CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-281

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 30, 2009
From	Joel Schiffenbauer, MD
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	22-281
Applicant Name	Schering-Plough
Date of Submission	June 6, 2009
PDUFA Goal Date	December 6, 2009
Proprietary Name / **Established (USAN) Name**	Zegerid OTC Omeprazole/sodium bicarbonate
Dosage Forms / Strength	Capsule/ 20 mg
Proposed Indication(s)	1. frequent heartburn
Action/Recommended Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Christina Chang/Daiva Shetty
Statistical Review	
Pharmacology Toxicology Review	
CMC Review/OBP Review	Christopher Hough/Moo Jhong Rhee
Microbiology Review	
Clinical Pharmacology Review	Kristina Estes/Sue Chih Lee
DDMAC	
DSI	
CDTL Review	
OSE/DMEPA	Zachary Oleszczuk/Kellie Taylor
OSE/DDRE	
OSE/DSRCS	
Other: Labeling review	Reynold Tan/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

Signatory Authority Review

1. Introduction

This review addresses the applicant's response to our previous complete response letter.

Zegerid capsules (20 mg and 40 mg) were approved under NDA 21-849 in 2006. Zegerid capsules differ from other omeprazole products in that the enteric coating in the delayed-release products is not present. Instead it is replaced by sodium bicarbonate to protect the naked omeprazole from degradation by gastric acid. The function of sodium bicarbonate in this product is therefore not as an antacid, but to assist in the absorption of omeprazole that would otherwise be degraded in the acid environment of the stomach.

The original approval for Zegerid capsules was based on two pharmacokinetic (PK)/pharmacodynamic (PD) studies (one for each dosage strength) comparing Zegerid and Prilosec delayed-release capsule. Although Zegerid 20 mg capsule did not meet bioequivalence criteria when compared with the Prilosec delayed-release capsule, PD comparisons demonstrated similar levels of acid suppression at steady-state.

This review will discuss the applicant's response to the complete response letter the applicant received after the first round of review. Specifically, this review will cover the following: 1) the clinical pharmacology information addressing the issue of cross study comparisons to demonstrate that the Cmax of Zegerid 20 mg is less than that of 40 mg omeprazole (Prilosec 40 mg); 2) the data provided to address the safety of Zegerid based on the Cmax of the 20 mg dose being less than 40 mg of omeprazole; 3) the use of Zegerid in the Asian population; and 4) labeling issues.

2. Background

On March 10, 2008, Schering-Plough submitted a 505(b)(2) application to change the marketing status of Zegerid 20 capsule from Rx to OTC, referencing the Agency's findings for Prilosec OTC 20 mg tablet. On January 6, 2009, DNCE issued a Complete Response action citing the following:

1. Zegerid OTC 20 mg capsule is not bioequivalent to Prilosec OTC 20 mg tablet. Zegerid demonstrates a higher Cmax than Prilosec OTC and a comparable AUC.
2. You have not presented adequate data to demonstrate that the Cmax of Zegerid OTC 20 mg capsule is lower than that of prescription Prilosec 40 mg capsule. You have presented a crossstudy comparison of PK results to support your contention that the Cmax 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 Cmax, 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 Cmax.

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 Cmax 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 Cmax 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 Cmax 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 Cmax, 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 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 g 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 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.

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"; b(4)

2. If bioequivalence is demonstrated, such data will not support a claim in labeling or advertising suggesting that Zegerid OTC 20 mg capsule is b(4)

The Agency held a post-Action meeting with Schering-Plough and Santarus, the sponsor for prescription Zegerid products, on March 3, 2009. The following agreements were reached:

1. Schering will provide details on the pharmacokinetic studies as well as a summary table (or tables) of side-by-side comparisons of the studies to support that the Cmax of Zegerid 20 mg capsule does not exceed the Cmax of omeprazole 40 mg tablet. The CR submission will address the appropriateness of pooling these PK studies. The analysis will also examine pooled individual Cmax values in addition to mean Cmax values.
2. Schering will provide an integrated assessment of safety for Zegerid and omeprazole in the CR, including information from clinical trials, postmarketing data for Zegerid and omeprazole, and an updated literature review. Where relevant, the analysis will utilize appropriate denominators for calculating the frequency of adverse events.
3. Regarding postmarketing information from AERS and WHO databases, Schering will provide a safety analysis proposal for FDA review and comment.
4. Schering will perform additional analyses including an analysis of WHO safety data to address the safety profile in the Asian population. Schering may also propose labeling changes to address safety concerns for the Asian population.
5. Schering will propose alternative statement of identity language for sodium bicarbonate in their complete response.

