated product and the reference products under fasted state, and repeat the food effect study if necessary.

### 1.2 Phase IV Commitments

Not applicable

### 1.3 Summary of Clinical Pharmacology Findings

The clinical pharmacology program included in this submission to support the approval of HC and GUA oral solution contained data from two new studies (Study #S11-0028 and Study #S11-0029) submitted on 06/24/11.

#### 1.3.1 Study #S11-0028: Drug-Drug Interaction Information

##### Title

A drug-drug interaction and relative bioavailability study of HC bitartrate 5 mg/PSE HCl 60 mg/GUA 400 mg oral solution

##### Objectives

The objectives of this study were to investigate the relative bioavailability of the test and reference active drugs by comparing the rate and extent of exposure of active drugs in the proposed combination solution and reference products as described below:

- *Treatment A (Test)* Sponsor's proposed HC bitartrate/PSE HCl/GUA oral solution

- *Treatment B (References 1)* HC bitartate/homatropine methylbromide oral solution
- *Treatment C (References 2)* A combination of both Robitussin Chest Congestion (GUA) and PSE HCl oral solution

The comparisons of interest were Treatment A versus treatment B, and Treatment A versus Treatment C.

Total Dose = HC bitartrate 5 mg/PSE HCl 60 mg/GUA 400 mg administered under fasting conditions to healthy adult subjects.

### **Study Design**

This was an open-label, single-dose, randomized, three-period, three-treatment crossover study under fasting conditions. At study check-in, subjects reported to the clinical site at least 10 hours prior to Day 1 dosing and were required to stay for 24 hours after Day 1 dosing. Subjects observed an overnight fast of at least 10 hours before dosing. On study Day 1 (Periods I, II, and III) each subject received the following treatments:

- Treatment A - a single 10 mL oral dose of proposed solution of HC bitartrate/PSE HCl/GUA, 2.5/30/200 mg per 5 mL,
- Treatment B - a single 5 mL oral dose of HC bitartrate/homatropine methylbromide solution, 5/1.5 mg per 5 mL, or
- Treatment C - a single oral dose of the combination of 20 mL Robitussin Chest Congestion oral solution (100 mg GUA per 5 mL) and 10 mL PSE HCl oral solution (30 mg per 5 mL).

Following a washout period of at least 7-days, subjects returned to the clinical facility to be dosed with an alternative treatment as per the randomization schedule.

Drug was administered with approximately 240 mL (8 fluid ounces) of room temperature water. No fluid, except that given with drug administration, was allowed from 1 hour prior to dose administration until 1 hour after dosing. Fluid consumption resumed at approximately 1 hour after dose administration. Water was allowed *ad libitum* 1 hour post-dose. A fast was maintained until at least 4 hours after dosing. Lunch was provided at approximately study Hour 4, dinner was provided at approximately study Hour 10, and an evening snack was provided at approximately study Hour 14. Study schematic is provided in Appendix-1.

### **Blood Sample Collection**

Treatment A: Within 90 minutes prior to each subject's scheduled dose time (0 hour) and after dose administration at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours. Twenty two blood samples were collected (total blood volume = 212 mL).

Treatment B: Within 90 minutes prior to each subject's scheduled dose time (0 hour) and after dose administration at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 hours. Twenty blood samples were collected (total blood volume = 120 mL).

Treatment C: Within 90 minutes prior to each subject's scheduled dose time (0 hour) and after dose administration at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours. Twenty two blood samples were collected (total blood volume = 184 mL).

A total of 64 blood samples were collected over the 3 periods of the study (516 mL total blood withdrawn). Plasma was transferred into separate aliquots for each analyte to be measured.

### **Key Inclusion Criteria**

- The study drugs are not significantly metabolized by CYP1A2. Smokers, tobacco users, or subjects currently using nicotine products (patches, gums, etc.) were allowed to participate in this study. Smoking was restricted from 1 hour prior to dosing until 4 hours after dosing.

### **Key Exclusion Criteria**

- Use of any investigational drug within 30 days prior to dosing
- Use of any Rx medications for a period of 14 days prior to dosing
- Use of CYP enzyme inducers for a period of 28 days prior to dosing
- Use of CYP enzyme inhibitors for a period of 14 days prior to dosing
- Use of any herbal or dietary supplements for a period of 14 days prior to dosing
- Use of any monoamine oxidase inhibitor (MAOI) for a period of 14 days before the first dose through 14 days after the final dose of the study
- Use of any over-the-counter medications for a period of 7 days prior to dosing, with the exception of topical spermicides
- Use of grapefruit, seville oranges, and pomelo containing products for a period of 14 days prior to dosing

### **Bioanalytical Methods**

#### Determination of HC

Bioanalytical method for HC quantification in human plasma was validated according to procedure AP2011\_008\_00 (method validation SOP (b) (4) Version 2) and was determined to be selective, specific and sensitive for HC. The lower limit of quantification (LLOQ) was 0.10 ng/mL and the upper limit of quantification (ULOQ) was 50 ng/mL. Further analytical details are provided in Appendix-1.

