CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022283Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022283

COMPLETE RESPONSE

MSD Consumer Care, Inc.
Attention: Verna Mecadon
Associate Director, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Ms. Mecadon:

Please refer to your New Drug Application (NDA) dated March 19, 2008, received March 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid® OTC (omeprazole 20mg/sodium bicarbonate 1680) powder for oral suspension.

We acknowledge receipt of your amendments dated April 24, May 5, July 2, 11 and 16, August 19 and 27, September 25 and 28, October 8, 16, 22, 27 and 30, November 19, and December 18, 2008; January 13, June 11, 22 and 25, August 5 and October 21, 2010; and April 5 and 12, June 14 and 29, September 23 and 30, November 22, 29 and 30, and December 15, 2011.

The June 29, 2011, submission constituted a complete response to our July 12, 2010, 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.

FACILITY INSPECTIONS

During a recent inspection of the two manufacturing facilities (b) (4) for this submission, our field investigators conveyed deficiencies to the representative of the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

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 Mary Vienna, Regulatory Project Manager, at (301) 786-4150.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

JOEL SCHIFFENBAUER
12/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022283 **COMPLETE RESPONSE**

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Cochran:

Please refer to your new drug application (NDA) dated March 19, 2008, received March 20, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid® OTC (omeprazole 20mg & sodium bicarbonate 1680 mg) powder for oral suspension.

We acknowledge receipt of your amendments dated April 24, May 5, July 2, 11 and 16, August 19 and 27, September 25 and 28, October 8, 16, 22, 27 and 30, November 19, and December 18, 2008, and January 13, June 11, 22 and 25, 2010.

The January 13, 2010 submission constituted a complete response to our January 16, 2009 action letter.

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.

You were informed in our January 16, 2009 action letter that you should either perform a new PK study or analyze the existing data to support the contention that the Cmax and AUC of Zegerid powder is less than that of omeprazole 40 mg. The letter also stated that cross-study comparisons are inappropriate unless there is a bridge to link these studies. In your complete response submission, you provided cross-study comparison data. Therefore, based on our review of your application we note the following deficiencies:

CLINICAL PHARMACOLOGY

1. While the data provided indicate that these studies had similar study-design and assay method, they did not have a common treatment that can be used as a bridge to link the studies. The data provided in cross-study comparison are inadequate to conclude that the Cmax for Zegerid® OTC 20 mg Powder for Oral Suspension does not exceed that of Prilosec 40 mg capsules. With respect to AUC, your cross-study comparison appears to adequately support the conclusion that Zegerid 20 mg Powder is lower than Prilosec 40 mg Capsules. However, with respect to Cmax, for both single and multiple dosing, the differences between

Zegerid 20 mg Powder and Prilosec 40 mg Capsules were not convincing. Especially considering that there is only one study examining Cmax after multiple dosing, inter-study variabilities resulting from assay, study subjects, and study conduct, you have not provided sufficient data to conclude that the Cmax of Zegerid OTC 20 mg Powder for Oral Suspension does not exceed that of Prilosec 40 mg Capsules.

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

1. Perform a PK study to demonstrate that the Cmax and AUC of Zegerid OTC Powder for Oral Suspension is less than that of Prilosec 40 mg Capsules. This would involve a 3-arm study comparing Zegerid OTC 20 mg powder, with the Prilosec OTC 20 mg tablet and prescription Prilosec 40 mg capsule under fasted conditions. We recommend that you submit any protocols to us for review and comment before proceeding.

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'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 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 Drug Evaluation IV
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22283	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	Zegerid OTC (omeprazole 20 mg & sodium bicarbonate 1680mg) powder.

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/s/

JOEL SCHIFFENBAUER
07/12/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-283

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 19, 2008, received March 20, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid® OTC (20 mg omeprazole & 1680 mg sodium bicarbonate) powder for oral suspension.

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

We also acknowledge receipt of your submission dated December 18, 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 powder for oral suspension was not bioequivalent to Prilosec OTC 20 mg, you would need additional efficacy and/or safety data and that a clinical study may be required. The data you presented demonstrates that Zegerid is not bioequivalent to Prilosec OTC 20 mg. Furthermore, you have not presented data to demonstrate any added benefit of Zegerid OTC 20 mg powder over Prilosec OTC 20 mg despite the increased Cmax and AUC. However, you have chosen to present data to support the safety of Zegerid 20 mg, and you have presented data that you believe demonstrates that the Cmax and AUC of Zegerid is lower than that of prescription Prilosec 40 mg. Therefore, based on our review of your application we note the following deficiencies*:*

CLINICAL PHARMACOLOGY AND CLINICAL

1. Zegerid OTC 20 mg powder is not bioequivalent to Prilosec OTC 20 mg tablet. Zegerid demonstrates a higher Cmax and AUC than Prilosec OTC.