An Advice Letter was sent to Schering on April 2, 2009, requesting submission of case report numbers (ISR numbers) for deaths and cases with serious adverse events involving the following settings (see additional information under the "Safety" section below):

1) Omeprazole was the sole suspect drug
2) Available re-challenge and de-challenge information
3) Labeled adverse events vs. adverse events not already labeled

3. CMC/Device

In the last review of this application, a recommendation for approval from the CMC

perspective could not be made because of an unresolved issue with labeling and an inspection. All issues have now been resolved. This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" recommendation is made from the Office of Compliance for the site inspections. Therefore, from the CMC perspective, this NDA is recommended for approval.

Therefore, I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues.

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

The Complete Response for NDA 22-281, Zegerid OTC 20 mg capsules, has been reviewed by the Office of Clinical Pharmacology / Division of Clinical Pharmacology III. The sponsor has adequately addressed the concerns related to clinical pharmacology. Specifically, the sponsor has provided data demonstrating that the Cmax for Zegerid 20mg is below the Cmax for Prilosec 40 mg as requested by DNCE even taking into account the cross study comparisons.

Therefore I concur with the conclusions reached by the clinical pharmcology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. See also comments under the "Clinical Efficacy" section, below.

6. Clinical Microbiology

It was determined that there were no clinical microbiology issues presented by this NDA. Therefore there is no clinical microbiology review for this product.

7. Clinical/Statistical-Efficacy

The reader is referred to the original clinical and pharmacology reviews from the first review cycles for additional details.

No clinical efficacy studies were submitted. Two pharmacokinetic studies were conducted for the original submission, comparing Zegerid 20 mg capsule to Prilosec OTC 20 mg tablet.

Study CL2007-03, a pilot study was used to obtain information on sample size calculation for the pivotal study CL2007-15. Study CL2007-15, enrolled 136 subjects, and was a single-dose, randomized, crossover bioequivalence study of Zegerid OTC 20 mg capsule vs Prilosec OTC 20 mg tablet.

Based on results of the pivotal PK study (CL2007-15), the Cmax of Zegerid OTC capsule was demonstrated to be more than twice that of the reference drug, Prilosec OTC tablet, with the ratio of geometric mean of 2.2037. The inclusion of all evaluable subjects in study CL2007-15 provides an AUC0-t, with a 90% confidence interval for % mean ratio 110.34 to 125.11. The Office of Clinical Pharmacology has determined that, though bioequivalence is not demonstrated between Zegerid OTC 20 mg capsule and Prilosec OTC 20 mg tablet, both AUC0-inf and AUC0-t are comparable.

The GI reviewer Dr. Gao, previously recommended approval based on a review of the PK data. He commented that he did not believe that the higher Cmax is a safety issue or is of concern because much higher doses of omeprazole are used in patients with Zollinger-Ellison and "do not seem to be associated with serious adverse events."

My previous concerns raised during the first round of review (see review for the original submission) including cross study comparisons for Cmax, as well as safety for Zegerid, have been addressed by review of the clinical pharmacology and safety data during this second round of reviews. Specifically, the applicant has addressed concerns based on the information presented regarding Cmax findings for Zegerid (below that of Prilosec 40 mg), and the safety data provided for 20 and 40 mg of omeprazole (see below).

8. Safety

The applicant has provided a re-analysis of safety data for Zegerid specifically, and omeprazole in general, as the active ingredient. Submitted analyses are based on sources from the following:

1) Data from nine Zegerid pharmacokinetic studies (demonstrating that mean Cmax for Zegerid 20 mg is below the mean Cmax for Prilosec 40 mg).
2) Clinical trial data comparing the safety profile of 20 mg and 40 mg omeprazole and that Zegerid OTC capsules.
3) Safety data supporting the use of Zegerid OTC capsules in Asian populations.
4) A comprehensive postmarketing safety data (from three different sources: Santarus, AERS, and WHO) update.
5) Literature review.

