CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022424Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date	May 14, 2015
From	Lydia Gilbert-McClain, M.D., FCCP
Subject	Summary review of regulatory action
NDA#	NDA 22-424
Applicant	Mikart, Inc.
Date of Submission	November 18, 2014
PDUFA Goal Date	May 18, 2015
Proprietary Name/Established (USAN) Names	Flowtuss Oral Solution/hydrocodone bitartrate and guaifenesin
Dosage forms/strengths	Oral solution/hydrocodone bitartrate 2.5 mg/ guaifenesin 200 mg/5 mL
Proposed indication (s)	For symptomatic relief of cough, and to loosen mucus associate with the common cold
Action/Recommended action for NME	*Approval*
Material Reviewed/consulted	**Names of discipline reviewers**
Action package including:	
Medical officer review	Xu Wang, M.D., Ph.D.
Cross Discipline Team leader	Anthony Durmowicz, M.D.
Clinical Pharmacology review	Yunzhao Ren, MD, Ph.D, Suresh Doddapaneni, Ph.D.
CMC review	Arthur Shaw, Ph.D.

1. Introduction

This is a complete response submission to a Complete Response action taken on this NDA on September 28, 2011. The submission is a 505(b) (2) new drug application and the Applicant is Mikart, Inc. (previously Tiber). The application is for a fixed dose combination oral solution comprised of hydrocodone bitartrate, and guaifenesin as an antitussive, and expectorant for use in patients 18 years of age and older. The reference product is Hycodan (NDA 5-213) for the hydrocodone component and the Division is relying on the accepted safety and efficacy of the monograph (21 CFR 341.18) for the guaifenesin ingredient. The NDA was originally submitted on November 29, 2010 and relies on the clinical pharmacology and CMC data submitted to NDA 22-279 for the triple combination product containing hydrocodone, pseudoephedrine, and guaifenesin. That NDA was initially submitted on August 22, 2008 and went through 4 review cycles (that includes this current review cycle with a PDUFA goal date of June 4, 2015). Previous clinical pharmacology studies failed to establish the bioequivalence of guaifenesin but the Applicant has now been able to successfully address this issue in a new study. This complete response cross-

references the clinical pharmacology study submitted to NDA 22-279. The formulation for both products is identical except for the presence of pseudoephedrine in NDA 22-279.

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 another hydrocodone and guaifenesin oral solution combination product (same dosage strength) was approved on November 14, 2014. However, as Mikart's combination product was already under review the application continued to be reviewed under the 505(b) (2) pathway (instead of submission under 5005(j). The NDA was originally submitted November 29, 2010 but was given a complete response action. In the action letter, the Division noted that the guaifenesin component failed to demonstrate bioequivalence in the clinical pharmacology studies. The clinical pharmacology study submitted to NDA 22-279 has addressed this deficiency.

3. CMC/Device

The proposed product in this NDA is for an aqueous oral solution containing hydrocodone bitartrate (HC) 2.5 mg, and guaifenesin (GU) 200 mg per 5 mL. The product will be available in 16 oz plastic HDPE bottles containing 473 ml of solution. These active substances are USP ingredients that have been previously assessed to support other NDA applications in the past. There are no unresolved DMF issues. There are no issues with the inactive ingredients which are all compendial except for the colors (FD&C red and blue) and the flavoring (raspberry flavor). The inactive ingredients include methyl- and propyl-parabens (b) (4), glycerin and water (b) (4) polyethylene glycol (b) (4) citric acid and sodium citrate (b) (4) sorbitol and saccharin (b) (4) There are no outstanding facilities or inspection issues.

