CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-281

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	1/06/2009
From	Joel Schiffenbauer
Subject	Deputy Division Director Summary Review
NDA/BLA # Supplement #	22-281
Applicant Name	Schering-Plough
Date of Submission	3/10/2008
PDUFA Goal Date	1/10/2008
Proprietary Name / Established (USAN) Name	Zegerid/Omeprazole/Sodium bicarbonate
Dosage Forms / Strength	capsule
Proposed Indication(s)	1. treatment of frequent heartburn 2. 3.
Action/Recommended Action for NME:	*complete response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christina Chang, Daiva Shetty, Wen-Yi Gao
Statistical Review	
Pharmacology Toxicology Review	Wafa Harrouk
CMC Review/OBP Review	Christopher Hough
Microbiology Review	
Clinical Pharmacology Review	Tien-Mien Chen
DDMAC	
DSI	Lisa Capron
CDTL Review	
OSE/DMETS	Todd Bridges
OSE/DDRE	
OSE/DSRCS	
Other/ peds	Ann Taylor (peds)/ C. Ganley letter

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. Omeprazole is a member of the proton pump inhibitor family which suppresses the action of the terminal step of gastric acid production. Delayed release omeprazole has been available by prescription in the U.S. since 1989 for treatment of various acid-related gastrointestinal disorders, and omeprazole magnesium over-the-counter (OTC) as Prilosec OTC since 2003 for the 14-day treatment of frequent heartburn. Omeprazole 20 mg tablets (Dexcel) was approved under NDA 22-032 in 2006.

Zegerid capsules (20 mg and 40 mg) were approved under NDA 21-849 in 2006. Zegerid capsules differ from omeprazole products in that the enteric coating in the delayed-release products is not present. Instead it is replaced by that of 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. 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: 1) the results of PK studies, specifically the differences from Prilosec OTC; 2) safety data provided; and 3) other issues raised in regards to the labeling for use in various subpopulations. One of the main issues addressed in this review is the fact that the Cmax for Zegerid is greater than that for Prilosec OTC.

2. Background

The applicant, Schering-Plough, is requesting a switch of the 20 mg Zegerid capsule for OTC use in treating frequent heartburn. The development program for this switch consists of two PK studies as well as reliance on previous Agency findings regarding the safety and efficacy of omeprazole, as well as postmarketing safety data.

Of note, a meeting was held with the applicant and an advice letter was subsequently issued on July 18, 2007 by Dr. Ganley. Comments from that letter are summarized here because they are relevant to a number of issues discussed in this review (including labeling issues; see later):

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

b(4)

2. Bioequivalence criteria must be met with data from the PK study with direct comparison to Prilosec OTC, the reference listed drug for the OTC indication. If PK data do not

bridge Zegerid products to Prilosec OTC, then additional data will be needed to support the efficacy or safety of the product.This may require a clinical study.
3. If bioequivalence is demonstrated, such data will not support a claim in labeling or advertising suggesting that Zegerid / / Also, the/ / / / / b(4)
4. Label comprehension and possibly actual use studies may be required to demonstrate correct consumer understanding and use of the products.
5. The product should contain sodium labeling to comply with criteria listed in 21 CFR 201.64.
6. Warnings applicable to sodium bicarbonate should be included given the daily exposure for consumers during the 14-day course of treatment.
7. Labeling of potential safety issues in patients with contraindications for Zegerid (given the fixed dose of sodium bicarbonate) need to be addressed.

For further comments regarding the issues raised in the letter from Dr. Ganley, please see under section 13 Decision/Action, below.

3. CMC/Device

The chemistry reviewer writes:

The application is a 505 (b)(2) application relying on the Agency's finding of safety and efficacy for Prilosec OTC tablets, 20 mg (NDA 21-229). The drug product of this OTC version is identical to the Rx version, Zegerid→ 20 mg Capsule (NDA 21-849). Their formulations are identical. Consequently, raw material controls, manufacturing processes and controls, specifications, and stability are identical to those of the approved Rx product (NDA 21-849), which was extensively referenced in this application. The only difference is the tamper-resistant seal added to the capsule.

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review[October 7, 2008]. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

The expiration interval of 36 months for the drug product packaged for marketing is adequately supported from the information submitted in the application, and given in reply to the Agency's request.

I agree with this assessment. See also section 11 for comments about inspections.

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 clinical pharmacology reviewer Dr. Chen writes:

NDA 22-281 for Zegerid OTC 20 mg capsules has been reviewed by Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III). From the OCP standpoint, bioequivalence (BE) is not demonstrated between Zegerid OTC 20 mg caps and Prilosec OTC 20 mg tablet. As expected, Zegerid OTC 20 mg cap (Test) had higher mean C_{max} than that of Prilosec OTC 20 mg tablet (Reference), with the ratio of Test/Reference being 2.2 and its 90% CI being 193.3-251.2 (n=134). The results, however, showed comparable $AUC_{0-\infty}$ (90% CI: 109.0-124.2; n=120 out of 134) and AUC_{0-t} (90% CI: 110.3-125.11; n=134) between these two products.
The implication of the higher C_{max} for the proposed Zegerid OTC 20 mg capsule compared to Prilosec OTC 20 mg tablet should be considered by the Office of Non-Prescription Products.