In this re-submission the applicant provided data to support the safety of the proposed product with existing safety data for omeprazole 20 mg and 40 mg. In addition, the applicant provided available safety data in the Asian population including those who are slow metabolizers.

The applicant provided safety data obtained from clinical trials conducted with 10 mg, 20 mg, and 40 mg omeprazole which were presented at the 2000 and 2002 Advisory Committee meetings, convened to discuss the OTC switch of Prilosec. Postmarketing information obtained from Santarus, AERS, WHO, and literature also provided data to support the similar safety profiles of 20 and 40 mg omeprazole.

The applicant further provided an extensive literature review of clinical trials conducted in Asian populations as well as available postmarketing safety data which appears to demonstate that omeprazole use up to 40 mg daily did not raise any cause for concern in the Asian population.

The data reviewed by the medical officer, will be summarized further below.

Data from clinical trials
The applicant referenced safety data for omeprazole from 35 clinical trials as summarized in the public briefing document provided previously by Procter & Gamble previously, to support the OTC switch of omeprazole. This is data that has previously been reviewed.

Of the 35 trials, 18 were controlled trials. Table 1 (appendix) summarizes the most common adverse events by omeprazole dose from the non-U.S. controlled and uncontrolled, short-term trials. These AEs were mild and included (among others) diarrhea (3.2 – 3.9%), headache (2.0 – 3.8%), abdominal pain (1.5 – 2.5%), and flatulence (1.4 – 2.6%). The proportion of subjects taking 40 mg omeprazole (25%, N = 456) with AEs was not greater than those treated with 10 mg omeprazole (31%, N = 1364), or those taking 20 mg omeprazole (27%, N = 2113). There did not appear to be any dose relationship for AE's.

In short-term trials (≤ 12 weeks, both U.S./non-U.S. and controlled/uncontrolled), 105 serious non-fatal adverse events were reported by 65 subjects. These events were similar among patients receiving omeprazole or comparator treatments. In the longer-term trials (>12 weeks to 1 year), there were 61 serious non-fatal adverse events reported by 51 subjects, of which two events (syncope and atrial fibrillation) in two patients were considered to be related to treatment by the applicant.

Ten deaths occurred among subjects treated with omeprazole in the 35 trials reviewed. Most deaths were in elderly subjects, with the frequent reported causes being myocardial infarction, carcinoma, embolism, and pneumonia. None of the deaths were considered related to use of omeprazole.

In summary, based on the data presented to the Joint Advisory Committee to support OTC switch of omeprazole, the adverse events were well-characterized and mostly not serious, and there did not appear to be a dose-related increase in adverse event reporting.

Safety data from trials conducted during the development of Zegerid
The previous submission referenced studies conducted to support the prescription marketing of Zegerid formulations as well as the OTC switch of capsule and powder formulations. The reader is referred to the MO review for the original NDA submission for additional details.

The frequencies and nature of adverse events were similar to those identified with omeprazole in general. The referenced studies are presented in Table 2 (appendix).

The applicant provided a synopsis of available safety information for four additional PK/PD studies performed in healthy volunteers (not submitted for formal review; see Dr. Chang's review for additional details), initiated since the original NDA submission. A total of 169 subjects participated, reporting a total of 35 adverse events. The majority of AEs reported were mild in severity, and nine were moderate in severity; all nine moderate AEs were considered unlikely to be treatment-related. These adverse events are consistent with those seen in other clinical trials conducted with omeprazole. There were no reports of deaths, serious adverse events, or discontinuation due to adverse events.

Summary of Santarus Postmarketing Safety Data

The applicant provided a summary of spontaneous reporting of adverse events associated with Zegerid from the launch in 2004 through December 31, 2008. This analysis is based on estimates of relative incidence for each system organ class (SOC) and individual AE preferred terms (as categorized by MedDRA) based on the number of patients who received Zegerid at the 20 mg and 40 mg dose, respectively. The numbers of patients treated with Zegerid were obtained from the IMS Patient Estimator database. Using the IMS Patient Estimator, there were / / individual patients treated with Zegerid at the 20 mg and 40 mg dose-strengths, respectively. b(4)

During the period covered by this analysis, the Santarus database contained reports from 904 individual patients treated with Zegerid. These patients reported a total of 1626 AEs; 302 AEs were associated with the use of 20 mg Zegerid while 1324 AEs were reported with the 40 mg dose. The numbers of patients treated with each dose are used to calculate the relative adverse event incidences associated with use of these two doses shown in Table 3 (appendix).