#### Determination of GUA

Bioanalytical method for GUA quantification in human plasma was validated according to procedure AP2011\_007\_00 (method validation SOP (b) (4) Version 2) and was determined to be selective, specific and sensitive for GUA. The LLOQ was

5.0 ng/mL and the ULOQ was 1500 ng/mL. Further analytical details are provided in Appendix-1.

**Criteria for BE Evaluation**

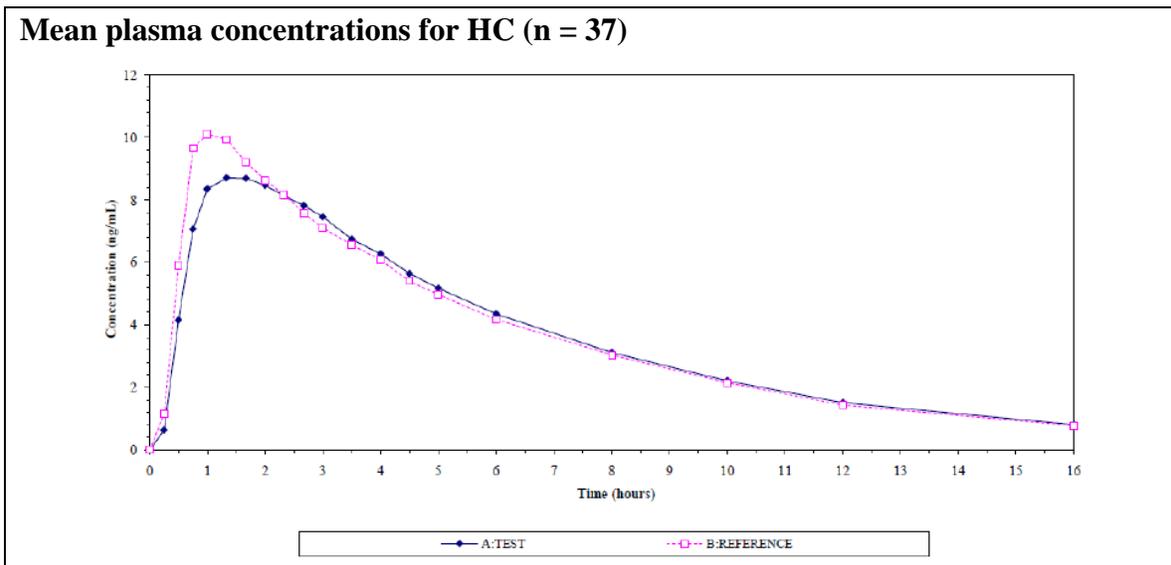
The primary PK parameters AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> were transformed to their natural logarithms. To conclude that there was no drug-drug interaction and the test solution was bioequivalent to the reference solutions, Treatment A/Treatment B ratios of means and their 90% confidence intervals (CIs) were to be within 80.00% to 125.00% for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> for HC; and Treatment A/Treatment C ratios of means and their 90% CIs were to be within 80.00% to 125.00% for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> for GUA.

**Results**

**Hydrocodone** (Treatment A versus Treatment B): The test A/reference B ratios of geometric means were 99.01% (90% CI 94.73% - 103.49%) for AUC<sub>0-t</sub>, 99.60% (90% CI 95.10% - 104.30%) for AUC<sub>0-inf</sub>, and 87.12% (90% CI 82.54% - 91.96%) for C<sub>max</sub> (table below). The point estimates and their corresponding 90% CIs were all contained within acceptance range of 80.00% to 125.00% and therefore, *HC met the BE criteria.*

Test Product A vs. Reference Product B Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI) Ln-Transformed data Hydrocodone N = 37				
Parameter	Test A	Reference B	% Ratio	90% CI
AUC <sub>0-t</sub> (ng-hr/mL)	56.65	57.21	99.01	(94.73, 103.49)
AUC <sub>0-inf</sub> (ng-hr/mL)	61.15	61.40	99.60	(95.10, 104.30)
C <sub>max</sub> (ng/mL)	9.00	10.33	87.12	(82.54, 91.96)

Test A: HC bitartrate/PSE HCl/GUA 2.5/30/200 mg per 5 mL oral solution  
Reference B: HC bitartrate/homatropine methylbromide 5/1.5 mg per 5 mL oral solution