The reviewer also recommends the following language for dosing Zegerid: *" take Zegerid on empty stomach at least one hour before a meal."* This language is different than the dosing for Prilosec OTC. However, I agree with this recommendation as a previous PK study for Zegerid demonstrates a food effect. On the other hand, Prilosec OTC labeling, which does not specify a time before eating when the medication is to be taken, was based on dosing direction in clinical efficacy studies for the treatment of heartburn.

An addendum by Dr. Chen also states that following a review of the DSI report, the quality of the plasma concentration data for the BE study is acceptable.

See also discussion of PK data under the Clinical Efficacy section, below.

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

Two pharmacokinetic studies were conducted 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. The results of both studies are provided in Tables 1 and 2 in the Appendix.

Based on results of the pivotal PK study (CL2007-15), the C_{max} 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 (see Tables in Appendix). The inclusion of all evaluable subjects in study CL2007-15 provides an AUC_{0-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 AUC_{0-inf} and AUC_{0-t} are comparable.

The GI reviewer Dr. Gao recommends approval based on a review of the PK data. He comments that he does 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." I do not agree with approval at this time and my comments are presented in section 13, below.

8. Safety

One of the goals of this safety review was to identify any new safety concerns for Zegerid 20 mg. This was performed by relying on AE reports for Zegerid but also on reports for Prilosec OTC as well as an examination of the safety profiles of omeprazole 20 mg vs 40 mg, because the Cmax of Zegerid was two-fold higher than Prilosec OTC. There were difficulties with the presentation of the data by the applicant.

The clinical data utilized in the MO review of safety include:

1) Safety data from NDA 21-849 prescription Zegerid capsules
2) Current U.S. prescription Prilosec delayed-release capsule label (latest version, approved April 27, 2007)
3) Current Prilosec OTC Drug Facts label
4) Current prescription Zegerid capsule and powder for oral suspension labels
5) An analysis of adverse events from the Santarus (owner of Zegerid) postmarketing drug safety database from
November 2, 2004 to June 13, 2008
6) A report summarizing adverse event reporting to the FDA from the Adverse Event Reporting System (AERS) databases from 2003 to December 31, 2007
7) A report summarizing adverse event reporting to the World Health Organization's (WHO) International Drug Monitoring Program from 2003 to December 31, 2007
8) A report summarizing adverse event reporting to the American Association of Poison Control Centers' (AAPCC) National Poison data system (NPDS) from 2005 to June 21, 2008

9) A summary of reports from the Drug Abuse Warning Network (DAWN) database from 2003 to June 23, 2008
10) A review of published medical literature relevant to the safety of omeprazole/sodium bicarbonate

Since launch, Santarus Inc. has distributed [ ] doses of the 20 mg Zegerid products and [ ] doses of the 40 mg products (according to the data in the latest Santarus Inc. Safety Update). This is in contrast to the [ ] prescription omeprazole treatments distributed worldwide prior to Prilosec OTC launch in 2003 as well as nearly [ ] Prilosec OTC tablets distributed since its launch. b(4)

Summary of data from approved omeprazole product:

Safety data from NDA 19-810 prescription Prilosec delayed-release capsules and safety data contained in NDA 21-229 Prilosec OTC tablet have already been previously reviewed by the Agency. While the omeprazole label describes studies for erosive esophagitis etc with efficacy findings of 20 mg omeprazole directly compared to 40 mg omeprazole and either placebo or active control (ranitidine), the label does not specifically detail any safety findings with respect to stratification by dose in these studies. Interestingly, 40 mg was not described in the label as being studied for GERD (which would be analogous to the OTC indication of heatburn), and so there is no safety comparison for 20 and 40 mg for the treatment of GERD.

Summary of data from PK studies:
Referenced studies:

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	Oral suspension 40 mg	BE (PK/PD)	NDA 21-706
OME-IR(SUSP)-CO3	Oral suspension 40 mg	Efficacy (upper GI bleeding in critically ill patients	NDA 21-706
OME-IR(SUSP)-CO5	Oral suspension 40 mg	PK loading dose	NDA 21-706
OME-IR(SUSP)-CO6	Oral suspension 20 mg	BE (PK/PD)	NDA 21-636
OME-IR(SUSP)-CO7	Oral suspension 40 mg	Safety	NDA 21-706

Studies submitted in present application:

Protocol number	Type of study
CL2007-03	BE (PK), pilot study
CL2007-15	BE (PK)
Study # 234	Label Comprehension

There were no deaths reported in the two PK Zegerid OTC capsule studies (CL2007-03 and CL2007-15) included in this application. Nor were there deaths reported in the clinical development of Zegerid 20 mg capsule [study OME-IR(CAP)-CO1].

There were no serious adverse events (SAEs) reported in studies CL2007-03, CL2007-15, or OME-IR(CAP)-CO1.