Overall, 0.48% and 0.22% of all AEs were associated with the use of Zegerid 20 mg and 40 mg, respectively. Diarrhea, nausea, and upper abdominal pain were reported with highest frequencies for both dosage strengths. Nervous system disorders represent the second most frequent group of AEs reported with the use of Zegerid, with 273 reported events (16.8%). Headache, dizziness and somnolence accounted for 70% of reports in this category. Although there are differences in reporting frequencies for some AE's, there are no major differences.

In summary, based on this analysis provided, there do not appear to be clinically significant differences between the safety profiles of the two Zegerid dose strengths.

Summary of AERS and WHO Vigibase Data

The applicant provided a new analysis of the AERS and WHO data, written by an outside consultant, Dr. James W. Freston. The analysis is based on a proposal submitted on March 25, 2009, with the Agency's concurrence (Advice Letter April 2, 2009).

Safety data from AERS and WHO were analyzed based on the period that omeprazole was

available by prescription (1999-2003, period A) versus that after omeprazole became available OTC (2004-2009, period B). This analysis provided for any changes in the frequency of AE's or for new AE's that might have occurred during the OTC use of the product.

The following parameters were included in conducting the analysis:
The AEs contained in AERS database occurring in at least 5 cases in both time periods and had ≥ 2-fold increases in the rate of occurrence after OTC switch (Period A vs Period B, see below) are further analyzed with the areas of focus listed below. Although 2-fold was arbitrarily used as the cutoff for this analysis it appears to be a reasonable rate at which to capture most differences of importance (and is analogous to rates used in data mining analyses).

1) Denominators for calculating adverse events incidences were actual unit sales for OTC use and actual units dispensed for prescription use
2) The OTC units are the number of Prilosec OTC and Store Brand omeprazole tablets sold, based on Nielsen data.
3) The prescription units are the counts of omeprazole formulations that are received by the patients when they fill a prescription, based on data from IMS' National Prescription Audit (NPA+).

Based on data from IMS and Nielsen, total distribution of omeprazole products was:
1) Period A (1999 – 2003). [redacted] units
2) Period B (2004-2008Q3): [redacted] units

Areas of focus for this analysis are: b(4)
1) Omeprazole being the sole suspect drug
2) Concomitant medications
3) Available re-challenge and de-challenge data
4) Duration of therapy
5) Dose
6) Labeled AEs vs. AEs not already labeled.

Importantly, ISR numbers for deaths and cases with serious adverse event outcomes were provided to the Agency for validation of the sponsor's analysis (and were reviewed by the medical officer).

Fatalities
The total numbers of fatalities were similar in the two periods. In AERS there are 347 vs. 335 deaths in Period A vs. Period B. In WHO (ex-US) there are 65 vs. 44 deaths in Period A vs. Period B.

In AERS, 54 cases in Period A and 34 cases in Period B were reported with omeprazole being the sole identified suspect drug, totaling 88 reports of fatalities. The medical officer examined all these case narratives in AERS based on the ISR numbers provided by the applicant and provides the following comments:

Omeprazole was in fact the sole suspect drug in twelve cases out of the 84 (four reports of the 84 were duplicate cases) cases. These twelve cases reported deaths due to (in the order of frequency) granulocytopenia, thrombocytopenia, toxic epidermal necrolysis, interstitial nephritis, or Stevens-Johnson syndrome, and the ensuing complications. All of these are rare events and already described in the prescription omeprazole label. In all the other cases, there were underlying medical conditions (such as malignancies, suicide, or myocardial infarction) which were more likely to have been responsible for the deaths. Further, many of the narratives contained other concomitant medications also likely to have been associated with the deaths; the medications were simply not listed in the "suspect medications" section. Overall, the data pertaining to fatalities do not support a hypothesis that there is a surplus of deaths in Period B. In view of widespread use of omeprazole, twelve cases of fatalities in nearly 10 years use should not rise to the level as to warrant designation of an adverse OTC safety profile.

I agree with Dr. Chang's assessment.

