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LABORATORIES

June 11, 2002

Sandra Titus, PhD
Executive Secretary
Food and Drug Administration
Center for Drug Evaluation and Research
Nonprescription Drug Advisory Committee
Division of Over-the-Counter Drug Products, HFD-21
5630 Fishers Lane, Room 1093
Rockville, MD 20857

Subject: Public Advisory Committee meeting of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee, June 21, 2002

Dear Dr. Titus:

Please find attached the following briefing book for my presentation for the Rx to OTC switch for omeprazole magnesium.

Thank you for allocating me 5 minutes to speak to the Advisory panel and I will be providing 30 copies of the briefing book to the advisory panel.

Sincerely,

Robert Niecestro phs

Robert Niecestro, PhD
Senior Executive Director, Clinical Research

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Possible drug-food and drug-antacid interactions with OTC omeprazole magnesium

INTRODUCTION

This Advisory Committee Meeting is being held to follow-up a prior meeting which voted definitively against approval of OTC use of omeprazole magnesium. The decision of the prior meeting was based on solid proof that omeprazole magnesium is no better than placebo as a treatment for heartburn in an OTC environment in five controlled clinical trials. The lack of efficacy as a treatment is the reason why the sponsor is now requesting approval only for prophylaxis. We believe your deliberations today should take into account the important results presented in the prior meeting. We have identified two issues that we believe must be addressed before omeprazole magnesium can be used safely and effectively for prophylaxis in an OTC environment. The first issue is the reason why the treatment protocols consistently failed to demonstrate benefit over placebo even though prescription omeprazole is known to be a safe and effective product. The second issue relates to the fact that a prophylactic agent will be used in combination with agents that are effective as treatment and therefore the potential for interactions must be evaluated.

Prilosec (omeprazole) delayed-released capsules are designed to pass through the highly acidic stomach milieu and to dissolve and be absorbed at the higher pH of the small intestine. The delayed release of omeprazole imparts a certain amount of inherent variability in absorption pattern which may be expected with enteric-coated products. The erratic absorption of omeprazole is evident in the plasma concentration-time profiles in several studies in the Summary Basis Of Approval (SBOA) for NDA 19-810, the package insert for Prilosec (omeprazole) delayed-release capsules, and the published literature. The erratic absorption of omeprazole may be compounded in the presence of either food or antacids and these issues have not been adequately addressed since the original approval of Rx omeprazole (Attachment 1).

Issue 1 – What are the effect of food on omeprazole magnesium?

Significant evidence from the prescription use of omeprazole suggest that a high proportion of treatment failures are related to inappropriate dosing in relation to food. Gunaratnam, et al. (Attachment 2) have concluded that over 50% of the patients taking proton pump inhibitors (omeprazole, pantoprazole, rabeprazole, and lansoprazole) in a community setting were taking their proton pump inhibitors incorrectly due to insufficient data on proper administration of proton pump inhibitors in relationship to food. **Patients have developed inappropriate dosing habits which lead to ineffective symptom control and inappropriate dose escalation.** They concluded that further studies are required to assess "the impact of optimizing dosage schedule on GERD symptom control in patients taking proton pump inhibitors." Since current labeling for Rx omeprazole does not adequately instruct both Physicians and Patients on how to take prescribed proton pump inhibitors, how can we expect Consumers to take an OTC preparation of omeprazole magnesium safely?

The lack of adequate information on food effects was noted during the initial review of the omeprazole NDA in 1988 and has been raised repeatedly during subsequent reviews (See Attachment 1). The lack of data on prescription omeprazole is compounded in the case of the product proposed for OTC use which is a different chemical salt and therefore may behave differently than prescription omeprazole. Thus, unless the effects of food on the performance of the OTC product have been completely investigated, we believe there will be both unnecessary treatment failures (leading to the possibility of potential inappropriate dose escalation) and excessively high systemic drug levels due to effects of food on absorption. In addition, unless the relationship of dosing to food intake was carefully evaluated in the prophylaxis clinical trials, they have uncertain relevance to the potential performance of the drug in OTC market use.

Issue 2 – Are potential interactions with other OTC treatments for heartburn understood well enough to allow safe and effective OTC use?