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 was bioequivalent to the reference product, in that the 90% CI for the ratios of the geometric means of the test/reference products for the AUC and Cmax were within 80–125% in the clinical pharmacology studies submitted with the July 18, 2011 complete response (the 3rd review cycle) for NDA 22-279. However, the guaifenesin component of the combination product was not bioequivalent to the reference product (b) (4)
In this submission, the Applicant relies on the submitted pivotal bioavailability study 11467601 to NDA 22-279 that evaluate the bioavailability of guaifenesin. This was an open-

label, randomized single-dose 2-treatment, 2-period crossover study under fasting conditions comparing equal doses of guaifenesin from the Test product and Reference. A total of 36 healthy adult subjects were used in this study. The reference in this study was Refenesin™ (b) (4) (Reese Pharmaceuticals) 200 mg/5 mL. The Test (HC/PSE/GU combination product) met the 90% criterion for bioequivalence compared to an equal dose of guaifenesin the reference product. Geometric mean ratio of the Test/Reference for $AUC_{0-\infty}$ was 0.9674 (0.9188, 1.0186), and for C_{max} was 0.9253 (0.8500, 1.0072)

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 Hycodan and the OTC monograph products pseudoephedrine, and 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. Of the 36 healthy adult subjects exposed to the hydrocodone/pseudoephedrine/guaifenesin oral solution, there were 6 subjects who reported adverse events. These adverse events were mild and resolved without treatment and included nausea 92) asthenia 91) paresthesia (1), anxiety (1) hyperhidrosis 91), macule (1) headache (1), and dizziness (1). Other anticipated serious adverse events with this product are events known to occur with opioids such as CNS and respiratory depression. Pseudoephedrine is also known to cause CNS effects and also has the potential to cause cardiovascular effects and increase blood pressure. The applicant did not submit any new safety data in the complete response. In the original application the applicant conducted 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 and these searches did not reveal any new safety signals. For the 120-safety update there are no clinical or animal studies to report.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. The three 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 original proposed indication was for (b) (4) adults only (18 years of age and older). (b) (4) The product is contraindicated in

children less than 6 years because of the risk of respiratory depression and therefore, studies in this age group are waived under PREA. An identical product Obredon (hydrocodone and guaifenesin) Oral Solution was approved on November 14, 2014 and has an ongoing PREA commitment. Therefore, no studies are required under PREA for this product as this product is not a new dosage form, dose, route of administration, or for a new indication.

11. Other Relevant Regulatory Issues

Data Quality, Integrity, and Financial Disclosure
The study site for the pivotal clinical pharmacology study was not inspected. The Office of Study Integrity and Surveillance (OSIS) in their Bioequivalence Establishment Inspection Report Review recommended accepting the data without an on-site inspection because ISIS had inspected the relevant site within the last four years and the results from the inspections were classified as NAI (No Action Indicated). 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

Physician labeling

The Applicant submitted a label in Physician's Labeling Rule (PLR) format. The label was identical to the previously approved hydrocodone-guaifenesin oral solution product (Obredon) approved on November 14, 2014.

Carton and Immediate Container Labels
A detailed review of the carton and immediate container labels was conducted by the individual disciplines of the Division in consultation with the other labeling review groups in the Agency. The Division and Applicant have agreed on final carton and container labeling.

Patient Labeling and Medication Guide
There is no separate medication guide for this product. The Applicant has proposed a patient package insert and the Applicant and the Division have come to agreement on the patient labeling.

13. Action and Risk Benefit Assessment

Regulatory action

The regulatory action on the application will be approval. The applicant has adequately addressed the deficiencies in the complete response letter of September 29, 2011 and the application can be approved.

- Risk Benefit Assessment

The overall risk and benefit assessment of the individual ingredients hydrocodone, pseudoephedrine, and guaifenesin does not suggest an unfavorable risk benefit for these individual ingredients for the proposed adult population

- Recommendations for Postmarketing Risk Management Activities

Hydrocodone is a controlled substance known to have a certain level of abuse potential. This combination product if approved will be labeled as a Schedule IInarcotic and will be available by prescription only. The abuse potential will be managed with appropriate labeling and routine pharmacovigilance.

- Recommendations for other Postmarketing Study Commitments

There are no PREA required post marketing studies for this application. As stated before, an identical product was approved on November 14, 2014 and PREA studies are to be conducted under that NDA (205-474). As noted earlier, the evaluation of this application under the 505(b) (2) pathway while there is an identical product approved on the market for the same indications is an issue of timing of the submissions. Mikart's application was already submitted (but not yet approved) when NDA 205-474 (Sovereign pharmaceuticals) was submitted.

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/s/

LYDIA I GILBERT MCCLAIN
05/14/2015