

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**22279Orig1s000**

*Trade Name:* Hycofenix

*Generic Name:* Guaifenesin; Hydrocodone Bitartrate;  
Pseudoephedrine Hydrochloride

*Sponsor:* Mikart Inc

*Approval Date:* May 14, 2015

*Indications:* HYCOFENIX is a combination of hydrocodone, an opioid antitussive, pseudoephedrine, a nasal decongestant, and guaifenesin, an expectorant indicated for the symptomatic relief of cough, nasal congestion, and to loosen mucus associated with the common cold.

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## 22279Orig1s000

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RESEARCH**

*APPLICATION NUMBER:*

**22279Orig1s000**

**APPROVAL LETTER**



NDA 22279

**NDA APPROVAL**

Mikart, Inc.  
1750 Chattahoochee Avenue, NW.  
Atlanta, GA 30318

Attention: Jason Waldroup  
Director, Regulatory Affairs

Dear Mr. Waldroup:

Please refer to your New Drug Application (NDA) dated August 22, 2008, received August 22, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Hycofenix (hydrocodone/guaifenesin/pseudoephedrine), Oral Solution, 2.5 mg/5 mL hydrocodone bitartrate, 30 mg/5 mL pseudoephedrine hydrochloride, and 200 mg/5 mL guaifenesin.

We acknowledge receipt of your amendments dated September 17, October 9, and 30, November 12, and December 1, 2008; March 6 and 30, April 24, and November 9 and 20, 2009; July 22, August 18 and 23, September 16, 20, and 28, and December 20, 2010; July 18, September 16, October 4, and December 7, 2011; December 2, 2014; January 23, February 18, March 19, April 20 and 27, May 11, and 14, 2015.

The December 2, 2014, submission constituted a complete response to our January 11, 2012, action letter.

This new drug application provides for the use of Hycofenix (hydrocodone, guaifenesin and pseudoephedrine) Oral Solution for the temporary relief of nasal congestion, and to loosen mucus associated with the common cold.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on May 14, 2015, enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22279.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages zero to less than 6 years, because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group. The use of hydrocodone in children under the age of 6 years has been associated with fatal respiratory depression.

We are deferring submission of your pediatric studies for ages 6 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

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 (6-11 years, 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

Submit the protocols to your IND 76365, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Laura Musse, Regulatory Health Project Manager, at (240) 402-3720

Sincerely,

*{See appended electronic signature page}*

Lydia Gilbert-McClain, M.D.  
Deputy Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure(s):

Content of Labeling  
Carton and Container Labeling

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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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LYDIA I GILBERT MCCLAIN  
05/14/2015