In the pilot PK study CL2007-03, one subject (no. 18) out of 36 was lost to follow up. This subject completed the Zegerid capsule dosing phase but did not return for subsequent dosing of Prilosec OTC tablet. This subject did not report any adverse events. From the pivotal PK study CL2007-15, 17 out of 151 total (11.3%) subjects were discontinued early. Of the 17 subjects who were discontinued, 15 withdrew consent after errors in the conduct of Period 1 of the study resulted in excessive number of missed or significantly delayed blood draws. There were only two subjects (no. 84 and no. 59) who were discontinued prematurely. One subject (no. 084) was withdrawn due to an unrelated adverse event (otitis media). The other subject (no. 059) was discontinued by the investigator due to elevated creatinine level. This abnormal laboratory value was determined to be a laboratory error based on repeat blood draw the following day.

For study OME-IR(CAP)-CO1, one subject (no. 19) out of 36 was discontinued from the study after experiencing hypersensitivity of moderate severity one hour after Zegerid administration. The subject was given one dose of 50 mg diphenhydramine; the symptoms subsided and resolved within one day.

Summary of all adverse events reported to the Santarus post-marketing database:

Since the launch of Zegerid, there have been 1335 adverse events from 764 patients reported to Santarus. Five adverse events showed a strong predominance (> two-fold difference) when comparing the two doses. The 20 mg Zegerid dose was associated more frequently with flatulence and vomiting, whereas the 40 mg dose was associated more frequently with fatigue, oedema peripheral, and pruritic rash.

Deaths from Santarus postmarketing data

One death was identified in the Santarus pharmacovigilance database. This event was identified in a published report by Haizlip et al. evaluating the efficacy of nasogastric administration of omeprazole suspension in raising gastric pH in critically ill pediatric patients. Patients were 22 mechanically ventilated children (age range 3 months to 16 years) in a tertiary care pediatric intensive care unit who were at risk for stress ulcer formation. Omeprazole was administered as "simplified omeprazole solution" and was not the commercially manufactured Zegerid formulation. In follow-up discussion, the author reported to Santarus that the patient was a 4-year-old, 20-kg Caucasian girl who had received a single dose of omeprazole (1 mg/kg). She subsequently died from parainfluenza sepsis.

Adverse Events associated with serious cases (postmarketing) from Santarus database

Since the launch of Zegerid, there have been 11 cases associated with serious outcomes reported to the Santarus internal database. These cases are described in detail in the Appendix. Together these 11 cases with serious outcome did not suggest any new safety signal for omeprazole. However, two cases of cardiac failure (4 and 10) may be a result of the increased sodium intake associated with Zegerid administration which, in predisposed patients, may lead to increased fluid retention that in turn precipitates or exacerbates heart failure.

The current Zegerid label does not list cardiac failure specifically as an adverse event. The proposed Zegerid OTC label asks individuals who are on a sodium-restricted diet to "ask a doctor before use." This appears reasonable.

Summary of adverse events reported to FDA's AERS database:

The medical officer found the applicant's analyses of deaths and cases with serious outcomes in these two databases were inadequate. The applicant never provided the total number of cases reported to these two databases. Specifically, only crude counts of these cases were provided, without narrative explanation, and without purging potential duplicate cases. However, FDA's AERS database differentiates between Prilosec and Prilosec OTC (but Descel omeprazole is not specifically mentioned); 22% of total Prilosec reports were described as associated with the OTC products. The relative distribution information for 20 mg vs. 40 mg omeprazole formulations is also unknown.

The safety information from AERS was submitted from the years 2003-2008. Of the 14,775 AEs reported to AERS, 14,007 events were associated with serious outcomes, and there were 330 deaths identified during this time frame. The applicant has not provided explanation or analysis regarding these deaths.

The medical officer comments:

To further investigate whether deaths or cases with serious outcomes reported to AERS may be more clearly linked to either 20 mg or 40 mg omeprazole formulations, case report forms from AERS were requested from the applicant. The applicant was unable to supply the actual case report forms but did submit "line items" from fatal cases in AERS on October 22, 2008. Limited information was available from the reports, including patients' age, gender, country of residence, date of onset, report source/type, preferred term, concomitant medications, dosing information, outcome data, and indication for medications. Not all fields were populated with requested information and no clinical narratives were included in these line items.

In an attempt to analyze the cases provided, the medical officer further examined the information available. The medical officer comments that 34 reports out of the 330 may reasonably be eliminated as duplicates (based on patient demographic information, date of onset, and concomitant medications taken), and another 123 reports may be eliminated, with the death reasonably attributed to causes likely other than omeprazole (such as advanced cancer, completed suicide, septic or hemorrhagic shock, underlying cardiac/pulmonary/hepatic conditions, or cerebral vascular accidents etc). Thus, 172 reports of deaths remained for

further analysis. The medical officer comments that the majority of these reports lacked dose information and would thus not be helpful in differentiating the safety profile between 20 mg and 40 mg omeprazole.