Only one event type occurred in Period B at a frequency of $\geq$ 3x that of Period A, and only six additional event types occurred at a frequency of $\geq$ 2x that of Period A. Cases may be confounded by indication, since presumably, the cases associated with prescription use, at least in some instances, were in sicker individuals, than those associated with OTC use. This may lead to greater number of cases in Period A.

These adverse events are discussed below:

Serious adverse events reported at an increased rate of $\geq$ 2x from Period A to Period B
The seven events are listed in Table 4(appendix). The reader is referred to the medical officer review for additional details.

Hypocalcemia
This event has the highest Period B/Period A ratio (3.71) among the seven events listed.

However, the medical officer identified only 10 unique cases from the list submitted, and of the 10 cases, six were case reports from literature. All ten cases reported hospitalizations due to complications from severe hypocalcemia and severe hypomagnesemia following long-term (> one year duration) use of omeprazole. Positive dechallenge was seen in all 10 cases, with serum calcium and magnesium levels normalizing within two weeks following discontinuation of omeprazole. The mechanism hypothesized was interference by omeprazole on magnesium absorption, which in turn causes hypocalcemia.

Nevertheless, these cases are rare given the large number of uses, and are unlikely to be of significance for short term OTC use.

A review of the cases for the other AE's including (cytolytic) hepatitis, drug eruption, somnolence, general health deterioration, gastric disorder, and therapeutic agent toxicity, are otherwise unrevealing or are labeled events (see Dr. Chang's review for additional details).

Overall, it may be concluded that, with the exception of hypocalcemia, there is little evidence to support causal relationships in the databases. Hypocalcemia is unlikely to occur in the OTC setting given the short-term, periodic nature of heartburn treatment. The Agency is reviewing the safety data related to the chronic use of PPI's and the risk for fracture. There were no other clinically important AE's identified in this analysis that have not been recognized previously.

Literature on direct comparison of safety profile between 20 mg and 40 mg omeprazole
The applicant provided a literature review of English language publications comparing 20 mg to 40 mg omeprazole; this literature survey was absent from the original submission. The applicant provided studies with designs permitting comparison with respect to adverse events associated with the two omeprazole doses.

Of the 18 publications provided and reviewed by the applicant, 11 publications contained original data from trials in which 20 mg and 40 mg omeprazole were examined (one trial also included a 60 mg omeprazole arm). The other seven publications had designs that did not allow this comparison.

Overall, 1235 individuals were given 20 mg omeprazole, while 1265 individuals were given 40 mg omeprazole up to 8 weeks. In the 11 trials reviewed, there did not appear to be significant difference in the nature or frequency of adverse events associated with 20 mg and 40 mg omeprazole (and 60 mg omeprazole19).

Thus, available literature and postmarketing information appear to support the contention that no appreciable differences in the safety profile are seen between 20 mg and 40 mg omeprazole.

Literature on omeprazole safety in the Asian population
The applicant provided a literature review conducted by an outside consultant, Dr. Richard H. Hunt. The search was undertaken in Medline for all published randomized clinical trials (1950 – April 2009) involving Asian subjects enrolled in any omeprazole treatment (literature search up to March, 2009), as well as the Japanese literature database CINII (htt://library.mcmaster.ca/articles/cinii, reviewed literature originally from Japan with English abstracts). Dr. Chang reviewed the references provided. I also examined the references.

The search yielded 45 full reports from randomized clinical trials from which safety data were extracted. In general, the studies enrolled either healthy volunteers, (e.g., for PK and PD studies), or patients with GERD, duodenal and gastric ulcers.

Omeprazole was used as a single dose in 14 studies PK/PD studies (n = 245, 49 of them are slow metabolizers of CYP2C19). All used 20 mg omeprazole except for four studies which used 40 mg omeprazole. Two studies reported that no adverse events were seen in omeprazole users (both 20 mg per day and 40 mg per day groups) while the others did not report on AE's.

Eight studies reported omeprazole use for 7-8 days (n = 89, 16 of them are slow metabolizers of CYP2C19). Omeprazole dose used ranged from 10 mg, 20 mg or 40 mg once daily to 10 mg or 20 mg twice per day. None reported any AEs.