**Guaifenesin** (Treatment A versus Treatment C):

(b) (4)

*GUA failed the BE criteria.*

(b) (4)

**Conclusions:**

Overall, the pharmacokinetic results of this study demonstrated that HC met the BE criteria, however, GUA failed the BE criteria

(b) (4)

### **1.3.2 Study #S11-0029: Food Effect PK Information**

#### **Title**

A food effect study of HC bitartrate 5 mg/PSE HCl 60 mg/GUA 400 mg oral solution

#### **Objectives**

This study assessed the impact of food on the bioavailability of proposed HC bitartrate 2.5 mg/PSE HCl 30 mg/GUA 200 mg, per 5 mL oral solution, by comparing the PK parameters under fed and fasted conditions.

#### **Study Design**

This was an open-label, single-dose, randomized, two-period, two-treatment crossover study under fasting and fed conditions. At study check-in, subjects reported to the clinical site at least 10.5 hours prior to Day 1 dosing and were required to stay for 24 hours after Day 1 dosing. Subjects observed an overnight fast of at least 10 hours before dosing. Water was allowed *ad libitum* during fasting. Throughout the study, standardized meals and beverages were served. Meals were same in content and quantity during each confinement period.

No fluid, except that given with drug administration (240 mL of room temperature water) and the standardized high-fat and high-calorie meal (depending on the randomization), was allowed from 1 hour prior to dose administration until 1 hour after dosing. Fluid consumption resumed at approximately 1 hour after dose administration.

At 30 minutes before dose administration, those subjects who were to be dosed under fed condition were served a standardized, high-fat and high-calorie meal. The standardized, high-fat and high-calorie meal consisted of the following:

- two eggs cooked in butter
- two strips of bacon
- two slices of toast with butter
- four ounces of hash brown potatoes
- eight fluid ounces (240 mL) of whole milk

A fast was maintained until at least 4 hours after dosing. Water was allowed *ad libitum* 1 hour after dosing. Lunch was provided at approximately study Hour 4, dinner was provided at approximately study Hour 10, and an evening snack was provided at approximately study Hour 14. Study schematic is provided in Appendix-2

On study Day 1 (Periods I and II), each subject received either a single 10 mL oral dose of HC bitartrate/PSE HCl/GUA (2.5/30/200 mg per 5 mL) solution, 30 minutes after initiation of a standardized, high-fat and high-calorie meal, preceded by an overnight fast of at least 10 hours, or a single 10 mL oral dose of HC bitartrate/PSE HCl/GUA (2.5/30/200 mg per 5 mL) solution after an overnight fast of at least 10 hours. Following a washout period of at least 7 days, subjects returned to the clinical facility to be dosed with the alternative treatment as per the randomization schedule.

Blood samples were collected within 90 minutes prior to each subject's scheduled dose time (0 hour) and after dose administration at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours while subjects were confined to the clinic. Subjects returned to the clinic for a blood sample collection at Hour 36. Twenty two blood samples were collected per period x 2 study periods (total of 44 samples, 424 mL total blood withdrawn).

HC was analyzed in samples collected for hour 0 (pre-dose), and 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 16 hours post-dosing.

GUA was analyzed in samples collected for hour 0 (pre-dose), and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5 and 4 hours post-dosing.

### **Key Inclusion Criteria**

- The study drugs are not significantly metabolized by CYP1A2. Smokers, tobacco users, or subjects currently using nicotine products (patches, gums, etc.) were allowed to participate in this study. Smoking was restricted from 1 hour prior to dosing until 4 hours after dosing.

### **Key Exclusion Criteria**

- Use of any investigational drug within 30 days prior to dosing
- Reported intolerance to fatty foods or inability to consume a high fat meal
- Use of any Rx medications for a period of 14 days prior to dosing
- Use of CYP enzyme inducers for a period of 28 days prior to dosing
- Use of CYP enzyme inhibitors for a period of 14 days prior to dosing
- Use of any herbal or dietary supplements for a period of 14 days prior to dosing
- Use of any monoamine oxidase inhibitor (MAOI) for a period of 14 days before the first dose through 14 days after the final dose of the study
- Use of any over-the-counter medications for a period of 7 days prior to dosing with the exception of topical spermicides
- Use of grapefruit, seville oranges, and pomelo containing products for a period of 14 days prior to dosing

### **Bioanalytical Methods**

Plasma drug concentrations were measured using validated bioanalytical methods. The quantification range was 0.10 to 50 ng/mL for HC, and 5.0 to 1500 ng/mL for GUA in plasma. Further analytical details are provided in Appendix-1.

### **Criteria for Evaluation**

The primary PK parameters AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> were transformed to their natural logarithms. No significant impact of food was concluded if the fed/fasted ratio of geometric means of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub>, and their 90% CIs were all contained within 80.00% to 125.00% for HC and GUA.