The medical officer also notes in her review that there is a potential safety concern with acute renal failure events. The higher frequency of acute renal failure associated with 40 mg dose strength compared to 20 mg (22.92% vs. 18.18%) may warrant further investigation. However, based on post-marketing data I do not believe that this small difference indicates a significant signal that would warrant further followup at this time. It is also possible that these cases are confounded in that higher doses of omeprazole may be used in sicker patients.

Summary of adverse events reported to WHO

This portion of the safety review will focus on the ex-US component in Vigibase, since U.S. reports are already detailed in AERS. According to the medical reviewer, the WHO database does not identify any Prilosec suspect drug specifically as "Prilosec OTC," therefore, differentiation between events associated with prescription use vs. non-prescription use of Prilosec is not feasible. In contrast to the AERS database where serious cases predominate, a quarter of cases (24.70% of these 2275 cases, or 562 cases) in Vigibase were associated with serious outcomes. Serious events were mainly represented by hematologic, skin, and liver & biliary system disorders.

The applicant further examined the Vigibase data by different omeprazole doses [10 mg, 20 mg, 40 mg, 80 mg, other (presumably an aggregate of doses higher than 80 mg), and dose information unknown]. This analysis is displayed in Table 4 in the Appendix. When deaths and serious AEs were examined by dose, fewer cases were associated with 40 mg omeprazole than 20 mg omeprazole, although the denominator is not provided. However, 14 (42.42% of total deaths, the majority) deaths had no dose information. Similarly, 63.17% of SAEs had no associated dose information. No case report forms/case narratives was provided.

The medical officer comments:

With respect to deaths and serious AEs, the analysis actually favored 40 mg omeprazole formulations. However, it must be emphasized that the large proportion of reports had no dose information; therefore, the absence of dose-related safety profile cannot be established with certainty. The higher frequency of thrombocytopenia associated with 40 mg dose strength compared to 20 mg (10.32% vs. 6.8%) may represent a safety concern.

The Applicant provided no substantive narrative for analysis of the WHO ex-US data. The Applicant was unable to supply the actual case report forms but did submit "line items" from these cases in Vigibase on October 28, 2008. Limited information was available from the reports, including patients' age, gender, country of residence, date of onset, report source/type, preferred term, concomitant medications, dosing information, outcome data, and indication for medications. Not all fields were populated with requested information and no clinical narratives were included in these line items. According to this submission, there were a total of 56 reports of deaths in the entire database involving omeprazole during the period of

January 1, 2003 to December 31, 2007. Of these 56 reports, 23 reports were from the U.S., leaving 33 ex-US reports of fatalities for the worldwide market. Since the U.S. cases were already included in AERS database, only the ex-US reports will be discussed here. Again, the Applicant provided no narrative or summary analysis.

Again, the small differences in frequency of events is not supported by information from databases other than Vigibase. Thrombocytopenia, is however, noted as an adverse event in the omeprazole label, from post-marketing data.

Summary of other databases
The Applicant provided information from the National Poison Data System (NPDS, formerly known as the Toxic Exposures Surveillance System, TESS) maintained by the American Association of Poison Control Centers. Data from the period 2003 through June 23, 2008 were analyzed.

Within this time frame, there were 168 reports in which Zegerid exposure was related to the poisoning episode. It is not clear from the submission whether there were any deaths in the database. Nearly half of the reports (78, 46.4% of total) were characterized as unintentional therapeutic errors such as incorrect dosing, inadvertently taking someone else's medication, exposure through breast milk, and several other categories. Another quarter of reports (43, 25.6%) were further characterized as unintentional general exposure. Adverse drug reactions, which are defined as exposure associated with normal prescription use of the product, involved 33 (19.6%) of the reports. A total of 12 reports (7.1%) were intentional suspected suicides.

The Applicant submitted information requested from the Drug Abuse Warning Network (DAWN) database. DAWN information was search for all reported cases involving Zegerid, identified as Omeprazole-sodium bicarbonate from 2003 through June 23, 2008. Zegerid had 19 reports. Fourteen of these reports involve female patients and five were from male patients. Reports involved nine white, two black, two Hispanic and six unidentified racial/ethnic subgroups. All patients were adults, with age distribution between 25 and 65 years or older.

The majority of reports were for adverse drug effects, only two additional reports were identified as over-medication. Overall, there was no evidence of suicides, accidental ingestion, malicious poisonings or patient seeking of detoxification services. Therefore, omeprazole-sodium bicarbonate, or Zegerid, does not appear to have significant abuse potential.

Summary of literature
The Applicant submitted references obtained on the safety of Zegerid identified in a literature search. MEDLINE, BIOSIS, EMBASE and SciSearch databases were queried using the keywords "Zegerid" or variations of the phrase "immediate release omeprazole." The search included published research articles and meeting abstracts results, limited to the English language, published between 2003 and June 2008. Only four publications were identified

that contained pertinent Zegerid safety information. No significant, new safety information emerged after survey of these publications.

