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RESEARCH**

APPLICATION NUMBER:

022424Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 29, 2015
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22424
Supplement#	
Applicant	Mikart, Inc.
Date of Submission	November 18, 2014
PDUFA Goal Date	May 18, 2015
Proprietary Name / Established (USAN) names	Flowtuss/hydrocodone bitartrate and guaifenesin
Dosage forms / Strength	Oral Solution/2.5 mg and 200 mg, respectively, in each 5 ml
Proposed Indication(s)	For symptomatic relief of cough and to loosen mucus associated with the common cold.
Recommended Action:	Approval

1. Introduction

This current resubmission by the Applicant, Mikart Inc. (previously Tiber), received November 18, 2014, is a 505(b)(2) new drug application based on a clinical pharmacology program for a hydrocodone bitartrate and guaifenesin combination immediate release oral solution (proposed name Flowtuss) 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 November 29, 2010, contained data from 2 clinical pharmacology studies that had been previously submitted to support approval of a related NDA application (22279) on July 26, 2010, by the then NDA holder, Tiber, for a triple combination cough and cold drug which contained the same hydrocodone and guaifenesin components as the current submission with the addition of the decongestant pseudoephedrine. The intent at the time was that the data from those studies would also support approval of this related 2 drug hydrocodone and guaifenesin product by demonstrating bioequivalence of the 2 test products to respective reference products. However, during the review cycle of NDA 22279, an audit performed by the Division of Scientific Investigations identified deficiencies related to documentation irregularities and the integrity of bioanalytical data and, as a result, the studies could not be used to support the clinical pharmacology program. The issue (that the Division had already determined that the studies were inadequate to support an NDA) was communicated to the Applicant in a filing communication for this NDA (22424) on February 11, 2011. Subsequently, the Applicant performed two new clinical pharmacology studies and submitted the study reports during the review period on June 23, 2011, to support this NDA. These studies were reviewed and a CR action was taken due to failure to demonstrate bioequivalence for the guaifenesin drug component.

For this submission, the Applicant submitted a new set of studies in to support the bioequivalence of the guaifenesin component of their proposed product to that of an approved reference guaifenesin product. New bioequivalence studies were not conducted for the hydrocodone component as BE had been determined during the previous review cycle.

This CDTL review will provide an overview of the application, with a focus on the newly conducted clinical pharmacology studies submitted to support BE of the guaifenesin component of the hydrocodone/guaifenesin combination product. The PDUFA date for this application is May 18, 2015.

2. Background

The product under development is one of the hydrocodone-containing cough/cold products belonging to a group of previously illegally marketed products. According to the Agency's Federal Register notice [(published on October 1, 2007 [Docket No. 2007N-0353], all manufacturers of hydrocodone-containing products had to stop manufacturing these products by December 31, 2007. The Agency has encouraged manufacturers of these and other unapproved products to submit NDAs to obtain approval for marketing these products in the United States. This application is to market a combination product containing hydrocodone bitartrate and guaifenesin, as an immediate release oral solution containing 2.5 mg and 200 mg of hydrocodone and guaifenesin, per 5 mL 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 (b) (4)

The Applicant had a pre-IND meeting on March 26, 2007, with the Division to discuss plans to develop two immediate release oral cough and cold solutions, the current NDA 22424 (hydrocodone and guaifenesin) and the already mentioned related NDA, 22279, in which pseudoephedrine was added to the hydrocodone and guaifenesin combination. The formulations for the proposed drugs were exactly the same for the double and triple combination products except for an addition of pseudoephedrine component in the triple combination product. The Applicant planned to conduct all pharmacological studies using the triple combination product in order to obtain data to support both combination products. The Applicant submitted an opening IND on September 25, 2007, for the proposed hydrocodone, pseudoephedrine and guaifenesin oral solution (IND 76,365). To date, the Applicant has received three complete responses for the proposed triple combination product (June 22, 2009, January 25, 2011, and January 11, 2012) citing inadequacies in their clinical pharmacology program, deficiencies found upon inspection of the analytical site, and failure to show BE for guaifenesin, for the first and second, and third submissions, respectively.