**Results**

**Hydrocodone:**

(b) (4)

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(b) (4)

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**Guaifenesin**

(b) (4)

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(b) (4)

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**Conclusions:**

The PK results of the food-effect study for HC bitartrate/PSE HCl/GUA oral solution administered to healthy volunteers demonstrated that:



(b) (4)

## 2. QUESTION BASED REVIEW

### 2.1 General Attributes of the Drug

#### 2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

##### Introduction

Hydrocodone is approved in various forms and in combinations with other drugs as a narcotic analgesic and as an antitussive agent. HC is an opioid, a Schedule III controlled substance, was not included in the OTC Monograph process, and is available only on a prescription basis (21CFR §1306.21 and 21CFR §1308.13). The safety and effectiveness of HC as a prescription drug for the relief of cough are supported by Drug Efficacy Study Implementation (DESI) review and by the FDA's approval of Hycodan (NDA 5-213). The OTC monograph 21CFR §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. Therefore, the proposed combinations of HC/GUA is not in compliance with the OTC monograph, and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed product as the regulation requires (21CFR §300.50). However, there is a regulatory precedence regarding the combination of HC with an OTC monograph product (for details, please see Clinical Review by Dr. Charles Lee, IND (b) (4), 09/25/2006). Based on Dr. Lee's review, the FDA has previously determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. Considering this policy, the Division has approved drug development programs for HC and OTC monograph product combinations, concluding that 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. Further, HC combination product containing monograph active ingredient chlorpheniramine (Tussionex, NDA 19-111) was approved based on establishment of BE only.

Guaifenesin is an OTC monograph drug. Directions for products containing GUA identified in 21CFR §341.78(d) are as follows: adults and children 12 years of age and over: oral dosage is 200 to 400 mg every 4 hours not to exceed 2,400 mg in 24 hours. Children 6 to <12 years of age: oral dosage is 100 to 200 mg every 4 hours not to exceed 1,200 mg in 24 hours."

##### History of this Submission

The two clinical pharmacology studies [a drug-drug interaction and relative bioavailability study (S09-0009) and a food effect study (S09-0010)] originally submitted for NDA 22-424 on 11/29/2010 (SDN 1) were previously submitted to NDA 22-279 for HC, PSE and GUA triple combination product which was given CR on 01/25/2011. For NDA 22-279, an audit performed by the Agency for studies S09-0009 and S09-0010 identified deficiencies relating to (i) documentation irregularities, and (ii) integrity of the bioanalytical data generated at the (b) (4) site. Because of these deficiencies,

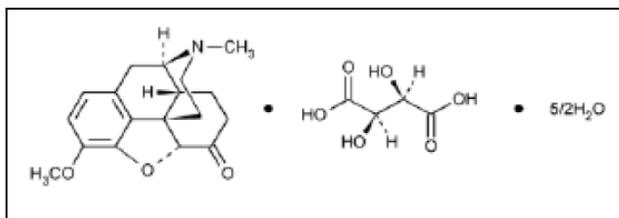
these studies were not relied upon to support the clinical pharmacology program of HC, PSE, and GUA oral solution. Therefore, sponsor was informed at the time of filing of NDA 22-424 (02/11/2011) that these two studies (S09-0009 and S09-0010) may not be used to support NDA 22-424 submission unless the deficiencies stated above have been addressed. In response to this, sponsor repeated those two studies for their triple combination (HC, PSE and GUA) product and submitted data (Study #S11-0028 and S11-0029) to the Agency on 06/24/2011 as “Clinical Pharmacology/Response to Information Request” (SDN 8). Although, submitted studies included data for their triple combination (HC, PSE, and GUA) product, since NDA 22-424 is seeking approval for HC and GUA dual combination oral solution, only data pertaining to HC and GUA components is reviewed here. Sponsor submitted results of the following two studies and is seeking approval for their HC and GUA oral solution:

1. Drug-Drug Interaction Information (Study #S11-0028)
2. Food Effect PK Information (Study #S11-0029)

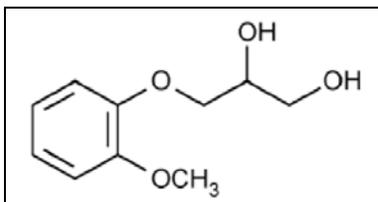
### 2.1.2 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

**Hydrocodone Bitartrate** is morphinan-6-one, 4,5- $\alpha$ -epoxy-3-methoxy-17-methyl-, (5 $\alpha$ ), (R-(R\*,R\*))-2,3-dihydroxybutanedioate (1:1), hydrate (2:5); also known as 4,5 $\alpha$  - Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5), and has a MW of 494.49. It is a fine white or slightly yellow-white powder. (b) (4)

