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APPLICATION NUMBER:

22-281

OTHER ACTION LETTER(s)



NDA 22-281

COMPLETE RESPONSE

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
56 Livingston Avenue
Roseland, NJ 07068

Dear Mr. Cochran:

Please refer to your new drug application (NDA) dated March 10, 2008, received March 10, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid™ OTC (20 mg omeprazole & 1100 mg sodium bicarbonate) capsules.

We acknowledge receipt of your amendments dated April 24, May 5, June 23, July 2, 9 and 11, August 19 and 21, September 25 and 28, and October 8, 16, 22, 23 and 27, 2008.

We also acknowledge receipt of your submission dated December 11, 2008, which was not reviewed for this action. You may incorporate applicable sections of this amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application 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.

You were informed in a letter dated July 18, 2007 that if Zegerid OTC 20 mg capsule was not bioequivalent to Prilosec OTC 20 mg tablet, you would need additional efficacy and/or safety data and that a clinical study may be required. The data you presented demonstrates that Zegerid OTC 20 mg capsule is not bioequivalent to Prilosec OTC 20 mg tablet. Furthermore, you have not presented data to demonstrate any added benefit of Zegerid OTC 20 mg capsule over Prilosec OTC 20 mg tablet to treat frequent heartburn despite the increased C_{max}. However, you have chosen to present data to support the safety of Zegerid OTC 20 mg capsule, and you have presented data that you believe demonstrates that the C_{max} of Zegerid OTC 20 mg capsule is lower than that of prescription Prilosec 40 mg capsule. Therefore, based on our review of your application we note the following deficiencies:

CLINICAL PHARMACOLOGY AND CLINICAL

1. Zegerid OTC 20 mg capsule is not bioequivalent to Prilosec OTC 20 mg tablet. Zegerid demonstrates a higher C_{max} than Prilosec OTC and a comparable AUC.
2. You have not presented adequate data to demonstrate that the C_{max} of Zegerid OTC 20 mg capsule is lower than that of prescription Prilosec 40 mg capsule. You have presented a cross-study comparison of PK results to support your contention that the C_{max} for Zegerid OTC 20 mg capsule is lower than that of prescription Prilosec 40 mg capsule but you have not provided adequate rationale for why such a comparison is appropriate.
3. You have not presented adequate safety data to demonstrate that despite the higher C_{max}, Zegerid OTC 20 mg capsule is as safe as Prilosec OTC 20 mg tablet or that there is no clinically important difference in the safety profiles of prescription Prilosec 20 and 40 mg capsules. This is especially of concern for deaths and serious adverse events. In addition you have not presented data to demonstrate any increase in benefit of Zegerid OTC 20 mg capsule over Prilosec OTC 20 mg tablet to support a favorable risk benefit analysis despite the increase in C_{max}.

Therefore to address these deficiencies you will need to provide additional data as follows:

1. You may perform a clinical trial to demonstrate the added benefit of Zegerid OTC 20 mg capsule over Prilosec OTC 20 mg tablet for the treatment of frequent heartburn. If you pursue this route you should discuss any protocols with us before proceeding.
2. Alternatively you may provide additional PK data and rationale to support your contention that the C_{max} of Zegerid OTC 20 mg capsule is less than that of prescription Prilosec 40 mg capsule. You may address this issue by either performing a new PK study or providing additional data. Therefore you may either: a) perform a PK study to demonstrate that the C_{max} of Zegerid OTC 20 mg capsule is less than that of prescription Prilosec 40 mg capsule. This would involve a 3 arm study comparing Zegerid OTC 20 mg capsule, with Prilosec OTC 20 mg tablet and prescription Prilosec 40 mg capsule under fasted conditions; or b) analyze and present data to support your contention that the C_{max} of Zegerid OTC 20 mg capsule is indeed less than that of prescription Prilosec 40 mg capsule. Cross-study comparisons are inappropriate unless you can present a bridge to link these studies. We recommend that you submit any protocols to us for review and comment before proceeding.
3. Whether you conduct a clinical trial or submit PK data, you should also provide data to demonstrate that despite the higher C_{max}, Zegerid OTC 20 mg capsule has an acceptable safety profile. You can do this either by demonstrating that Zegerid OTC 20 mg capsule has a comparable safety profile to Prilosec OTC 20 mg tablet or that there is no clinically important difference in the safety profiles of prescription Prilosec 20 and 40 mg capsules. In performing an analysis of safety for Zegerid OTC 20 mg capsule you should be aware that you are required to analyze the data for differences in safety for various demographic groups including analyses by gender, age, racial group for example (21 CFR 314.50). We are particularly interested in the safety profile of Asians because they are known to have a fourfold increase in AUC for omeprazole and

4. Under the "Use" heading in the Drug Facts label, revise the second bulleted statement by inserting a period after "heartburn" and capitalizing the "t" in "this drug may take 1 to 4 days for full effect."
5. Revise the direction "swallow 1 capsule with a glass of water before eating in the morning" to read "swallow 1 capsule with a glass of water 1-hour before eating in the morning." The revision reflects bioequivalence fed-study results which show that C_{max} and AUC of plasma omeprazole are significantly decreased when prescription Zegerid IR 40mg capsules are taken 1-hour post-meal compared to being taken 1-hour pre-meal.
6. Under the "questions" heading in the Drug Facts, we encourage the inclusion of the days and times when someone is available to answer phone calls next to the toll-free number.
7. Provide an area for lot number and expiration date to appear.

SAFETY UPDATE

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.

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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

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/2125fn1.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 Mary Vienna, Regulatory Project Manager, at (301) 796-4150.

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

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/s/

Joel Schiffenbauer
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