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 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

The proposed product is an aqueous oral immediate release solution containing hydrocodone bitartrate 2.5 mg and guaifenesin USP 200 mg per 5 mL. Inactive ingredients (excipients) include sorbitol, glycerin, polyethylene glycol, methylparaben, propylparaben, citric acid, sodium citrate, saccharin, D&C Red #33 and FD&C Blue (as colorants), and (b) (4) black raspberry flavor.

Hydrocodone bitartrate USP used in the test formulation was manufactured (b) (4)
(b) (4) Guaifenesin USP used in the test
formulation was manufactured (b) (4)
(b) (4)

The proposed combination drug product is manufactured and supplied by Mikart, Inc. 2090 Marietta Blvd, Atlanta, GA 30318. This facility's EES status is acceptable. The drug product release specifications include appearance, pH, specific gravity, identification, and assays for (b) (4) impurity, (b) (4) and microbial limits.

Stability data conducted in 16 oz and 4 oz HDPE bottles support a 24 month expiry.

The one outstanding product quality issue identified during review of the last submission, that the product release specification lacks a test and acceptance criterion for *Burkholderia cepacia*, has been addressed. Specifically, the product's release and stability specifications have each been updated to include testing for *Burkholderia cepacia* with the acceptance criterion for this test being "absent"(refer to microbiology reviewer John Metcalfe's review, dated December 8, 2014).

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 5 clinical pharmacology studies to support the BE of guaifenesin to the listed reference product (Table 1). The bioequivalence of hydrocodone was already demonstrated (the 90% CI for the ratio of the geometric means of the test/reference products for the AUC and C_{max} were within 80 – 125%) during the first review cycle in study S11-0028, a single-dose, randomized, three-treatment crossover study under fasting condition in 42 male and female healthy volunteers aged 18 to 64 years. In that study, the geometric mean ratio (test/listed) of AUC 0–t, AUC 0–∞, and C_{max} were 0.990 (90% CI = 0.947, 1.035), 0.996 (90% CI = 0.951, 1.043), and 0.871 (90% CI= 0.825, 0.920), respectively (see the clinical pharmacology review by Dr. Arun Agrawal, dated January 28, 2011).

Note that the Applicant is developing a triple combination product, hydrocodone, pseudoephedrine and guaifenesin oral solution, which has the same formulation, except for an additional component of pseudoephedrine. As the pharmacology studies were performed to support the 2 combination products (NDAs 22424 and 22279), they include pseudoephedrine. This review will focus on study 1147601, the pivotal clinical pharmacology study which demonstrated BE between the test and reference guaifenesin components.

Table 1. List of Applicant's submitted BE studies

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

*Study 11467601 was the pivotal BE study for guaifenesin
Source: Clinical pharmacology review by Dr. Yunzhao Ren

Bioequivalence for guaifenesin

Study 1147601:

Design

Study 11467601 was the pivotal study conducted by Mikart, Inc. to address guaifenesin BE deficiency from the prior submission. It 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 listed product. A total of 36 healthy adults enrolled and completed the 2-period study. A total of 18 PK samples per subject per period were collected within 5-hour post-dose. There was a 24 hour washout between treatments. Subjects received the following 2 treatments:

Test product (A): Hydrocodone bitartrate, Guaifenesin, and Pseudoephedrine HCl oral solution 2.5 mg/200 mg/30 mg per 5 mL (supplied by (b) (4))

Listed product (B): Refenesen™ (b) (4) (guaifenesin), 200 mg/5 mL distributed by Reese Pharmaceutical

Results

The results showed that Applicant’s test guaifenesin product was BE to the listed product. The geometric mean ratio (test/listed) 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).