Chemical structure of HC bitartrate is given below:



**Guaifenesin** is 1,2-propanediol, 3-(2-methoxyphenoxy)-, ( $\pm$ )-; also known as ( $\pm$ )-3-(o-Methoxyphenoxy)-1,2-propanediol, and has a MW of 198.22. Chemical structure of GUA is given below:



Formulation of the proposed double-ingredient drug product is identical to the formulation of the triple-ingredient drug product, except for the absence of PSE HCl (Table below):

**Formulation Comparison Table (Three-Ingredient vs. Two-Ingredient Products)**

Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution			Hydrocodone and Guaifenesin Oral Solution	
% w/v	mg/5mL	Ingredient	% w/v	mg/5mL
0.050	2.5	Hydrocodone Bitartrate USP	0.050	2.5
4.000	200.0	Guaifenesin USP	4.000	200.0
0.600	30.0	Pseudoephedrine Hydrochloride USP	----	----
(b) (4)		Sorbitol (b) (4) USP	(b) (4)	
		Glycerin USP		
		Polyethylene Glycol (b) (4) NF		
		Methylparaben NF		
		Propylparaben NF		
		Citric Acid (b) (4) USP		
		Sodium Citrate (b) (4) USP		
		Saccharin Sodium		
		D & C Red #33		
		FD & C Blue #1		
		(b) (4) Black Raspberry Flavor		
		Purified Water USP		

**Test and Reference Products used in this NDA**

Treatment	Drug(s)
A	<ul style="list-style-type: none"> <li>• Combination solution (Mikart, Inc. for Tiber Laboratories) (Hydrocodone 5 mg, Guaifenesin 400 mg, Pseudoephedrine 60 mg)</li> </ul>
B	<ul style="list-style-type: none"> <li>• Mycodone<sup>®</sup> Syrup (Morton Grove) (Hydrocodone 5 mg, Homatropine Methylbromide 1.5 mg)</li> </ul>
C	<ul style="list-style-type: none"> <li>• Robitussin<sup>®</sup> Chest Congestion solution (Wyeth Consumer Healthcare) (Guaifenesin 400 mg)</li> <li>• Pseudoephedrine HCl* (Pseudoephedrine 60 mg)</li> </ul>

**Table 9.4.2.1 Identity of Study Product**

Product	Test
Treatment ID	A / B
Product Name	Hydrocodone Bitartrate / Pseudoephedrine HCl / Guaifenesin
Manufacturer	Manufactured by Mikart, Inc. for Tiber Laboratories
Batch/Lot No.	K100447B
Manufacture Date	11/16/10
Expiration Date	N/A
Strength	Hydrocodone Bitartrate 2.5 / Pseudoephedrine HCl 30 / Guaifenesin 200 mg per 5 mL
Dosage Form	Oral Solution
Dose Administered	1 x 10 mL (Hydrocodone Bitartrate 5 mg / Pseudoephedrine HCl 60 mg / Guaifenesin 400 mg)
Route of Administration	Oral
Cumulative Maximum Dose	2 x 10 mL (Hydrocodone Bitartrate 10 mg / Pseudoephedrine HCl 120 mg / Guaifenesin 800 mg)

**2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?**

**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 HC and other opiates is not known; however, HC is believed to act directly on the cough center. In excessive doses, HC, like other opium derivatives, will depress respiration. The effects of HC on the cardiovascular system are insignificant at the therapeutic doses. HC can produce miosis, euphoria, and physical and psychological dependence. HC bitartrate is available only on a prescription basis. It is approved in various forms and in combinations with other drugs as a narcotic analgesic and as an antitussive.

Guaifenesin is an OTC monograph drug. 21CFR§341.78(b) states that the labeling of a product containing GUA must state, "under the heading "Indications," the following: "Helps loosen phlegm (mucus) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive")."

**Dosage and Administration**



#### **2.1.4 What are the core studies submitted in this NDA?**

Following two core Clinical Pharmacology studies are submitted in this NDA:

- **Study #S11-0028** - A drug-drug interaction and relative bioavailability study of HC bitartrate 5 mg/PSE HCl 60 mg/GUA 400 mg oral solution
- **Study #S11-0029** - A food effect study of HC bitartrate 5 mg/PSE HCl 60 mg/GUA 400 mg oral solution

### **2.2 General Clinical Pharmacology**

#### **2.2.1 Was hydrocodone and guaifenesin oral solution bioequivalent to the reference products?**

Pharmacokinetic results of drug-drug interaction study S11-0028 demonstrated that HC met the BE criteria, however, GUA failed the BE criteria (b) (4)

