CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022113Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-113

Wyeth Consumer Healthcare
Attention: Neil Napolitano
Assistant Director, Global Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Mr. Napolitano:

Please refer to your new drug application (NDA) dated September 25, 2007, received September 25, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (b) (4) (ibuprofen 200 mg/phenylephrine HC1 10 mg/chlorpheniramine maleate 4 mg)

We acknowledge receipt of your submissions dated November 19 and December 18, 2007, and January 25, 30 and 31, March 5, April 15 and 18, and May 16, 2008.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. The submitted PK data for phenylephrine are not reliable due to major flaws in the analytical assay methodology. Further, any differences noted between the original and repeat results between samples within a subject, were highly variable and did not demonstrate a similar level of underestimation within a batch. Therefore, we do not believe that extrapolating the results of reanalysis of a subset of subject samples from Study AD-06-06 to Study AQ-05-05, that were analyzed using the flawed original method, is justified.

   A cross-study comparison of ibuprofen PK data from your proposed triple combination caplet (Study AD-05-05) to the historical ibuprofen PK data suggested that the mean T_{max} values of ibuprofen increased approximately 1 hr in the presence of phenylephrine and chlorpheniramine. Further analysis is needed to assess the potential impact of delayed T_{max} of IBU from your proposed product on clinical efficacy.

   Therefore, you should submit pharmacokinetic data for phenylephrine using an adequately validated analytical assay method. With advances in analytical method for free phenylephrine, we recommend that you develop a sensitive assay for quantifying unmetabolized (free) phenylephrine in the plasma samples. Then, you have the option of either 1) reanalyzing the stored PK samples from study AD-05-05, provided stability of these samples can be assured or 2) conducting an entirely new PK study identical in design to study AD-05-05 with the to-be-marketed caplet formulation of IBU/PE/CHLOR. We recommend that you analyze the PK

samples (stored or newly acquired) using the newly validated analytical method for PE. We recommend that you also include ibuprofen (single ingredient) in any new PK study that you perform. The repeat BE study should include the to-be-marketed formulation.

2. We note that the qualifying study for the (b) (4) degradant was 14 days in duration. However, the indication for this product, treatment of allergy symptoms is such that chronic use is likely to occur.

   Therefore, you will need to perform a qualifying study of maximum duration of 90 days as specified by the ICH Q3B given the potential exposure of this drug to treat allergy symptoms for a chronic duration. The study should use sufficiently high levels of the degradant ((b) (4) that can be analytically confirmed. You should submit any new protocols for our review.

3. In addition, we have the following labeling comments:
   a. The label should convey a 7-day limit for duration of use (b) (4)) in keeping with the monograph dosing for phenylephrine. Labeling should be changed under the "Warnings" and "Directions" sections.
   b. Under the subsection "Ask a doctor before use if you have", we agree with the inclusion of the term "asthma."
   c. Under the "Do not use" subsection of Warnings, we agree with adding the bulleted statement "in children under 12 years of age". In addition, under Directions, we agree with changing the statement (b) (4) to read "children under 12 years of age: do not use".

   These are preliminary labeling comments. Further labeling recommendations are expected based on our review of the data in the next review cycle.

4. One of the facilities involved in your submission is deemed not to comply with cGMP requirements. Satisfactory resolution of any deficiencies of the facility is required to assure identity, strength, purity and quality of the drug product.

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 non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Nonprescription Clinical Evaluation to discuss what steps need to be taken before the application may be approved.

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 Elaine Abraham, Regulatory Project Manager, at (301) 796-0843.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
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/

Joel Schiffenbauer

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