In addition, literature search [search term: omeprazole AND sodium bicarbonate OR Zegerid; limits: humans, clinical trials, meta-analysis, randomized controlled trial, review, English language] conducted by this medical officer yielded 18 references. The literature review did not reveal any new, serious safety concerns.

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

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 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 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" which I believe addresses this issue.

11. Other Relevant Regulatory Issues

In regards to inspections for NDA 22-281, the substance manufacturing site in Spain was inspected but deficiencies were identified and a 483 was issued. The manufacturer has just resolved the deficiencies.

12. Labeling

Labeling discussions were not held with the applicant as it was determined that Zegerid was not bioequivalent to Prilosec OTC and additional data would be needed. However, some labeling comments are included in this section to address issues raised in the reviews. In addition, changes to the label may be needed after reviewing any additional safety data supplied by the applicant in response to deficiencies identified in the action letter.

Captain Laura Shay, social scientist in the Division of Nonprescription Clinical Evaluation (DNCE) reviewed the submitted Label Comprehension studies (study # 234 and #237). Captain Shay's recommendations are as follows:

1. Remove sodium bicarbonate and the descriptor [redacted] from the Principal Display Panel.
2. Under 'Active ingredient' in Drug Facts the purpose of sodium bicarbonate change [redacted] to "assists in the absorption of omeprazole." b(4)

The medical officer, Dr. Chang, also made the following general recommendations and comments:

1) The Division of Medical Error Prevention and Analysis (DMEPA) has deemed the proposed trade name "Zegerid OTC" acceptable.
2) [redacted] does not adequately describe the purpose of sodium bicarbonate, as reflected in the label comprehension study. An alternative previously suggested to the Applicant in the Advice Letter, "assisting in the absorption of omeprazole," should be considered. b(4)
3) Clarithromycin, which when administered with omeprazole concurrently, nearly doubles the total exposure of omeprazole ($AUC_{0\text{-}24hr}$ increased by 89%). This degree of exposure to omeprazole would exceed indicated for the OTC heartburn treatment. Therefore, Clarithromycin should be added to the list of medications for which there is warning to "Ask a doctor or pharmacist before use if you are taking."
4) Warnings for Asian population should be added to "Ask a doctor" section. The Applicant's literature references included only four slow metabolizers in the pharmacokinetic study and 20 slow metabolizers in the safety study. Therefore, the justification submitted for removing this warning is inadequate to mitigate the labeling concern. Class labeling should be considered to incorporate this warning in the Prilosec OTC labeling.
5) A warning for patients with chronic liver disease (in whom the prescription omeprazole label and both prescription Zegerid capsule and powder labels call for dose adjustment due to increased exposure) should be incorporated.
6) The OTC label should contain a warning for patients who are prescribed Zegerid 40 mg capsule not to substitute two doses of 20 mg Zegerid capsule for one dose of Zegerid 40 mg capsule. This substitution would result in the patients being administered 2200 mg of sodium bicarbonate per day, twice the amount of sodium bicarbonate in each dose of Zegerid 40 mg capsule.

7) The OTC label should include a warning "Do not use if you are breast feeding."

These recommendations will be addressed in the next section.

13. Decision/Action/Risk Benefit Assessment

The applicant submitted an NDA to switch Zegerid 20 mg (omeprazole 20 mg plus sodium bicarbonate) from prescription to OTC status for the treatment of frequent heartburn. Of note, Prilosec OTC 20 mg is available OTC and the 40 mg dose has never been developed for OTC use.

A PK study comparing Zegerid to Prilosec OTC 20 mg is presented in support of the efficacy of Zegerid, and safety data from a number of sources is provided to support the safety of this formulation. It should be noted that the applicant was provided specific advice in a meeting and subsequent letter, that if Zegerid was not bioequivalent to Prilosec OTC, additional efficacy and/or safety studies would be needed to support approval (see Dr. Ganley's letter). Indeed, Zegerid 20 mg is not bioequivalent to Prilosec OTC with a Cmax that is 2.2 times greater than that of Prilosec and an AUC that falls just at the upper limit of the 90% confidence interval (110.34-125.11). To support the safety of Zegerid, the applicant argues that the Cmax of this product is less than that of Prilosec 40 mg and therefore safety data for Prilosec 40 mg can be used to support the safety of Zegerid. However, PK comparisons between Zegerid and Prilosec provided by the applicant are cross-study comparisons (the relevant C_{max} values from different studies are presented in the appendix in Table 3), and the applicant has provided no rationale for their attempt to link the PK of Zegerid 20 mg with Prilosec 40 mg. Furthermore, the applicant has provided safety data that does not adequately and clearly address the safety profile of 20 mg omeprazole vs 40 mg.