There were 13 publications reporting the use of omeprazole for 2-4 weeks (n = 1057) in Asian healthy volunteers and those with GERD, DU, or GU patients. Omeprazole doses studied ranged from 10 mg to 40 mg per day. None of the trials reported clinically significant adverse outcomes. The reported adverse events were mild and consistent with known safety profile of omeprazole. Nine publications reported using omeprazole for 6-8 weeks (n = 354). The trials evaluated omeprazole at doses 10 mg and 20 mg. No trial reported severe AEs in the omeprazole group.

One non-randomized study evaluated 121 Japanese patients with recurrent reflux esophagitis treated with omeprazole (10 mg vs. 20 mg). This 6-12 month study also evaluated the outcome with respect to the patients' CYP2C19 genotype. Omeprazole was well-tolerated by all subjects, including the slow metabolizers (n = 20).

In summary, available information does not suggest that omeprazole is associated with an adverse or unique profile in the Asian population relative to other populations. Both the nature and frequencies of adverse events reported in the literature from trials conducted in the Asian population were similar to known profile of omeprazole.

9. Advisory Committee Meeting

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

10. Pediatrics

Approval of an NDA for Zegerid OTC product triggers PREA because it contains a new indication, treatment of heartburn. Currently Prilosec OTC 20 mg and Dexcel omeprazole are available over-the-counter for the treatment of frequent heartburn (2 or more days per week), and are approved for patients 18 years and older. The omeprazole OTC products 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 heartburn symptoms, and for children 12-17, pediatric gastroenterologists recommend that children with symptoms of gastroesophageal reflux or frequent heartburn be examined by physicians for possible complications including esophagitis, poor growth, respiratory tract problems, and food aversion.

The waiver request was discussed with the Pediatric and Maternal Health Staff (PMHS) and at a PeRC meeting. There was 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.

PMHS suggests language be added to the label such as "Children under 18 years of age with frequent heartburn should be examined by a doctor and use this product only under the direction of a doctor."

The label already reads "ask a doctor" and states that "Heartburn in children may sometimes be caused by a serious condition" which I believe addresses this issue.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Based on the labeling reviewer's comments, the issues related to the statement of identity for sodium bicarbonate, and use in the pediatric population, have been adequately addressed and all other labeling issues have been resolved. Dr. Tan comments:

Inform the sponsor that the labels submitted in NDA 22-281 Supporting Document 33 are "Approved." Request final printed labeling, when available, identical to the draft labeling submitted 10/22/09 for all SKUs of the product.

DMEPA had no further comments or recommendations on the container labels, cartons, and drug facts labeling.

I agree with the labeling changes as reviewed by Dr. Tan.

At the time of this approval the Agency was reviewing additional safety issues related to the use of PPI's in general. There issues are: 1) interaction with clopidogrel; and 2) the development of fractures with long term use. At such time as the Agency has finalized its recommendations for these issues, changes will have to be applied to the labeling for Zegerid and other PPI's.

13. Decision/Action/Risk Benefit Assessment

Three unresolved issues remained from the previous review cycle. With this CR submission, the applicant has provided sufficient evidence to satisfactorily address all issues.

First, the information submitted demonstrates that cross study comparisons for the Cmax determination of Zegerid are acceptable and that the Cmax for Zegerid is less than that of omeprazole 40 mg (addresses points 1 and 2 in the CR letter). Therefore the Cmax for Zegerid can be bracketed between that of omeprazole 20 mg and 40 mg, and safety information for the 20 and 40 mg omeprazole doses can be used to support the safety of Zegerid 20 mg.

Second, the data submitted demonstrates that there are no clinically significant safety differences between 20 mg and 40 mg omeprazole (addresses point 3 in the CR letter). Because we can now accept that the Cmax value for Zegerid falls between the two omeprazole dose strengths (20 mg and 40 mg), based on the information provided, the safety of Zegerid OTC 20 mg capsule, can now be bracketed by existing safety data for the two omeprazole dose strengths. This safety data does not raise any clinically important issues.

Third, this submission adequately demonstrates that there are no significant safety differences related to different CYP2C19 genotypes (slow metabolizers), thereby obviating the need for additional warning statements for slow metabolizers (Asian population) in the proposed label (addresses point 3 in the CR letter).