#### **2.2.2 What is the effect of food on the BA of hydrocodone and guaifenesin following administration of the proposed product?**

Pharmacokinetic results of food-effect study (S11-0029) indicated that both HC and GUA did not meet the BE criteria (b) (4)

#### **2.2.3 Are there any drug-drug interactions between the components of the proposed hydrocodone and guaifenesin oral solution?**

Pharmacokinetic results of study S11-0028 demonstrated that no significant interaction was observed between the active drug components in the combination oral solution when compared to reference drug HC (b) (4)

## **2.2.4 What are the general PK characteristics of the drug?**

### **Hydrocodone**

T<sub>max</sub> has been reported to be around 1.25 hour. The V<sub>d</sub> after oral dosing has been reported to range from 3.3 to 4.7 L/kg. HC undergoes complex metabolism. The metabolite hydromorphone is a potent opioid formed from the O-demethylation of hydrocodone by CYP2D6 enzyme. As such, the PK of HC is subject to phenotypic differences. CYP3A4 is also involved in the N-demethylation of HC to norhydrocodone. The PK profile of HC is similar between CYP2D6 extensive and poor metabolizers, although the C<sub>max</sub> of hydromorphone is decreased five-fold in poor metabolizers. This suggests that conversion to hydromorphone is not a major metabolic pathway. Urinary recovery of a HC dose showed that 14% was hydromorphone, 20% was norhydrocodone, and 14% was the product of C6-keto reduction (6 $\alpha$ - and 6 $\beta$ -hydroxy metabolites). Hydrocodone and its metabolites are eliminated primarily in the kidneys. Less than 15% of a single dose was recovered in the urine as unchanged drug over a 72 hour period. The mean plasma half-life is 4.5 hours.

### **Guaifenesin**

Guaifenesin is well-absorbed following oral administration; T<sub>max</sub> was reported to be around 0.25-0.5 hour, and t<sub>1/2</sub> ~1 hour. No information is available on the distribution of guaifenesin in humans. Guaifenesin is metabolized by oxidation and demethylation metabolic pathways.

## **2.2.5 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Yes. HC and GUA were measured in plasma to assess the PK parameters.

## **2.2.6 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 BE to the reference products, no clinical efficacy and safety studies were conducted.

## **2.2.7 Exposure Response**

No exposure response relationship was provided in this NDA.

## **2.2.8 What are the characteristics of the dose-systemic exposure relationships for efficacy?**

No formal studies were conducted in this NDA to establish dose-systemic exposure relationships for efficacy.

**2.2.9 What are the characteristics of the dose-systemic exposure relationships for safety?**

No formal studies were conducted in this NDA to establish dose-systemic exposure relationships for safety.

**2.2.10 Does this Drug Prolong the QT or QTc Interval?**

No formal study was conducted in this NDA to establish the effect of HC or GUA on QTc.

**2.2.11 What are the single dose and multiple dose PK parameters?**

Single dose PK information is described in section 1.3.1 and 1.3.2. No multiple dose PK studies were done for this NDA.

**2.3 Intrinsic Factors**

**2.3.1 Does weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?**

No formal studies were conducted in special populations in this NDA.

(b) (4)



## 2.4 Extrinsic Factors

### 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of other drugs, herbal products and alcohol use were not evaluated in this NDA. Sponsor conducted a dedicated food effect study to investigate the effect of food on the PK of HC and GUA. For details, see section 1.3.2.

## 2.5 General Biopharmaceutics

### 2.5.1 What is the effect of food on the BA

The pharmacokinetic results of the food-effect study for HC bitartrate/PSE HCl/GUA 5/60/400 mg per 10 mL oral solution administered to healthy volunteers demonstrated that:

(b) (4)

### 2.5.2 Was the to-be-marketed formulation used in the PK/Clinical trials?

Yes. The to-be marketed formulation was used in the BE and food effect studies.

### 2.5.3 Is there a potential for dose dumping in the presence of alcohol?

Not applicable as this is an immediate release oral solution.

## 2.6 Analytical Section

### 2.6.1 Was the suitability of the analytical method supported by the submitted information?

Drug plasma concentrations were measured using validated bioanalytical methods. Plasma calibration standard curves and QC samples demonstrated acceptable

performance of the assay method during the analysis of the study samples. The accuracy and precision for calibration standards and QCs for HC and GUA were acceptable. Additional details are provided in Appendix-1.

### 3. LABELING COMMENTS

Label is not being reviewed during this cycle because this submission is considered Not Acceptable from a clinical pharmacology perspective.