It should be emphasized that there is no data demonstrating increased efficacy for omeprazole 40 mg vs 20 mg for the indication of "treatment of frequent heartburn". Furthermore, since there is no data to demonstrate any increased efficacy of Zegerid 20 mg over Prilosec OTC 20 mg, it is important to know that there is no increase in adverse events with the use of a product that provides greater exposure through a higher Cmax. The data presented by the applicant to support the safety of Prilosec 40 mg compared to 20 mg is incomplete and poorly presented as confirmed by the medical officer's review (see footnote below for some comments from the medical officer in regards to the submission quality[1])and numerous

[1] "Applicant did not submit any clinical study reports from any of those studies. In the original submission, the postmarketing adverse events from AERS, WHO, and Santarus databases were submitted as mere line-listings in tabular format by MedDRA terms in Module 2, with no analyses or narrative summaries provided. Further, the section of "Integrated Summary of Safety" was omitted from Module 5 entirely from the original submission: Indeed, Module 5 required complete revision to attain filability for this application. The revised Integrated Summary of Safety" in Module 5 represented barely any improvement. In addition, the initial submission mistook the content of Module 4 as containing "Safety" information rather than preclinical information, and stated that safety information was not necessary to support this

requests for additional data during the review cycle. Specifically, in reviewing the safety data, the applicant has not provided any clear comparison of the 20 and 40 mg data either from the original Prilosec NDA or from postmarketing reports, especially for deaths and other SAE's.

Based on these deficiencies, it is recommended that the action to be taken be a complete response, and this NDA not be approved until the deficiencies are addressed.

The medical officer raises a number of concerns regarding the use of omeprazole in the Asian population, the use of clarithromycin, and warnings on the label regarding the use of bicarbonate. These will be addressed here.

The concern was raised that since many Asians are slow metabolizers of omeprazole, a warning should be placed on the Zegerid label to "ask your doctor" for Asians using this product. This issue was discussed at the time of the Prilosec OTC and Dexcel omeprazole approvals and it was determined that a warning was not necessary because of the long period of prescription use of omeprazole and in many cases at higher doses, without significant clinical concerns. I do not believe this is an issue for Zegerid either. The concern in Asians is that there is a four fold increase in AUC. The AUC for Zegerid capsule and Prilosec OTC are comparable and it is only the Cmax that is higher for Zegerid. Therefore I do not believe additional labeling is needed for Zegerid. However, that being said, I note that Zegerid already exhibits an increased Cmax, and therefore Asians taking Zegerid may not only have an increase in Cmax but AUC as well, which would in effect, be equivalent to taking a higher dose of omeprazole. Labeling therefore, should be contingent on the applicant providing updated safety data demonstrating no specific concerns in this population. It is the applicant's responsibility when supplying safety data and analyses to provide the data by demographic factors such as race (21 CFR 314.50). Therefore, the applicant should be requested to provide an updated analysis looking at the Asian population for safety concerns. Similarly, I do not believe a specific warning is needed for those individuals with liver disease, for the same reasons, pending review of additional safety data.

In regards to clarithromycin, the label for the antibiotic says that co-administration of omeprazole and clarithromycin has resulted in increases in plasma levels of both omeprazole and clarithromycin. The increases in omeprazole levels are likely not clinically significant for similar reasons as discussed above for the Asian population. The steady state plasma concentrations of omeprazole were increased (Cmax, AUC0-24, and T1/2 increases of 30%, 89% and 34% respectively) by the concomitant administration of clarithromycin. Further, the increase in clarithromycin is minimal (AUC and Cmax increases of 15% and 10% respectively), and certainly this will not reduce the efficacy of clarithromycin. The issue of co-administration of omeprazole with clarithromycin was also addressed at the time of approval

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application (stated in the Cover Letter). Several analyses of various databases crucial to the interpretation of postmarketing experience were requested from the Sponsor. Numerous attempts were made to assist the Applicant in achieving the final, still-disorganized, submission. In addition, the overall postmarketing information may be unreliable because of discrepancy in number of cases and AEs among the Sponsor's submissions."

of Prilosec OTC and was not felt to result in clinically significant concerns. Therefore I do not agree with adding clarithromycin to the list of drugs that says "ask a doctor". Also the label has a warning related to the inclusion of bicarbonate that says to "ask a doctor" if the consumer is on other prescription drugs. I believe that this will be sufficient to address any potential safety concerns with co-administration.

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" which I believe addresses the issue.

In addition, the language related to breast-feeding warnings should be the same as that for Prilosec OTC and there is no new data to support additional changes in the label.

The biopharm reviewer also recommends the following language: *" take Zegerid on empty stomach at least one hour before a meal."* This language is different than the dosing for Prilosec OTC. However, I agree with this recommendation as a previous PK study demonstrated a food effect for Zegerid.

Warnings related to the presence of bicarbonate in Zegerid are similar to those for antacids containing sodium bicarbonate. Since the amount of bicarbonate in Zegerid is less than in sodium bicarbonate containing antacids, I do not believe any additional warnings related to the presence of bicarbonate, are needed. Warnings related to the presence of sodium are already included in the label.

The Division of Medication Error Prevention does not object to the use of the name Zegerid OTC and I agree with their recommendations.