Several additional issues will be further discussed here. In regards to the higher Cmax for Zegerid as compared to omeprazole in Prilosec, the precedent for accepting a higher Cmax has already been set by the original approval of Zegerid as a prescription product. In effect, the issue of the higher Cmax is no different for the prescription population than for the OTC population, as long as the safety of Zegerid has been established. The applicant presented data in this application to address this issue. Furthermore, the use of Zegerid OTC is clearly limited to short term use, and even if used off-label for longer in the OTC setting, has a very acceptable safety profile.

In term of use in the Asian population or for those who may be slow metabolizers, again precedence has already been set with the approval of omeprazole for prescription and OTC use, as well as approval of Zegerid as a prescription product. Although the prescription label states that physicians may wish to consider dose reduction when used in the Asian population, on a practical basis, this is not done. An informal survey of several gastroenterologists performed by myself and Dr. Chang revealed that physicians are unaware of the issue of higher AUC for the Asian population specifically, and in general, may even use omeprazole 40 mg or more for recalcitrant cases of GERD, without concern. Furthermore, the applicant has again adequately addressed any safety concerns for use in this population based on the information provided. Finally, during the original approval of Prilosec OTC, Dr. Robert Justice addressed the issue of higher AUC in the Asian population in his review, and Prilosec OTC was approved OTC without any language regarding use in the Asian population in the label. The same was true for the approval of the Dexcel omeprazole product. At this time we have no indication that there are any unusual safety concerns in this population based on the data provided by the applicant.

Lastly, some comments regarding both the higher AUC and Cmax in the Asian population (addresses point 4 in the CR letter). As commented above, the OTC approval of Prilosec OTC,

which has the same concern at least regarding the higher AUC, has already been addressed during approval of the other OTC omeprazole products. The prescription approval of Zegerid has already set the precedence for approving a product with a higher Cmax and AUC in the Asian population for the Rx indications. Furthermore, the Division has provided guidance to applicants, in general, to provide additional safety data for any new products which are not bioequivalent but have a higher AUC and/or Cmax, compared to the reference product (which is essentially the issue for point 4 in the CR letter). The applicant for Zegerid has provided this data, and any potential safety concerns have been addressed in this submission by the applicant.

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It should be emphasized once again that the label calls for short term use (14 days, every / months) which should further address any potential safety concerns for the increase in AUC and Cmax associated with the use of Zegerid in the OTC setting in the subset of individuals who are slow metabolizers. Therefore, I do not believe that these issues surrounding Zegerid should preclude approval, nor do they require additional language in the OTC label regarding use in the Asian population.

Conclusions and recommendations

The applicant has satisfactorily addressed all of the issues listed in the CR letter. I recommend approval of this NDA with labeling language similar to Prilosec OTC and without any specific language regarding dosing directions in the Asian population. Issues regarding the purpose of sodium bicarbonate and pediatric use have been addressed in labeling.

Appendix:

Table 1: **Most common omeprazole AEs by dose; non-US, short-term, controlled and uncontrolled trials**

Dose of omeprazole	10 mg daily	20 mg daily	40 mg daily
# Patients	N=1360	N=2113	N=745
# Patients with AE (%)	419 (30.7)	567 (26.8)	110 (14.7)
Diarrhea	51 (3.7)	67 (3.2)	18 (3.9)
Headache	52 (3.8)	75 (3.5)	9 (2.0)
Respiratory infection	44 (3.2)	37 (1.8)	2 (0.4)
Abdominal pain	25 (1.8)	31 (1.5)	11 (2.4)
Nausea/nausea aggravated	27 (2.0)	35 (1.7)	4 (0.9)
Flatulence	19 (1.4)	41 (1.9)	12 (2.6)
Pharyngitis	17 (1.2)	33 (1.6)	1 (0.2)
Constipation	23 (1.7)	20 (0.9)	9 (2.0)
Dizziness/vertigo	24 (1.8)	27 (1.3)	10 (2.2)
Vomiting	12 (0.9)	20 (0.9)	10 (2.2)
Back pain	18 (1.3)	19 (0.9)	1 (0.2)
Infection, viral	15 (1.1)	14 (0.7)	3 (0.7)
Epigastric pain/epigastric pain aggravated	6 (0.4)	8 (0.4)	5 (1.1)

Adapted from Table 7.12 of Proctor & Gamble briefing document to joint AC.
AEs experienced by at least 1% of the patients in omeprazole total column are given.
The AEs are sorted by the omeprazole total column.