2. You have not presented adequate data to demonstrate that the Cmax and AUC of Zegerid 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 Zegerid powder is less bioavailable than omeprazole 40 mg 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 Cmax and AUC, Zegerid is as safe as Prilosec OTC 20 mg or that there is no clinically important difference in the safety profiles of omeprazole 20 and 40 mg capsules. This is especially of concern for deaths and serious adverse events. Finally, you have not presented data to demonstrate any increase in benefit of Zegerid OTC 20 mg powder over Prilosec OTC 20 mg to support a favorable risk benefit analysis despite the increase in Cmax and AUC.

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

1. You should perform a clinical trial to demonstrate the added benefit of Zegerid OTC 20 mg powder over Prilosec OTC 20 mg tablet for the treatment of frequent heartburn, or else provide a rationale as to why consumers should be treated with a formulation that provides greater exposure than Prilosec OTC but without evidence for additional benefit. You should discuss any protocols with us before proceeding.

2. You should provide additional data and rationale to support your contention that the AUC and Cmax of Zegerid powder are less than that of Prilosec 40 mg. 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 Cmax and AUC of Zegerid powder is less than that of Prilosec 40 mg capsule. This would involve a 3-arm study comparing Zegerid OTC 20mg powder, with the 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 Cmax and AUC of Zegerid powder is indeed less than that of omeprazole 40 mg. 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. You should also provide data to demonstrate that despite the higher Cmax and AUC, Zegerid OTC powder has an acceptable safety profile. You can do this either by demonstrating that Zegerid OTC 20mg powder has a comparable safety profile to Prilosec OTC 20 mg 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 20mg powder, 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 therefore will exhibit both a higher AUC as well as Cmax, as compared to Prilosec OTC. You should analyze the databases that you have already referenced in your application as well as any other data available to you comparing the 20 and 40 mg doses of omeprazole.

4. Many consumers who are Asian will exhibit both an increase in Cmax as well as AUC, effectively receiving a higher dose of omeprazole than Prilosec OTC 20 mg. You will need to demonstrate that Zegerid OTC 20 mg powder is more effective than 20 mg omeprazole for the treatment of heartburn in this population, or else provide a rationale as to why these consumers should be treated with a formulation that provides greater exposure than Prilosec OTC without evidence for additional benefit.

We also wish to remind you of several points that were communicated to you previously and which will need to be addressed when you re-submit your application:

1. Sodium bicarbonate is an active ingredient and should be listed in the active ingredient section of the Drug Facts label. Its purpose is not as an antacid but as an "adjuvant to assist the absorption of omeprazole".

2. Pharmacokinetic data will not support a claim in labeling or advertising suggesting that Zegerid OTC 20 mg capsule is superior to Prilosec OTC 20 mg tablet. Also, labeling implying an immediate effect will not be acceptable based on such data.

LABELING

We reserve final comment on the proposed labeling until the application is otherwise adequate, as changes to the label may be needed after reviewing any additional data supplied by you in response to deficiencies identified in this action letter. However, some labeling comments are included in this section to address issues raised in the reviews:

1. We will not accept the proposed term [redacted] (b) (4) as the purpose statement for sodium bicarbonate. The purpose statement should be sufficiently descriptive to enable the average consumer to understand the unique function of sodium bicarbonate in Zegerid OTC (e.g. "Permits absorption of this omeprazole product" or "Prevents breakdown of this omeprazole product"). In addition, the agency will not accept a claim for direct impact of sodium bicarbonate on providing heartburn relief.

2. Present the full tradename "Zegerid OTC™" on the same line, rather than having "OTC™" appear below "Zegerid".

3. Remove the term [redacted] (b) (4)

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 [redacted] (b) (4) to read "product should be taken in the morning 1-hour before eating." The revision reflects bioequivalence fed-study results for prescription Zegerid which show that omeprazole is significantly less bioavailable when Zegerid is administered 1-hour after a meal compared to administration 1-hour before a 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. Include a Drug Facts panel on the 2-ct sample carton label as required by Section 502(c) of the Food, Drug and Cosmetic Act.

8. Remove the words [redacted] (b) (4) on the 1-dose powder packet label. [redacted] (b) (4)

9. Provide space for printing the lot (or control) number and the expiration date as required in 21 CFR 201.10(i)(1).

FACILITY INSPECTIONS

As of the date of this letter we are awaiting the overall recommendation from the Office of Compliance.

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/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 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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