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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 16, 2011
From	Daiva Shetty, MD
Subject	Cross-Discipline Team Leader Review
NDA#	22-283
Applicant	Merck Consumer Care
Date of Submission	June 30, 2011
PDUFA Goal Date	December 30, 2011
Proprietary Name / Established (USAN) names	Zegerid OTC®
Dosage forms / Strength	Powder for Oral Suspension
Proposed Indication(s)	Treatment of frequent heartburn (> 2 days per week)
Recommended:	Approval pending satisfactory results of the manufacturing facility inspection.

1. Introduction

This NDA proposes a new formulation of omeprazole, Zegerid powder for oral suspension, for over-the-counter marketing. It contains 20 mg of omeprazole and 1680 mg of sodium bicarbonate (460 mg of sodium). The function of sodium bicarbonate in this product is not an antacid, but an adjuvant to assist the absorption of acid-labile omeprazole.

Zegerid 20 mg powder for oral suspension was approved for prescription marketing under NDA 21-636 in 2004. Zegerid OTC 20 mg capsule is already available over-the-counter since 2009 (NDA 22-281).

2. Background

This is the third review cycle for this NDA. The original NDA was submitted in 2008. In the first resubmission dated January 13, 2010, the Sponsor satisfactorily addressed the clinical safety deficiencies outlined in the January 16, 2009 Complete Response action letter. The Sponsor adequately demonstrated that there are no significant dose-dependent differences in the safety profiles between 20 mg and 40 mg omeprazole. However, clinical pharmacologic data submitted were inadequate to provide assurance that Zegerid 20 mg powder was less bioavailable than Prilosec 40 mg capsule, the formulation from which the safety profile for 40 mg omeprazole was primarily generated. Therefore, in the CR letter issued on July 12, 2010, FDA requested either to perform a new PK study or analyze the existing data to support the contention that the Cmax and AUC of Zegerid 20 mg 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. Therefore, to address these deficiencies FDA requested to provide additional data as follows:

"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."

In this resubmission, to address the clinical pharmacology deficiencies outlined in the second Complete Response action letter, the Sponsor submitted one pivotal clinical pharmacology study CL2010-12.

3. CMC/Device

There were no CMC deficiencies identified during the two previous review cycles. However, as per the Office of New Drug Quality Assessment (ONDQA), one of the facilities supplying a drug substance was found to have significant deficiencies. There is no finalized CMC review or the Compliance assessment at this time. This NDA should not be approved until ONDQA and the Office of Compliance have determined the facility inspection to be acceptable.

4. Nonclinical Pharmacology/Toxicology

No new preclinical information was submitted in this Complete Response.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to the Dr. Dilara Jappar's review completed on November 30, 2011.

In the first review cycle, the applicant provided results of a single comparative bioavailability study (study CL2007-02), which showed that a single-dose administration of Zegerid OTC powder for oral suspension resulted in greater systemic exposure than the administration of a Prilosec OTC 20 mg tablet. Specifically, the AUCinf of Zegerid OTC powder was 16% higher than that of Prilosec OTC and narrowly exceeded the upper limit of the 90% confidence limit of 125% (127.24%). The Cmax of Zegerid OTC powder was almost three times that of the Prilosec OTC tablet (90% confidence interval for % mean ratio 220.11 to 335.15). However, pharmacodynamic comparisons demonstrated similar levels of acid suppression at steady-state on day 7. In the second review cycle, the applicant provided results of a post-hoc analysis, based on cross study comparison of single-dose and multiple-dose PK data, attempting to establish that Zegerid OTC powder was less bioavailable than Prilosec 40 mg capsule. However, FDA's clinical pharmacology reviewers rejected the applicant's analysis, citing the lack of a common treatment that could be used as a bridge to link the studies included in such analysis.

The sponsor conducted bioequivalence (BE) study CL2010-12 comparing bioavailability of Zegerid 20 mg Powder with Prilosec 40 mg capsule to address the clinical pharmacology

deficiencies outlined in the second CR letter dated July 12, 2010. The study results showed that Cmax and AUC of Zegerid 20 mg powder are about 30% and 70% lower than those of Prilosec 40 mg capsule, respectively.

The sponsor has also submitted summary data to demonstrate that percent increase in Cmax for Zegerid products after multiple dose, regardless of dosage form (powder for oral suspension, capsule, or chewable tablet) and dosage strengths (20 mg or 40 mg), are less than that of Prilosec 40 mg capsule. Following multiple dosing, the percent increase for Zegerid products were 29%-38%, whereas the percent increase for Prilosec 40 mg capsule was 51-61%. The Division of Clinical Pharmacology concluded that the Cmax and AUC for the proposed Zegerid 20 mg Powder for Oral Suspension are lower than those for Prilosec 40 mg capsules, and therefore, recommended an Approval regulatory action.