Since OTC omeprazole has been proven no better than placebo for acute treatment of heartburn and since many patients may want acute relief for their symptoms, it is quite likely that many patients would take OTC omeprazole in combination with other drugs. In particular, a number of antacids and H_2 blockers are available OTC and are effective as acute treatment. Thus, we believe it is critical that the use of antacids and H_2 blockers be well characterized in any trials done to support OTC use, that these agents be allowed in the trials and that potential drug interactions be well characterized. This is necessary to properly label the product for OTC use and to assure that safety and efficacy data obtained in OTC clinical trials is relevant to potential OTC use in the marketplace. A review of the antacid and H2 blocker data available for the prescription product reveals the potential for significant interactions as judged by FDA. Given that food interactions are believed by some investigators to be an important cause of treatment failures and inappropriate dosing, there is a high likelihood that interactions with H2 blockers and antacids could interfere with safe and effective OTC use.

Over the last 13 years, the Sponsor (AstraZeneca) has not addressed FDA concerns regarding drug-food and/or drug-antacid interactions with Prilosec (omeprazole) delay-released capsules via post-marketing clinical studies or in the product label (United States Package Insert). There is either inadequate or conflicting information available on how to administer Prilosec (omeprazole) delayed-released capsules with food and/or antacids. Moreover, the antacids studied did not utilize antacids marketed in the U.S. At best, erroneous administration of OTC omeprazole magnesium will result in reduced efficacy and at worst, we can expect an increased frequency of labeled gastrointestinal events (e.g., nausea, vomiting, diarrhea, abdominal pain, etc.) and intentional overdose due to lack of efficacy. Currently, the Sponsor is unable to properly label OTC omeprazole magnesium for Consumer, nor can the Sponsor provide proper Information for Patients.

I recommend that the Advisory Panel consider the following questions in order to prevent injury to Consumers, to provide Consumers with a product that is safe and efficacious, to

prevent potential overdose situations, and to provide Consumers with proper instructions and guidance for taking an OTC omeprazole magnesium. Without a better understanding of the effects of food and/or antacids on the absorption characteristics of omeprazole, an OTC preparation cannot be adequately labeled at this time.

QUESTIONS

1. We have already seen in a community setting with Rx omeprazole that over 50% of the patients incorrectly take proton pump inhibitors because of inadequate data regarding the optimal time to take proton pump inhibitors in relationship to food and this has lead to inappropriate dose escalation, lack of symptom control, and treatment failures. How do we instruct patients to take OTC omeprazole magnesium in relationship to food and how do we prevent inappropriate dose escalation (intentional overdose) of the OTC preparation in the hands of the Consumers?
2. It has been clearly demonstrated that the concomitant administration of antacids will alter the pharmacokinetics (Cmax, AUC, and/or Tmax) and the dissolution rate of omeprazole. How will patients be instructed to take OTC omeprazole with antacids given the fact that in two independent studies concurrent administration of antacids with omeprazole in one study increased bioavailability, while in the other decreased Cmax and Tmax?
3. OTC famotidine and cimetidine are indicated for the prevention of heartburn associated with heartburn with acid indigestion and sour stomach brought on by consuming food and beverages. Can Consumers take either OTC famotidine or cimetidine with OTC omeprazole magnesium?

PUBLISHED INFORMATION

Drug-Food Interaction

In the Biopharmaceutics Summary of NDA 19-180 for Losec (omeprazole) 20 mg, dated July 26, 1998, two studies examined the effect of food on omeprazole bioavailability (Study Code I-252 and Study Code I-292). The FDA concluded the following on page 97 of this summary:

"Studies I-252 and I-292 which looked at the effect of food on omeprazole bioavailability are not definitive since subjects were not administered the dose under true fasting conditions. The sponsor should conduct a proper food effect study which includes a 10 hour fast pre-dosing and a four hour fast post-dosing for the fasted leg, and the meal should be the standard FDA breakfast. The sponsor is advised to submit the study protocol to the Agency for possible comments prior to initiation of the study."