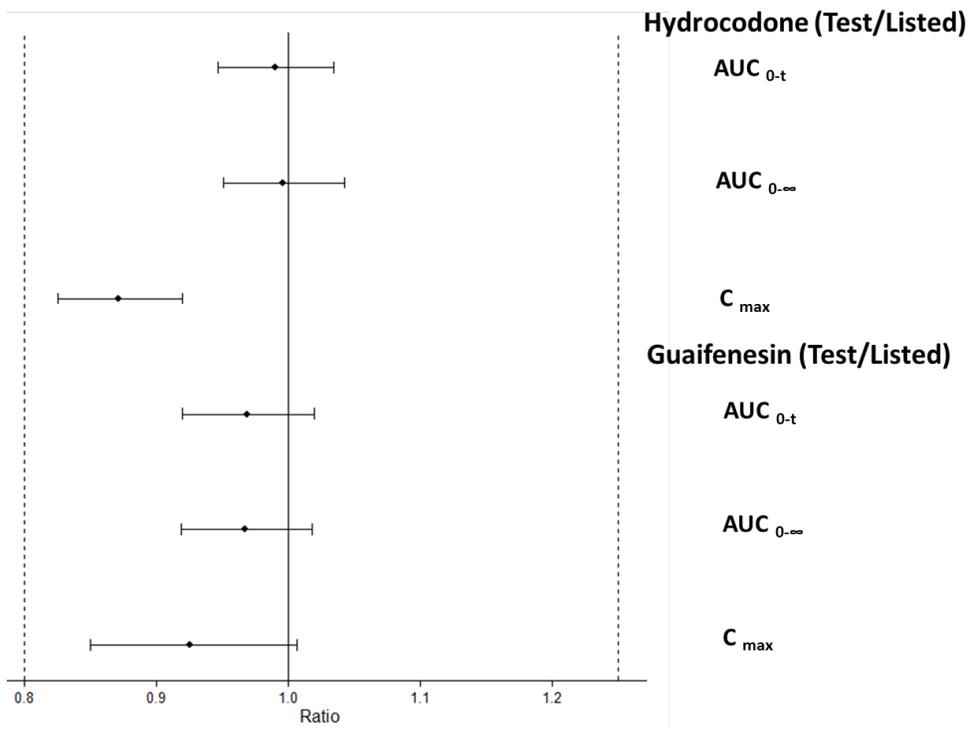
Table 2. Study 11467601: Comparison of PK of guaifenesin between the test product (A) and the listed product (B)

Parameter	Test product (A)*	Listed 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. Tmax 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

A summary of the PK data demonstrating BE between both the hydrocodone (from previous submission) and guaifenesin test products and their respective reference products can be found in Figure 1.

Figure 1. Forest-plot display of guaifenesin BE results of study 11467601 from the current submission and hydrocodone BE results of study S11-0028 from the prior submission. (Source: Table 2and CSR study-report-s11-0028-ich-sections-1-15.pdf, page 53, Table 11.4.7.1)



Food effect

Study S11-0029 (previously reviewed):

Design

This was a single-dose food effect cross-over study to assess the impact of food on the bioavailability of Mikart's hydrocodone and guaifenesin oral solution that was submitted and reviewed at the time of the first submission by Dr. Arun Agrawal (review dated January 28, 2011). Eighteen 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 solution under fed and fasting conditions with 15 subjects completing the study. At least a 7-day washout period was observed between the doses.

The systemic exposure of hydrocodone was comparable between fed condition and fasted condition for both products. The T_{max} of hydrocodone was delayed approximately 40 minutes under fed condition compared to fasted condition, which is consistent with the observations from other cough and cold hydrocodone-containing immediate release preparations.

For guaifenesin the point estimates and their 90% CIs for both AUC_{0-t} 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 3). The median T_{max} (range) of guaifenesin under fed and fasted conditions was not different.

Table 3: Food effect study results for guaifenesin

Parameter	Guaifenesin (fed) N = 15	Guaifenesin (fasted) N = 15	% Ratio	90% CI
AUC_{0-t} (ng h/mL)	2010.64	2728.44	73.69	(66.45, 81.72)
AUC_{0-inf} (ng.h/mL)	2246.31	2757.21	81.47	(75.64, 87.75)
C_{max} (ng/mL)	987.96	2156.59	45.81	(37.18, 56.45)

Source: Clinical Pharmacology review by Dr. Arun Agrawal, January 28, 2011

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 hydrocodone and guaifenesin. No clinical efficacy studies were conducted to support this application.