### 4. APPENDICES

#### Appendix-1 Bioequivalence Study (S11-0028)

##### Study Summary

<b>Study Number</b>	S11-0028
<b>Study Title</b>	A Drug-Drug Interaction and Relative Bioavailability Study of Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg Oral Solution
<b>Clinical Site (Name, Address, Phone #)</b>	Cetero Research – St. Charles 400 Fountain Lakes Blvd. St. Charles, MO 63301, USA (636) 947-1200
<b>Principal Investigator</b>	James C. Freeman, M.D.
<b>Dosing Dates</b>	Period I: 20 March 2011 Period II: 27 March 2011 Period III: 03 April 2011
<b>Analytical Site (Name, Address, Phone #)</b>	(b) (4)
<b>Analysis Dates</b>	
<b>Analytical Director</b>	
<b>Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)</b>	

## Study Schematic

TRIAL PHASE (EACH TREATMENT PERIOD)	Screening Day -28 to Day -2 (Performed Once)	CONFINEMENT and RETURNS AT CLINICAL RESEARCH UNIT (EACH TREATMENT PERIOD)		Early Discontinuation or End of Study Discharge
		Check-in Day -1	Treatment Day 1 thru Day 2	
Informed Consent	X	X <sup>a</sup>		
Eligibility (Inclusion/Exclusion)	X	X <sup>b</sup>		
Prior Medication Assessment	X	X <sup>b</sup>		
Medical History	X	X <sup>b</sup>		
Vital Signs	X		X <sup>c</sup>	X
Physical Exam	X <sup>f</sup>			X <sup>g</sup>
Clinical Laboratory Tests See <a href="#">Appendix 16.1.1</a> , <a href="#">Section 11.1</a> for specific tests	X			X
Serum Pregnancy Screen (Females only)	X			
Urine Pregnancy Screen (Females only)		X		X
FSH (if necessary to document postmenopausal status)	X			
Safety Hemoglobin		X <sup>e</sup>		
Urine Drug Screen	X <sup>i</sup>	X <sup>j</sup>		
Breath Alcohol Test		X		
Safety 12-lead ECG	X			
Study Drug Administration			X	
Pharmacokinetic Sampling			X <sup>d</sup>	
Adverse Events Query			X	X
Concomitant Medication			X	X

<sup>a</sup> Period I only.

<sup>b</sup> Updated and/or reviewed.

<sup>c</sup> Blood pressure and heart rate were measured (within 90 minutes prior to administration of study product to the first study participant) and at 1.33, 2.67, 5, 8, 24, and 36 hours (±30 minutes) after each dose and at the discretion of the clinical staff. Hour 36 vital signs were for Treatments A and C only. Blood pressure, heart rate, and temperature evaluation were measured at early termination or study exit.

<sup>d</sup> Pharmacokinetic samples were collected within 90 minutes prior to each subject's scheduled dose time (0 Hour) and 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24 and 36 hours after dose administration for subjects receiving treatments A and C. Pharmacokinetic samples were collected within 90 minutes prior to each subject's scheduled dose time (0 Hour) and 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 hours after dose administration for subjects receiving Treatment B.

<sup>e</sup> Collected at each check-in subsequent to Period I.

<sup>f</sup> May have been done at Period I check-in if not done at screening.

<sup>g</sup> If requested by the PI.

<sup>i</sup> 6 Panel Drug Screen.

<sup>j</sup> 5 Panel Drug Screen.

## Bioanalytical Details - Hydrocodone

Information Requested	Data
Bioanalytical method validation report location	Appendix 16.6
Analyte	Hydrocodone
Internal standard (IS)	(b) (4)
Method description	
Limit of quantitation	
Average recovery of drug (%)	
Average recovery of IS (%)	
Standard curve concentrations (ng/mL )	
QC concentrations (ng/mL )	
QC Intra-day precision range (%)	
QC Intra-day accuracy range (%Bias)	
QC Inter-day precision range (%)	
QC Inter-day accuracy range (%Bias)	
Bench-top stability (hrs)	
Stock stability (hours/days)	
Processed stability (hrs)	
Freeze-thaw stability (cycles)	
Long-term storage stability (days)	
Dilution integrity	
Selectivity	

## Bioanalytical Details - Guaifenesin

Information Requested	Data
Bioanalytical method validation report location	Appendix 16.6
Analyte	Guaifenesin
Internal standard (IS)	(b) (4)
Method description	
Limit of quantitation	
Average recovery of drug (%)	
Average recovery of IS (%)	
Standard curve concentrations (ng/mL )	
QC concentrations (ng/mL )	
QC Intra-day precision range (%)	
QC Intra-day accuracy range (%Bias)	
QC Inter-day precision range (%)	
QC Inter-day accuracy range (%Bias)	
Bench-top stability (hrs)	
Stock stability (hours/days)	
Processed stability (hrs)	
Freeze-thaw stability (cycles)	
Long-term storage stability (days)	
Dilution integrity	
Selectivity	