Finally in regards to the letter dated July 18, 2007 sent to the applicant a number of issues were raised that still need to be addressed by the applicant (and these are listed here):

1. Sodium bicarbonate is an active ingredient and should be listed in the active ingredient section on 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 is b(4)

Comments to applicant:

You were informed in a letter dated July 18, 2007 that if Zegerid 20 mg was not bioequivalent to Prilosec OTC 20 mg, you would need additional efficacy and/or safety data and that this may require a clinical study. The data you presented demonstrates that Zegerid capsules are not bioequivalent to Prilosec OTC. Furthermore, you have not presented data to demonstrate any added benefit of Zegerid 20 mg over Prilosec OTC 20 mg to treat frequent heartburn despite the increased Cmax. 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 of Zegerid is lower than that of Prilosec 40 mg.

Based on our review of your application we note the following deficiencies:

1) Zegerid 20 mg is not bioequivalent to Prilosec OTC 20 mg. Zegerid demonstrates a two-fold higher Cmax than Prilosec OTC and a comparable AUC.

2) You have not presented adequate data to demonstrate that the Cmax of Zegerid is lower than that of Prilosec 40 mg. You have presented a cross-study comparison of PK results to support your contention that the Cmax for Zegerid is lower than that of omeprazole 40 mg but you have not provided adequate rationale for why such a comparison is appropriate.

3) You have not presented data to demonstrate any increase in benefit of Zegerid 20 mg over Prilosec OTC 20 mg despite the increase in Cmax. Also, you have not presented adequate safety data to demonstrate that despite the higher Cmax, Zegerid is as safe as Prilosec 20 mg or that there is no difference in the safety profiles of omeprazole 20 and 40 mg. This is especially of concern for deaths and other SAE's.

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

1) You may perform a trial to demonstrate the added benefit of Zegerid 20 mg over Prilosec OTC 20 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 is less than that of Prilosec 40 mg. You may address this issue by either performing a new PK study or providing additional data. You may either: a) perform a PK study to demonstrate that the Cmax of Zegerid is less than that of Prilosec 40 mg. This would involve a 3 arm study comparing Zegerid, with Prilosec OTC 20 mg and Prilosec 40 mg; or b) analyze and present data to support your contention that the Cmax of Zegerid is indeed less than that of omeprazole 40 mg. You should provide evidence that the cross-study comparison that you have provided is appropriate including a description that the studies are comparable in regards to design, population studied, number of measurements, similar assays and other factors that may affect PK parameters.

3) Whether or not you do a clinical trial you should provide data to demonstrate that despite the higher Cmax, Zegerid has an acceptable safety profile. You can do this either by demonstrating that Zegerid is comparable in safety profile to Prilosec OTC 20 mg or that there is no clinically important difference in the safety profiles of omeprazole 20 and 40 mg. In

performing an analysis of safety for Zegerid and omeprazole, you should also 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 20 mg. 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 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 on 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 is b(4)

Appendix:

Table 1: Results of bioequivalence assessment, study CL2007-03

Parameters	Zegerid OTC 20 mg capsule (Test) Arithmetic mean (SD)	Prilosec OTC 20 mg tablet (Reference) Arithmetic mean (SD)	Ratio of geometric mean test/reference	90% confidence interval for % mean ratio
C_{max} (ng/mL)	550.2 (± 322.6)	399.7 (± 280.1)	1.3916	111.41-173.83
AUC_{0-inf} (ng*hr/mL)	532.4 (± 354.3)	580.2 (± 327.7)	0.8795	79.06-97.84
T_{max} (hr)	0.59 (± 0.27)	1.95 (± 1.07)	N/A	N/A

Table 2: Results of bioequivalence assessment, study CL2007-15

Parameters	Zegerid OTC 20 mg capsule Test Arithmetic mean (SD)	Prilosec OTC 20 mg tablet Reference Arithmetic mean (SD)	Ratio of geometric mean test/reference	90% confidence interval for % mean ratio
C_{max} (ng/mL)	623 (± 370)	362 (± 299)	2.2037	193.31-251.22
AUC_{0-inf} (ng*hr/mL)	743.3 (± 843.2)	730.2 (± 742.3)	1.1638	109.03-124.22
AUC_{0-t} (ng*hr/mL)	511.77	435.58	117.49	110.34-125.11
T_{max} (hr)	0.62 (± 0.28)	2.69 (± 2.06)	N/A	N/A

Table 3: Zegerid 20 mg capsule, Prilosec OTC 20 mg tablet, and Prilosec 40 mg capsule, day 1 plasma omeprazole pharmacokinetic parameters

	C_{max} mg/mL Arithmetic mean (SD)	AUC_{0-inf} ng*hr/mL Arithmetic mean (SD)	T_{max} hour Arithmetic mean (SD)
Zegerid OTC 20 mg capsule Study CL2007-15 NDA 22-281	623 ± 370	743.3 ± 843.2	0.62± 0.28
Prilosec OTC 20 mg tablet Study CL2007-15 NDA 22-281	362 ± 299	730.2 ± 742.3	2.69 ± 2.06
Prilosec Rx 40 mg capsule Study OME-IR(CAP)-C02 NDA 21-849	887.5 ± 694.0	1843 ± 2092	1.51 ± 0.40
Prilosec Rx 40 mg capsule Study OME-IR(SUSP)-C02 NDA 21-706	1040 ± 579.1	2658 ± 2888	2.34± 2.40

