CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22279Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22279

COMPLETE RESPONSE

Mikart, Inc
1750 Chattahoochee Avenue
Atlanta, Georgia 30318

Attention: Jason Waldroup, Director
Regulatory Submissions

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 for Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution.

We acknowledge receipt of your amendments dated September 17, October 9 and 30, November 12, and December 1, 2008, March 6 and 30, April 15, 21, and 24, November 9 and 20, and December 22, 2009, and July 22, August 18 and 23, September 16, 20, and 28, and December 20, 2010, and July 18 and September 16, October 4, and December 7, 2011.

The July 18, 2011, submission constituted a complete response to our January 25, 2011, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

1. 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 in that the 90% CI of the geometric mean ratio of the Cmax for guaifenesin (b) (4) .

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.

PRODUCT QUALITY

2. Your proposed drug product release specification lacks a test and acceptance criterion for *Burkholderia cepacia*, an organism requiring adequate control for aqueous drug products.

This deficiency may be addressed by doing the following:

a. Incorporate testing and acceptance criteria for the bacteria, *Burkholderia cepacia*, into the release specification for your proposed hydrocodone, guaifenesin, and pseudoephedrine combination product. Testing for this microorganism should be performed on stability using the same time points as for the other Microbial Test.

AND

b. Provide test method(s) for *Burkholderia cepacia* and the relevant method validations. The test method(s) validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

In addition to the above deficiencies, we have the following comments and/or requests for information:

3. To control the objectionable microorganism *Burkholderia cepacia*, we recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the

product and raw materials is recommended to develop sampling procedures and acceptance

criteria.

4. Reference is made to Module 3.2.P.5.1 which provides the drug product specification. The microbial limit acceptance criteria of NMT [redacted] yeast/molds, NMT [redacted] CFU Total Plate Count and an absence of *Escherichia coli* do not specify an amount of drug product tested (e.g.: per gram). In addition, the application does not contain methods and datasets which verify the suitability of use of the microbial limits tests with the subject drug product.

   a) Correct the acceptance criteria to identify an amount of drug product tested.
   b) Lower the criterion for yeast/molds to be consistent with the value suggested in USP<1111> for aqueous preparations for oral use.
   c) Provide methods and datasets which verify the suitability of use of the microbial limits tests with the subject drug product.

LABELING

5. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). You are advised to contact the Division of Pulmonary, Allergy, and Rheumatology Products regarding the extent and format of your safety update prior to responding to this letter.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Philantha M. Bowen, Senior Regulatory Project Management Officer, at (301)796-2466.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LYDIA I GILBERT MCCLAIN
01/11/2012
Deputy Division Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22279

COMPLETE RESPONSE

(b) (4)
c/o Mikart, Inc.
1750 Chattahoochee Avenue
Atlanta, Georgia 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 for hydrocodone, pseudoephedrine, and guaifenesin oral solution, 2.5mg/30mg/200mg in 5 ml.

We acknowledge receipt of your amendments dated September 17, October 9 and 30, November 12, and December 1, 2008, March 6 and 30, April 15, 21, and 24, November 9 and 20, and December 22, 2009, and July 22, August 18 and 23, September 16, 20, and 28, and December 20, 2010.

The July 22, 2010, submission constituted a complete response to our June 22, 2009, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

- 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 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.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). You are advised to contact the Division of Pulmonary, Allergy, and Rheumatology Products regarding the extent and format of your safety update prior to responding to this letter.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Philantha M. Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LYDIA I GILBERT MCCLAIN
01/25/2011
Deputy Division Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-279

COMPLETE RESPONSE

(b) (4)
c/o Mikart, Inc.
1750 Chattahoochee Avenue
Atlanta, GA 30318

Attention: Lisa Apolis
Director, Regulatory Submissions

Dear Ms. Apolis:

Please refer to your new drug application (NDA) dated August 22, 2008, received, August 22, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for hydrocodone bitartrate, pseudoephedrine hydrochloride, guaifenesin oral solution, 2.5 mg/30 mg/200 mg in 5ml.

We acknowledge receipt of your amendments dated, September 17, and October 9 and 30, and November 12, and December 1, 2008, and March 6 and 30, and April 15, 21, and 24, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

1. The single-dose, single arm, clinical pharmacology study #S07-0441 is not adequate to support this application because this study does not fulfill the bioavailability criteria for combination products as described in 21 CFR 320.25 (g). The study, as designed did not allow for comparison of the rate and extent of absorption of each active drug ingredient in your proposed hydrocodone, pseudoephedrine, guaifenesin oral solution to the rate and extent of absorption of each active drug ingredient administered concurrently in separate single-ingredient preparations.

2. Your proposed product contains sorbitol. Sorbitol has been found to affect the bioavailability of some compounds with low permeability in a dose-proportional manner. The permeability of hydrocodone, pseudoephedrine, and guaifenesin are not known and therefore, an assessment of food effect on your proposed product is necessary to support approval.

3. According to the amendment dated, April 24, 2009, the manufacturing site described in the application will not be used to manufacture drug product for the marketing of this drug. Therefore, the quality information for the manufacturing site as described can not be used to support the quality of the drug product.

These deficiencies may be addressed by doing the following:

a. Conduct a single-dose clinical pharmacology study to establish the bioequivalence of your proposed product to the reference products.

b. Conduct a food effect study of your proposed product under fed and fasted conditions.

c. Provide satisfactory quality information for drug product manufactured at the new manufacturing site.

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

Our field investigator could not complete inspection of your (b) (4) because these facilities were not ready for inspection. Satisfactory inspection is required before this application may be approved. Please notify us in writing when your facilities are ready for inspection.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level. You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796- 1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lydia McClain

6/22/2009 03:04:09 PM