## Appendix-2 Food Effect Study (S11-0029)

### Study Summary

<b>Study Number</b>	S11-0029
<b>Study Title</b>	A Food Effect Study of Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg Oral Solution
<b>Clinical Site (Name, Address, Phone #)</b>	Cetero Research – St. Charles 400 Fountain Lakes Blvd. St. Charles, MO 63301, USA (636) 947-1200
<b>Principal Investigator</b>	James C. Freeman, M.D.
<b>Dosing Dates</b>	Period I: 20 March 2011 Period II: 27 March 2011
<b>Analytical Site (Name, Address, Phone #)</b>	(b) (4)
<b>Analysis Dates</b>	
<b>Analytical Director Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)</b>	

## Study Schematic

TRIAL PHASE (EACH TREATMENT PERIOD)	Screening Day -28 to Day -2 (Performed Once)	CONFINEMENT and RETURNS AT CLINICAL RESEARCH UNIT (EACH TREATMENT PERIOD)		Early Discontinuation or End of Study Discharge
		Check-in Day -1	Treatment Day 1 thru Day 2	
Informed Consent	X	X <sup>a</sup>		
Eligibility (Inclusion/Exclusion)	X	X <sup>b</sup>		
Prior Medication Assessment	X	X <sup>b</sup>		
Medical History	X	X <sup>b</sup>		
Vital Signs	X	X	X <sup>c</sup>	X
Physical Exam	X <sup>e</sup>			X <sup>f</sup>
Clinical Laboratory Tests See <a href="#">Appendix 16.1.1, Section 11.1</a> for specific tests	X			X
Serum Pregnancy Screen (Females only)	X			
Urine Pregnancy Screen (Females only)		X		X
FSH (if necessary to document postmenopausal status)	X			
Urine Drug Screen	X <sup>g</sup>	X <sup>h</sup>		
Breath Alcohol Test		X		
Safety 12-lead ECG	X			
Study Drug Administration			X	
Pharmacokinetic Sampling			X <sup>d</sup>	
Adverse Events Query			X	X
Concomitant Medication			X	X

<sup>a</sup> Period I only.

<sup>b</sup> Updated and/or reviewed.

<sup>c</sup> Blood pressure and heart rate were measured prior to dosing (within 90 minutes prior to administration of study product to the first study participant) and at 1.33, 2.67, 5, 8, 24, and 36 hours ( $\pm 30$  minutes) after each dose and at the discretion of the clinical staff. Blood pressure, heart rate, and temperature were measured at early termination or study exit.

<sup>d</sup> Pharmacokinetic samples were collected within 90 minutes prior to each subject's scheduled dose time (0 Hour) and 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours after dose administration.

<sup>e</sup> May have been done at Period I check-in if not done at screening.

<sup>f</sup> If requested by the PI.

<sup>g</sup> 6 Panel Drug Screen.

<sup>h</sup> 5 Panel Drug Screen.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ARUN K AGRAWAL  
08/23/2011

SURESH DODDAPANENI  
08/23/2011



## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>	<input checked="" type="checkbox"/>	2		

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

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of	x			

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	the analytical assay?				
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

### IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

This NDA submission filing review is for Hydrocodone and Guaifenesin Oral Solution submitted under 505(b)(2) of the FDC Act. This double combination product is an immediate release solution that contains hydrocodone bitartrate (antitussive) and guaifenesin (expectorant) at the concentration of 2.5 mg and 200 mg per 5 mL, respectively. Tiber Labs is seeking approval of

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

this cough/cold product

(b) (4)

the clinical pharmacology perspective.

This NDA is fileable from

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

We have identified some potential review issues which should be conveyed to the sponsor. The two clinical pharmacology studies [BE (S09-0009) and food effect (S09-0010)] submitted for this NDA were previously submitted for NDA 22-279 for hydrocodone, pseudoephedrine and guaifenesin triple combination product (given CR on Jan 25, 2011). For NDA 22-279, an audit performed by the Agency of studies S09-0009 (a drug-drug interaction and relative bioavailability study) and S09-0010 (a food effect study) identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies were not relied upon to support the clinical pharmacology of hydrocodone, pseudoephedrine, and guaifenesin oral solution. Therefore, these studies may not be used to support this NDA submission unless the deficiencies above have been addressed.

Arun Agrawal

January 28, 2011

Reviewing Clinical Pharmacologist

Date

Yun Xu

January 28, 2011

Acting Team Leader

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ARUN K AGRAWAL  
01/28/2011

YUN XU  
01/28/2011