Furthermore, on pages 3, 4, and 98 of this summary, the FDA concluded the following:

Page 3: *"The results of studies looking at the effect of food on omeprazole bioavailability were not definitive since subjects were not administered the dose under true fasting conditions."*

Page 4; *"THE SPONSOR IS SUGGESTED TO CONDUCT A DEFINITIVE FOOD EFFECT STUDY (WHICH COULD BE CONDUCTED DURING PHASE IV)."*

Page 98: *"The sponsor is suggested to conduct a food effect study (which could be conducted during Phase IV) as outlined in Summary comment no. 17."*

In Study 18-Study Code I-252, the FDA concluded the following on page 81 of this summary:

"The design of this study was not the most appropriate to examine a possible food interaction with omeprazole bioavailability. A more appropriate comparison of potential food effect is to dose 30 minutes before breakfast and 5 minutes after. This would have simulated a more realistic clinical situation in which a patient remembers to take his dose after finishing breakfast. Furthermore, a more definitive approach would be to dose concurrently with breakfast and to dose in fasting state (i.e., no food for 10 hours before and 4 hours after the dose)."

Administration Before or After a Meal

It is unclear if the OTC dose of omeprazole should be taken immediately before, during or after a meal (i.e., breakfast). The current package insert (revised 11/01) has limited data on this subject and does not specify time of dosing in "Dosage and Administration Section."

The objective in Study 19 (Study Code I-298) was to study the bioavailability of omeprazole on the first and last days of seven days treatment with omeprazole given as enteric-coated granules to healthy subjects either before or immediately after breakfast.

In Study 19-Study Code I-298, the FDA concluded the following on pages 85 and 86 of this summary:

"Analysis by this reviewer indicated that the means of this parameters were not statistically different (Duncan's Multiple Range Test) between day 1 (2.3 h) and day 7 (1.7 h) after breakfast or between day 1 (1 h) and day 7 (0.7 h) before breakfast. However, they were statistically different between day 1 after breakfast and day 1 before breakfast and between day 7 after breakfast and day 7 before breakfast."

"The plasma concentration-time profiles after oral dosing indicated a very erratic (e.g., multiple peaks) absorption pattern in many of the subjects. The finding makes any truly meaningful interpretations of the data very difficult."

In the current package insert (revised 11/01) states the following:

"PRILOSEC Delayed-Released Capsule 40 mg was bioequivalent when administered with and without applesauce. However, PRILOSEC Delayed-Release Capsule 20 mg was not bioequivalent when administered with and without applesauce. When administered with applesauce, a mean 25% reduction in Cmax was observed without a significant change in AUC for PRILOSEC Delayed-Release Capsule 20 mg. The clinical relevance of this finding is unknown."

Drug-Antacid Interaction

In the Biopharmaceutics Summary of NDA 19-180 for Losec (omeprazole) 20 mg, dated July 26, 1998, two drug-antacid interaction studies were conducted (Study 20-Study Code I-213 and Study 21-Study Code I-307). The FDA concluded the following on page 91 of this summary:

"The results of this study (Study 21-Study Code I-307) *do not appear to coincide with drug release and bioavailability information gathered from another study* (Study 20-Study Code I-213) *with antacid. The results of Study I-213 indicated that administration of an antacid showed a trend to increase the bioavailability of omeprazole from capsule formulations. However, in this study* (Study 21-Study Code I-307) *there was a trend for decreased Cmax and Tmax after antacid treatment."*

Furthermore, on page 96 of this summary, the FDA concluded the following:

"The sponsor's conclusion in study 21 (study code I-307), that concomitant administration of an antacid suspension has no influence on the bioavailability of omeprazole cannot be supported."

In Study 20-Study Code I-213, the FDA concluded the following on page 88 of this summary:

"The sponsor's non-parametric statistical test indicated that there was no difference in pharmacokinetic parameters. However, using the standard parameter approach (as used to test for bioequivalence), antacid treatment had a marked effect on all parameters (AUC, Cmax and Tmax since all results were outside the 90% C.I. and 75/75-125 ratio analysis.

	90% C.I.	*Ratio analysis (within 75-125%)*
AUC	*[0.88-1.29]*	*50%*
Cmax	*[0.94-1.24]*	*50%*
Tmax	*[0.05-1.49]*	*0%*

It appears that administration of an antacid increases the rate an extend of bioavailability of omeprazole because there is a trend indicating AUC and Cmax are increased and Tmax is decreased."

