

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022279Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

sNDA/Serial Number: (b) (4) NDA22-279 (b) (4)

Drug Name: (b) (4) (Hydrocodone, pseudoephedrine, and guaifenesin, 2.5mg/30mg/200mg/5mL) Oral solution

Indication(s): The symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)

Applicant: (b) (4)

Date(s): Received 07/18/11; User Fee 01/19/12

Review Priority: 6-months

Biometrics Division: Division of Biometrics II/Office of Biostatistics
Zhou, Feng, M.S. (Statistical Reviewer)

Statistical Team: Joan Buenconsejo, Ph.D. (Acting Statistical Team Leader)
Permutt, Thomas J, Ph.D. (Division Director of Biometrics II)

Medical Division: Division of Pulmonary, Allergy, and Rheumatology Products
Wang, Xu, M.D. (Medical Reviewer)

Clinical Team: Durmowicz, Anthony, M.D. (Medical Team Leader)
Gilbert-McClain, Lydia, M.D. (Medical Division Director)

Project Manager: Bowen, Philantha

Keywords: NDA labeling

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

(b) (4) (2.5mg Hydrocodone bitartrate, 30mg pseudoephedrine, and 200mg guaifenesin per 5mL) Solution for oral administration. This NDA is a 505(b)(2) application based on a clinical pharmacology program. There are no efficacy and safety studies in this NDA. The applicant relies on the bioequivalent study to seek the approval for this product. This is the 3rd cycle re-submission. The applicant resubmitted this application (NDA 22-279) on July 19, 2011 as a complete, class 2 response to the Agency action letter on January 25, 2011.

The comments below are for the Complete Response action letter dated January 25, 2011

- 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.

This NDA 3rd cycle re-submission included two clinical pharmacology studies, single dose BE study (S09-0009) and food effect study (S09-0010). Dr. Arun Agrawal (clinical pharmacology reviewer) reviewed these studies in detail. The reader is referred to Dr. Agrawal's review for the information regarding the BE and food effect studies. There is no statistical review for this application.

-EOF-

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

/s/

FENG ZHOU
10/14/2011

JOAN K BUENCONSEJO
10/14/2011
I concur with Feng Zhou's review.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

sNDA/Serial Number: (b) (4) NDA22-279 (b) (4)

Drug Name: (b) (4) (Hydrocodone, pseudoephedrine, and guaifenesin, 2.5mg/30mg/200mg/5mL) Oral solution

Indication(s): The symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)

Applicant: (b) (4)

Date(s): Received 07/22/10; User Fee 01/26/11

Review Priority: 6-months

Biometrics Division: Division of Biometrics II/Office of Biostatistics
Zhou, Feng, M.S. (Statistical Reviewer)

Statistical Team: Buenconsejo, Joan, Ph.D. (Acting Statistical Team Leader)
Permutt, Thomas J, Ph.D. (Division Director of Biometrics II)

Medical Division: Division of Pulmonary, Allergy, and Rheumatology Products
Wang, Xu, M.D. (Medical Reviewer)

Clinical Team: Durmowicz, Anthony, M.D. (Medical Team Leader)
Chowdhury, Badrul A, M.D., Ph.D. (Medical Division Director)

Project Manager: Bowen, Philantha

Keywords: NDA labeling

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

(b) (4) (2.5mg Hydrocodone bitartrate, 30mg pseudoephedrine, and 200mg guaifenesin per 5mL) Solution for oral administration. The applicant resubmitted this application (NDA 22-279) on July 22, 2010 as a complete, class 2 response to the Agency action letter on June 22, 2009.

The comments below are for the Complete Response action letter

- 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 per 21 CFR 320.25 (g). The study, as designed, does not allow for comparison of the rate and extent of absorption of each active drug ingredient in your proposed Hydrocodone, Pseudoephedrine, and 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) The quality information for the manufacturing site described in the application, (b) (4) cannot be used to support the quality of the drug product because, according to the amendment submitted on April 24, 2009, this site will not be used to manufacture drug product for the marketing of this drug.

These deficiencies may be addressed by doing the following:

- 1) Conduct a single-dose clinical pharmacology study to establish the bioequivalence of your proposed Hydrocodone 2.5 mg/Pseudoephedrine 30 mg/Guaifenesin 200 mg per 5 mL Oral Solution to the reference products.
- 2) Conduct a food effect study of your proposed Hydrocodone 2.5 mg/Pseudoephedrine 30 mg/Guaifenesin 200 mg per 5 mL Oral Solution under fed and fasted conditions.
- 3) Provide satisfactory quality information for the drug product manufactured at the new manufacturing site. All drug substance and drug product manufacturing sites must be in compliance with Current Good Manufacturing Practices (CGMP).

This NDA re-submission included two clinical pharmacology studies, single dose BE study (S09-0009) and food effect study (S09-0010). Dr. Arun Agrawal (clinical pharmacology reviewer) reviewed these studies in detail. The reader is referred to Dr. Agrawal's review for the information regarding the BE and food effect studies. There is no statistical review for this application.

-EOF-

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

/s/

FENG ZHOU
10/25/2010

JOAN K BUENCONSEJO
10/26/2010
I concur with Feng Zhou's review