CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022283Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	6/17/13
From	Joel Schiffenbauer
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	22-283
Applicant Name	Merck Consumer Care
Date of Submission	
PDUFA Goal Date	6/17/13
Proprietary Name / **Established (USAN) Name**	Zegerid OTC/Omeprazole/Sodium bicarbonate
Dosage Forms / Strength	Powder for oral suspension
Proposed Indication(s)	1. treatment of frequent heartburn
Action/Recommended Action for NME:	*approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christina Chang/Daiva Shetty
Statistical Review	
Pharmacology Toxicology Review	
CMC Review/OBP Review	Swapan De
Microbiology Review	
Clinical Pharmacology Review	
DDMAC	
DSI	
CDTL Review	
OSE/DMEPA	
OSE/DDRE	
OSE/DSRCS	
Other/ peds/labeling	Ruth Scroggs/Colleen Rogers

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

Zegerid contains both omeprazole and sodium bicarbonate. Zegerid 20 mg powder for suspension was approved for prescription marketing under NDA 21-636 in 2004. Zegerid powder for suspension differs from omeprazole delayed-release products in that the protective function of enteric coating in the delayed-release products is replaced by that of sodium bicarbonate. The function of sodium bicarbonate in this product is therefore not as an antacid, but as an adjuvant to assist the absorption of acid-labile omeprazole.

This review will summarize the labeling and chemistry reviews, which were the only 2 outstanding issues from the previous review cycle. For additional discussion the reader is referred to multiple reviews for the 3 previous review cycles for this NDA.

2. Background

The Applicant of the current submission, Merck (originally Schering) is requesting a switch of the 20 mg Zegerid powder for oral suspension to OTC for use in treating frequent heartburn. The development program for this switch consists of PK studies as well as reliance on the Agency's previous findings regarding the safety and efficacy of omeprazole 20 and 40 mg.

The original submission was received on 3/08 and Schering received a complete response on January 16, 2009 with the issues as listed below:

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.

A complete response was received from the applicant on January 13, 2010 addressing these issues. The January 13, 2010 submission constituted a complete response to our January 16, 2009 action letter.

Subsequently, a second complete response letter was sent on 7/12/10 and described the following deficiencies:

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 betweenZegerid 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.

A complete response was received from the applicant on 6/30/11 addressing these issues. However the Office of Compliance issued a "withhold" recommendation due to 2 facilities inspections that did not comply with cGMP. Based on this, the NDA received another complete response letter.

A response to that letter was received on December 14, 2012 and is the subject of this review.

3. CMC/Device

The chemistry reviewer wrote:

The applicant updated manufacturing facilities in its resubmission (NDA 22-283) dated December 14, 2012 and an establishment evaluation request (EER) was placed (dated 30 January, 2013) to the Office of Compliance through the Establishment Evaluation System (EES) to assure the manufacturing facilities remain in acceptable status regarding cGMP compliance. In response to the EER, the Office of Compliance issued an overall "acceptable" recommendation on (b) (4) *(see attached EER report).*

Conclusion: There are no outstanding issues from a chemistry, manufacturing, and controls point of view and this NDA is recommended for "Approval".

4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical issues raised by this NDA. Therefore there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

There was no new clinical pharmacology data for this submission.

6. Clinical Microbiology

Therefore there is no clinical microbiology review for this product.

7. Clinical/Statistical-Efficacy

No new efficacy data was submitted for this review cycle.

8. Safety

No new safety data was submitted for this review cycle. The safety profile of omeprazole is well known and Zegerid as a capsule has already been approved.

9. Advisory Committee Meeting

Zegerid is approved as a prescription drug and there is already an approved PPI for OTC use. It was determined that no new issues were presented in this NDA that would warrant an AC meeting.

10. Pediatrics

No new pediatric data was submitted.

11. Other Relevant Regulatory Issues

On August 23, 2011, the consumer advocacy group Public Citizen petitioned FDA to strengthen warnings in current labeling for all Rx and OTC PPI products. This citizen petition

requested FDA to require the inclusion of black box (and OTC-equivalent) warnings identifying the risks for rebound acid hypersecretion, fracture, infection, and magnesium deficiency. In addition, the petition also requested FDA to implement labeling revisions for PPI products to include vitamin B12 deficiency, acute interstitial nephritis, and specification of treatment duration for gastroesophageal reflux disease GERD.

(b) (4)

This citizen petition is being assessed at this time. A memo addressing the CP in regards to Zegerid will be placed in the file for the CP response.

There are no other relevant regulatory issues pending at this time.

12. Labeling

Labeling for Zegerid powder is essentially identical to that for the previously approved Zegerid capsule. The labeling reviewer recommended approval.

13. Decision/Action/Risk Benefit Assessment

The applicant has submitted an NDA to switch Zegerid 20 mg (omeprazole 20 mg plus sodium bicarbonate) powder from prescription to OTC status for the treatment of frequent heartburn.

With this CR submission, the applicant has provided sufficient information to satisfactorily address all unresolved issues and it is recommended for approval.

APPEARS THIS WAY ON ORIGINAL

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
06/17/2013