In Study 21-Study Code I-307, the FDA concluded the following on pages 90 and 91 of this summary:

"Even though ANOVA results indicated that the means of AUC, Cmax and Tmax after the two treatments could not be judged statistically different, the two treatments can not be considered bioequivalent. 75/75-125 ratio analysis indicated the following: (sponsor's AUC – 67% within, FDA's AUC – 67% within, Cmax – 42% within and Tmax – 50% within). Using the treatment without antacid as the reference mean, sponsor's AUC, Cmax and Tmax all failed the 90% CI and two one-sided t-test. However, FDA's AUC passed.

CONCLUSION

At the last Advisory Meeting for OTC omeprazole, the following label instructions were suggested: 1) do not take more than one tablet a day; and 2) do not use for more than 10 days in a row unless directed by a doctor. I submit based on the data presented above that these instructions are inadequate for the safe use of OTC omeprazole magnesium. Further research is needed to fully understand the impact of food and/or antacid on the administration of OTC omeprazole. I respectfully submit that OTC omeprazole cannot be properly labeled, and should not be approved, until appropriate drug-food and drug-antacid studies are completed and reviewed by the FDA.

WELLPOINT.

June 12, 2002

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-21)
ATTN: Sandra Titus
5630 Fishers Lane
Rockville, MD 20857

Dear Sandra:

I am Robert Seidman, Chief Pharmacy Officer of WellPoint Health Networks. WellPoint provides health care coverage to 13 million Americans nationwide through a portfolio of products designed to place individuals in control of their health and financial future. WellPoint, in its desire to provide access to an affordable prescription drug benefit, supports the new drug application (NDA) 21-229, proposing over-the-counter (OTC) use of PRILOSEC1 (omeprazole magnesium), AstraZeneca LP/Procter and Gamble, for the prevention of the symptoms of frequent heartburn.

More Americans than ever before are using OTC medicines for symptom relief of common ailments, such as heartburn. Today, three in five Americans (59%) report having taken an OTC drug in the past six months. Of the OTC drugs consumed, 37% are for heartburn, indigestion and other stomach problems[1]. Heartburn amongst Americans is a common complaint and more than 60 million American adults experience heartburn at least once a month[2]. Most people who suffer from heartburn usually seek self-treatment options such as antacids and histamine H-2 receptor antagonists, seeking the care of a physician when their symptoms persist.

The currently available OTC therapies provide only partial relief for many heartburn sufferers. Heartburn relief from antacids is usually prompt but short lived, requiring frequent administration, making nighttime relief of heartburn symptoms problematic. Histamine H-2 receptor antagonists have a much longer duration of action than antacids (up to 10 hours), but are less effective and long lasting than the current gold standard — Proton Pump Inhibitors. The FDA approval of prescription Proton Pump Inhibitors has revolutionized the treatment of heartburn and gastroesophageal reflux disease (GERD), providing relief to many who found earlier generations of drug therapy ineffective. There are now five Proton Pump Inhibitors approved by the FDA for the prescription treatment or symptomatic relief of various gastric disorders including gastric and duodenal ulcers, GERD, or pathological hypersecretory conditions. We believe that the safety and efficacy profiles of Proton Pump Inhibitors warrant the addition of Prilosec® (omeprazole) to OTC status for the symptomatic prevention of heartburn.

Antacids and OTC strength histamine H-2 receptor antagonists are currently the mainstay of therapy for initial patient-directed therapy for heartburn, but the current OTC drugs available do not prevent heartburn symptoms over a 24 hour period. Over-the-counter Prilosec® (omeprazole), in the 20mg dosage and with proper labeling and packaging, can provide heartburn sufferers with

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[1] Attitudes and Beliefs About the Use of Over-the-Counter Medicines: A Dose of Reality. A National Survey of Consumers and Health Professionals. Prepared for: National Council on Patient Information and Education (NCPIE), January 2002
[2] National Digestive Disease information Clearinghouse. Gastroesophageal Reflux Disease (Hiatal Hernia and Heartburn). Available at: http//www.niddlk.nih.gov/health/digest/pubs/heartbrn/heartbrn.htm