Table 4: SAE's and deaths by dose#

	10 mg	2 mg	40 mg	80 mg	Other	Unknown	Total
Serious AEs	18	227	58	5	3	534	845
% SAEs*	2.14%	26.87%	6.94%	0.53%	0.36%	63.17%	
Deaths	0	10	7	2	0	14	33
% deaths**	0%	30.30%	21.21%	6.06%	0%	42.42%	
*Based on 845 total SAEs in WHO ex-US							
**Based on 33 total deaths in WHO ex-US							

the second column should read 20 mg instead of 2 mg

SAE's are described below:

1. Intracranial hemorrhage requiring hospitalization

Consumer report of a 38 y/o male who presents with visual disturbances attributable to hemorrhage from intracranial cavernoma while on Zegerid 40 mg powder for oral suspension for heartburn treatment.

2. Nephrolithiasis requiring hospitalization twice in nine days

Consumer report of a 33 y/o male hospitalized for kidney stone after taking three doses of Zegerid 40 mg powder for oral suspension for unknown indication. The stone was passed three days after his discharge and Zegerid was restarted two days after passage of the stone. Nine days after restart of Zegerid, he was re-hospitalized with another renal calculus and kidney infection. Three days after discharge he passed two calculi and recovered. The patient's report of renal failure was not supported by the laboratory results and treatment course.

3. Loss of consciousness requiring hospitalization

Consumer report of a 50 y/o male taking Zegerid 40 mg powder for oral suspension for reflux. Two hours after the first dose, he had a syncopal episode and was subsequently hospitalized for five days. No significant abnormalities were found except for bradycardia, which resolved. Zegerid was not resumed.

4. Cardiac failure requiring hospitalization

Physician report of a male patient hospitalized for treatment of heart failure after 6 weeks of Zegerid therapy. Zegerid was discontinued due to the event.

5. Dermatomyositis; medically significant event

Published report by Pan et alio regarding an 81 y/o female with reflux esophagitis being treated with omeprazole 40 mg (not Zegerid formulation, nor a formulation combining omeprazole with sodium bicarbonate). Muscle weakness and skin eruption began three days after commencing omeprazole therapy, and the symptoms were abating upon discontinuation of omeprazole. Histopathological and immunofluourescence findings were consistent with drug-induced reaction.

6. Convulsion requiring hospitalization

Spontaneous report by nurse regarding a 4 y/o male patient with a history of mitochondrial disorder and a seizure disorder. Patient required hospitalization after experiencing seizures. He was on Zegerid 10 mg powder for oral suspension twice daily for unknown indication.

7. Meralgia paraesthetica, weight increased and disability

Medically confirmed report of a 56 y/o female with history of gastritis and alpha-one antitrypsin deficiency being treated with Zegerid 40 mg capsule for gastritis refractory to therapy with esomeprazole and omeprazole. She gained 20 pounds after 14-week therapy with Zegerid. Symptoms of lateral femoral cutaneous nerve (LFCN) entrapment began after approximately three months of Zegerid therapy and two months after discontinuation the diagnosis was made based on electromyographic studies. Her physician could not determine any definitive cause for meralgia such as trauma or surgery, and considered the patient's rapid weight gain a possible reason. The physician also would not make an assessment if the meralgia would be reversible or not.

8. Pancreatitis requiring hospitalization

Physician report of a patient (identifiers, medical history and concomitant medications unknown) who developed pancreatitis while on Zegerid 40 mg (formulation unknown). The patient's physician, despite multiple follow-up contacts by Santarus, provided limited information but stated that the event pancreatitis was not considered to be related to Zegerid administration.

9. Nausea, diarrhoea, anorexia requiring hospitalization

Consumer report of a female (age and concomitant medications unknown) treated with Zegerid 40 mg capsule for GERD. One month into therapy, she experienced diarrhea and severe nausea requiring hospitalization. She reported loss of appetite and continuing diarrhea since the hospitalization.

10. Cardiac failure congestive requiring hospitalization

Consumer report of a 70 y/o female with a history of GERD, cervical cancer, and hypertension. Her concomitant medication included Hyzaar (losartan potassium plus hydrochlorothiazide). One day after being switched from esomeprazole to Zegerid 40 mg capsule, she began to experience worsening fatigue which resulted in hospitalization for the treatment of congestive heart failure. Following discharge and discontinuing Zegerid (she was switched back to esomeprazole), the event completely resolved without further sequelae two months after the hospitalization.

11. Rhabdomyolysis, inappropriate antidiuretic hormone secretion, hyponatraemic encephalopathy requiring hospitalization

Literature[11] report of a 46 y/o male hospitalized for treatment of omeprazole-induced hyponatremic delirium and rhabdomyolysis four months after starting omeprazole (dose and frequency not specified).

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/s/

Joel Schiffenbauer
1/6/2009 10:45:15 AM
MEDICAL OFFICER