I agree with their analysis and recommendation. There are no notable unresolved clinical pharmacology issues.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There is no clinical efficacy review for this application. No new controlled clinical efficacy and safety studies were conducted for this NDA; this NDA relies on the bioequivalence program.

8. Safety

Please refer to the clinical safety review by Dr. Christina Chang completed on November 17, 2011.

Safety data from several PK studies have been submitted and reviewed during previous two review cycles. Clinical safety data to support this Complete Response comes from two sources: safety data from the new PK study CL2010-12 and postmarketing safety data from NDA 22-281 (Zegerid OTC 20 mg capsule) from December 9, 2009 through August 31, 2011.

A total of 50 healthy adults (31 men and 19 women) aged 20 to 45 years were enrolled in study CL2010-12. Subjects received a single dose of Zegerid powder for oral suspension (treatment A) and Prilosec capsule (treatment B) based on a computer-generated randomization schedule. While 50 subjects participated in this study, 46 subjects completed both study periods. The four discontinuations were not related to adverse events. Of the 50 subjects, nine subjects reported 15 adverse events. There were no deaths or serious adverse

events. Three events reported by three subjects (dizziness, hematuria, and cough, respectively from subjects 135, 136, and 146) were deemed by the investigator to be unrelated to the study drugs. Other adverse events reported were headache, nausea, eructation, dry mouth, bloating, and abdominal crams; all were non serious events.

A review of the OTC postmarketing adverse events for Zegerid capsule did not reveal any new serious safety signals.

Based on the drug's safety profile, Dr. Chang recommended an Approval Regulatory Action. I agree with her recommendation. There are no notable outstanding safety issues.

9. Advisory Committee Meeting

No Advisory Committee was held for this application.

10. Pediatrics

This application triggers PREA because it proposes a new indication, treatment of heartburn, which is considered distinct from approved prescription uses in treating GERD and other acid-related disorders. Several proton pump inhibitors are available over the counter for the treatment of frequent heartburn (2 or more days per week) for patients 18 years and older. All of them were granted a wavier of the requirement for pediatric studies in all pediatric age groups because it was felt that pediatric patients under 12 years are not capable of accurately describing their symptoms, and for children 12-17, pediatric gastroenterologists recommend that children with symptoms of gastroesophageal reflux be examined by physicians for possible complications including esophagitis, poor growth, respiratory tract problems and food aversion.

The waiver request for Zegerid OTC was discussed with the Pediatric and Maternal Health Staff (PMHS) and at a Pediatric Review Committee meeting during the first review cycle. There was an agreement that a full waiver is appropriate under the PREA criterion that there is evidence strongly suggesting that the Zegerid OTC product would be unsafe in all pediatric age groups.

Labeling will include a statement: "children under 18 years of age: ask a doctor. Heartburn in children may sometimes be caused by a serious condition."

11. Other Relevant Regulatory Issues

A DSI inspection for this NDA at clinical and analytical sites for the BE study (Study CL2010-12) was requested by the Office of Clinical Pharmacology. Inspections at both sites have been completed and found to be satisfactory. The Sponsor submitted Form 3454

certifying that there were no financial conflicts of interest for any principal investigators and sub-investigators who conducted the BE study.

12. Labeling

The Sponsor is proposing to market 2-count sample and 14-count retail packages. There were no labeling deficiencies identified during the second review cycle. There will be no Consumer Information Leaflet (CIL) for this product, (b) (4) Labeling reviews for this resubmission have been conducted by Dr. R. Scroggs in the Division of Nonprescription Regulation Development (DNRD) (see her review entered in DARRTS on 12/2/2011) and by Dr. C-M. Tu from the Division of Medication Error Prevention and Analysis (DMEPA) (see her review entered in DARRTS on 9/12/2011). There were no labeling recommendations from DNRD. DMEPA have made few labeling changes, which after further discussions with the entire review team, were not conveyed to the sponsor. The proposed label contains all standard warnings consistent with other OTC drug products containing omeprazole.

The proposed proprietary name, Zegerid OTC, has been reviewed by DMEPA three times and was found to be acceptable.

There are no outstanding labeling issues.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend an Approval Action pending satisfactory results of the manufacturing facility inspection.

- Risk Benefit Assessment

Zegerid OTC for powder suspension has a favorable safety profile. It is also the first OTC proton pump inhibitor that can be dispensed in a liquid formulation, which will provide a benefit to consumers who are unable to swallow solid dosage forms.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

- Recommended Comments to Applicant

None.

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/s/

DAIVA SHETTY
12/16/2011