Table 2: **Clinical program supporting Zegerid formulations**

Protocol number	Product	Type of study	Submission
OME-IR(CAP)-CO1	Capsules 20 mg	BE (PK/PD)	NDA 21-849
OME-IR(CAP)-CO2	Capsules 40 mg	BE (PK/PD)	NDA 21-849
OME-IR(SUSP)-CO2	Powder for oral suspension 40 mg	BE (PK/PD)	NDA 21-706
OME-IR(SUSP)-CO3	Powder for oral suspension 40 mg	Efficacy (upper GI bleeding in critically ill patients	NDA 21-706
OME-IR(SUSP)-CO5	Powder for oral suspension 40 mg	PK loading dose	NDA 21-706
OME-IR(SUSP)-CO6	Powder for oral suspension 20 mg	BE (PK/PD)	NDA 21-636
OME-IR(SUSP)-CO7	Powder for oral suspension 40 mg	Safety	NDA 21-706
CL2007-03	Capsules 20 mg	BE (PK), pilot study	NDA 22-281, 1st cycle
CL2007-15	Capsules 20 mg	BE (PK)	NDA 22-281, 1st cycle
CL2007-02	Powder for oral suspension 20 mg	BE (PK)	[redacted] 1st cycle

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Table 3: **Summary of the most common AEs (> 1%) in the Santarus database: number of AEs and relative incidence by MedDRA preferred term (PT)**

Preferred term	#AEs		Relative incidence (% patients with AE)	
	20 mg	40 mg	20 mg	40 mg
Headache	14	85	4.64%	6.42%
Diarrhea	16	76	5.30%	5.74%
Nausea	10	66	3.31%	4.98%
Dizziness	6	66	1.99%	4.98%
Abdominal pain, upper	9	53	2.98%	4.00%
Drug ineffective	4	39	1.32%	2.95%
Constipation	6	34	1.99%	2.57%
Dyspepsia	8	29	2.65%	2.19%
Edema, peripheral	4	31	1.32%	2.34%
Abdominal pain	5	29	1.66%	2.19%
Flatulence	10	23	3.31%	1.74%
Abdominal distention	10	22	3.31%	1.66%
Vomiting	12	20	3.97%	1.51%
Blood pressure increased	5	22	1.66%	1.66%
Fatigue	1	24	< 1.00%	1.81%
Dry mouth	4	18	1.32%	1.36%
Somnolence	2	19	< 1.00%	1.44%
Chest pain	6	12	1.99%	< 1.00%
Muscle spasms	3	14	1.00%	1.06%
Feces discolored	4	13	1.32%	1.00%
Dysgeusia	4	13	1.32%	1.00%
Rash, pruritic	2	14	< 1.00%	1.06%
Asthenia	0	15	0.00%	1.13%
Weight decreased	2	13	< 1.00%	1.00%
Throat irritation	6	9	1.99%	< 1.00%
Anxiety	6	7	1.99%	< 1.00%
Back pain	5	10	1.66%	< 1.00%
Blood glucose increased	4	8	1.32%	< 1.00%
Cough	4	7	1.32%	< 1.00%
Eructation	4	6	1.32%	< 1.00%
Convulsion	4	0	1.32%	0.00%

Table 4: **Events in AERS expressed as preferred terms reported at least two times more frequently in Period B vs Period A**

Preferred term	1999Q1–2003Q4		2004Q1–2008Q3		Ratio of the rates
	N	Rate	N	Rate	
Gastric disorder	5	0.0097	16	0.0198	2.04
General physical health deterioration	14	0.0272	54	0.0670	2.46
Cytolytic hepatitis	15	0.0291	48	0.0595	2.04
Therapeutic agent toxicity	5	0.0097	19	0.0236	2.43
Hypocalcaemia	5	0.0097	29	0.0360	3.71
Somnolence	15	0.0291	53	0.0657	2.26
Drug eruption	5	0.0097	20	0.0248	2.56

Rate is calculated per 10 million tablets.
Ratio of rates is calculated from Period B/Period A.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES

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/s/

JOEL SCHIFFENBAUER
11/30/2009