8. Safety

The safety of the product is based on establishing bioequivalence of the proposed combination product compared to the approved reference product, Hycodan Syrup and Tablets, (NDA 5-213) and the OTC monograph for guaifenesin. Since the guaifenesin component of the proposed drug product failed to meet the bioequivalency criteria, the safety of the proposed drug product can not be supported by the Agency's previous findings for single ingredient or combination products containing guaifenesin. 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.

In the previously submitted clinical pharmacology studies (including adverse event reports from studies #S09-0009 and #S09-0010 which were previously reviewed under NDA 22279) in which a total of 120 healthy adult subjects received a single dose of 10 mL of an immediate release oral solution containing 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin there were a total of 34 adverse events (13 headache, 8 dizziness, 4 lightheaded, 3 hot flush, 3 hyperhidrosis, 2 pallor, and 1 drowsiness). These events were mild and resolved without intervention. For the 36 subjects in study 11467601 contained in this submission, there were a total of 16 adverse events, all designated as mild that included nausea (3), dizziness, headache, hyperhidrosis (2 each).

A review of the literature (via a MEDLINE and EMBASE search), and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof were also conducted to support the safety of the proposed product. The post-marketing adverse events from the AERS database covered the period from January 1, 2003 through December 31, 2007 while the literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required. However, there are no additional animal or clinical safety studies the Applicant has conducted for the test drug and the test drug has not been manufactured and marketed. Thus, there was no new information to include in the safety update.

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



11. Other Relevant Regulatory Issues

Withdrawal and Abuse Potential

Previously, for the related NDA (22-279), the Controlled Substances Staff (CSS) was consulted to give their opinion on the abuse potential for the Applicant's other hydrocodone containing triple combination product during its review cycle. The CSS was 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 combinations are currently in Schedule II and have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for 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.

Inspections

The Division sent a request for inspection of the analytical and clinical sites to the Division of New Drug Bioequivalence Evaluation (DNDBE) and the Office of Study Integrity and Surveillance (OSIS) on January 29, 2015. DNDBE and OSIS responded on February 4, 2015, by recommending accepting the data without an on-site inspection because OSIS inspected the site listed below within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated.

Compliance with Good Clinical Practices

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

Financial Disclosures

The Applicant certified that there was no financial arrangement with the clinical investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The 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 Flowtuss was reviewed and deemed to be provisionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

Physician Labeling

Appropriate labeling based on the labeling of recently approved similar hydrocodone-containing cough and cold products was submitted by the Applicant and has been reviewed by specific disciplines and consultants (OPDP, DMEPA, etc.). Minor edits are being discussed. Final labeling is pending at the time of this review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is approval. Mikart Inc. has submitted adequate data to support approval of hydrocodone and guaifenesin oral solution for use as an antitussive and expectorant in patients 18 years of age and older. The submitted bioavailability study demonstrated bioequivalence for the guaifenesin drug component and bioequivalence had already been established for the hydrocodone component. As a result, the company is able to rely on the Agency's previous determinations of safety and efficacy for both hydrocodone and guaifenesin.

- Risk Benefit Assessment

Based on the Agency's previous determination of safety and efficacy for hydrocodone and guaifenesin as antitussive and expectorant products, respectively, the overall risk and benefit assessment of the individual ingredients hydrocodone and guaifenesin is acceptable for the proposed cough and cold product indication.

- Recommendation for Postmarketing Risk Management Activities

Hydrocodone is a Schedule II controlled substance known to have a certain level of abuse potential. Therefore, this combination product will be labeled as a Schedule II narcotic and will be available by prescription only. The abuse potential will be managed with appropriate labeling and routine pharmacovigilance.

(b) (4)

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/s/

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04/29/2015