CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22279Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date	May 14, 2015
From	Lydia Gilbert-McClain, MD, FCCP
Subject	Summary review of regulatory action
NDA#	NDA 22-279
Applicant	Mikart, Inc.
Date of Submission	December 4, 2014
PDUFA Goal Date	June 4, 2015
Proprietary Name/Established (USAN) Names	Hycofenix Oral Solution/hydrocodone bitartrate/pseudoephedrine hydrochloride/guaifenesin
Dosage forms/strengths	Oral solution/hydrocodone bitartrate 2.5 mg/pseudoephedrine HCl 30 mg/guaifenesin 200 mg/5 mL
Proposed indication (s)	For symptomatic relief of cough, nasal congestion, 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, MD, Ph.D.
Cross Discipline Team leader	Anthony Durmowicz, M.D.
Clinical Pharmacology review	Yunzhao Ren, M.D., PhD, Suresh Doddapaneni, Ph.D.
CMC review	Arthur Shaw, Ph.D.

1. Introduction

This is the fourth review cycle for this 505(b) (2) new drug application. The Applicant is Mikart, Inc (b) (4) The application is for a fixed dose combination oral solution comprised of hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin as an antitussive, nasal decongestant, and expectorant for use in patients 18 years of age and older. The NDA was given a complete response (CR) action on June 22, 2009, and again on January 25, 2010, and January 11, 2012 because of clinical pharmacology and manufacturing deficiencies. All deficiencies have now been resolved. The clinical pharmacology and CMC data in this application is also submitted in support of the 2-ingredient (hydrocodone and guaifenesin) NDA 22-424.

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]. Manufacturers who wish to market a cough/cold

product containing hydrocodone must obtain FDA approval via the new drug application (NDA) or an abbreviated new drug application (ANDA) process Mikart's triple-combination product is one such product that was originally submitted August 22, 2008. The NDA was given a complete response action. In the action letter, the Division noted that the clinical pharmacology study submitted was not adequate to support the application because of inadequacies in the design. As designed, the study did not allow for comparison of the rate and extent of absorption of each active drug ingredient in the proposed fixed dose combination solution. In addition, the formulation contained a significant amount (b) (4) of sorbitol and the applicant had not conducted a food effect study. The applicant submitted two studies in the first complete response: a drug-drug interaction oral bioavailability study to compare the rate and extent of absorption of each active ingredient in the combination oral solution compared to the reference products (S09-0009), and a single dose food effect study (S09-0010) to compare the rate and extent of absorption of the combination product in the fasted vs. fed state. Repeat clinical pharmacology studies demonstrated the bioequivalence of the hydrocodone and pseudoephedrine ingredients but bioequivalence for guaifenesin was not established in previously conducted studies. In this resubmission, the Applicant has submitted the results of a new pivotal clinical pharmacology study to address this deficiency.

3. CMC/Device

The proposed product in this NDA is for an aqueous oral solution containing hydrocodone bitartrate (HC) 2.5 mg, pseudoephedrine hydrochloride (PSE) 30 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 NDAs 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 ((b) (4) 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. The stability data support an expiry of twenty-four months.

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-peirod 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™ Mucus Relief Expectorant (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 AUC0-∞ was 0.9674 (0.9188, 1.0186), and for Cmax 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

(b) (4) (b) (4) Similar

applications for hydrocodone-containing combination cough/cold products have ongoing post marketing required studies under the Pediatric Research Equity Act (Act) to evaluate the PK and safety in pediatric patients 6 to 17 years of age. (b) (4) in children less than 6 years because of the risk of respiratory depression and therefore, studies in this age group are waived under PREA. The Applicant will be asked to conduct PK and safety studies in children 6 to 17 years of age.

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

Proprietary name
The Applicant's proprietary name Hycofenix was reviewed and found to be acceptable.

Physician Labeling
The Applicant submitted a label in Physician's Labeling Rule (PLR) format. The label has been reviewed by all the various disciplines and groups within the Agency and the Division and Applicant have reached agreement on a final label.

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 January 11, 2012 and the application can be approved for use in adults 18 years of age and older.

- 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 in 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 II narcotic 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

The following studies are required under PREA.

2892-1 Conduct a single-dose pharmacokinetic study whose primary objective is to identify the dose(s) of Hycofenix oral solution that results in exposures of hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin in children (6 to 11 years) and adolescents (12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. The population eligible for enrollment should be otherwise healthy children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment.

Final Protocol Submission:	January 2016
Study Completion:	July 2017
Final Report Submission:	January 2018

2892-2 Conduct an open-label, multi-dose safety and tolerability study in children (aged 6 to 11) and adolescents (aged 12 to 17 years). The population eligible for the study would be children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The study will enroll a total of approximately 400 children aged 6 to 17 inclusive in two cohorts (6-11years, 12 to 17 years). The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6 to 17 years.

Final Protocol Submission:	July 2019
Study Completion:	January 2023
Final Report Submission:	July 2023

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/s/

LYDIA I GILBERT MCCLAIN
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