October 20, 2000 - Joint Meeting of the

Nonprescription Drugs & Gastrointestinal Advisory Committees

Food and Drug Administration
Center for Drug Evaluation and Research
Holiday Inn, 2 Montgomery Avenue, Gaithersburg, MD

Prilosec 1ä (omeprazole magnesium, Astra Zeneca & Procter & Gamble, NDA 21-229)

Currently, there are two classes of drugs, antacids and acid reducers (histamine-2 receptor antagonists), available in the OTC market to treat heartburn. Both antacids and acid reducers are indicated for the treatment of acute occasional heartburn symptoms. The acid reducers have an additional claim for the prevention of meal induced heartburn symptoms if ingested at specified times prior to a meal. At today's meeting, the sponsor is seeking the approval of omeprazole in the OTC setting for these indications and for the additional indication of 24-hour prevention of heartburn. Omeprazole, a proton-pump inhibitor, is currently indicated Rx for the treatment of duodenal and gastric ulcer, symptomatic Gastroesophageal Reflux Disease (GERD), erosive esophagitis, and pathological hypersecretory conditions. In support of the proposed OTC marketing, the sponsor conducted studies to evaluate the efficacy of omeprazole 10 mg and 20 mg for the treatment of acute symptomatic heartburn (studies 092, 095, 017, 018, 019), for the prevention of meal induced heartburn (studies 005 and 006) and for the 24 hour prevention of heartburn (studies 171 and 183). They also conducted five actual use studies (studies 003, 067, 014, 022 and 091) to evaluate consumer usage patterns and dosing compliance.

A. In studies 092 and 095, the primary endpoint for efficacy was the occurrence of sustained complete relief of the first treated episode of heartburn. Based on the primary measure of efficacy, is there a clinically significant improvement of acute symptomatic heartburn in either the 10 or 20-mg omeprazole groups compared to placebo? Please explain your answer.

B. In studies 005 and 006, the primary endpoint for efficacy was the percentage of subjects heartburn-free over the entire four-hour period after a provocative meal.
   1. Based on the primary measure of efficacy, is there a clinically significant improvement of heartburn symptoms in either the 10 or 20 mg omeprazole groups compared to placebo? Please explain your answer.
   2. Are the analyses of the pre-specified secondary endpoints supportive of the primary study outcome? Do they add information regarding clinically significant treatment effect?

C. In studies 171 and 183, the primary endpoint for efficacy was the complete prevention of heartburn between the first two doses of therapy.
   1. Based on the primary measure of efficacy, is there a clinically significant improvement of heartburn symptoms in either the 10 or 20 mg omeprazole groups compared to placebo? Please explain your answer.
   2. Are the analyses of the pre-specified secondary endpoints supportive of the primary study outcome? Do they add information regarding clinically significant treatment effect?

D. Based on the types and frequency of adverse events reported in the clinical trials and in the post-marketing adverse events database, are the safety concerns for the OTC marketing of omeprazole able to be addressed solely by labeling (identifying risks) to consumers for (a) short term or (b) chronic intermittent use? In answering this question, please consider the reports of anaphylaxis/angioedema/urticaria, liver toxicity, white blood cell disorders and severe skin reactions.

E. Do other safety concerns affect acceptability of the OTC marketing of omeprazole? In answering this question, please consider the questions raised by the FDA reviewer regarding: 1) the masking of serious disease; 2) the potential for genotoxicity, tumorigenicity, and fetal and developmental toxicity; 3) rebound hyperacidity reported in the literature with discontinuation of therapy; and 4) hypergastrinemia that may be associated with the chronic or chronic intermittent use of omeprazole.

F. Are there drug-drug interactions that affect acceptability of OTC marketing of omeprazole?

G. In the actual use studies, approximately 65% of the subset of subjects using the product only for the prevention of heartburn exceeded the 10 consecutive day limit for dosing recommended on the label. (Note: 19% to 22% of consumers using omeprazole for both acute symptoms and prevention similarly exceeded the 10 consecutive day limit for dosing recommended on the label). Do these results suggest that omeprazole will likely be used by consumers on a chronic basis for conditions other than episodic heartburn (e.g. GERD)? Is the treatment of GERD an acceptable OTC indication?

H. Based on the results of the actual use and label comprehension studies, has the sponsor presented adequate data to substantiate that consumers will be able to use omeprazole appropriately in the OTC setting for: 1) acute symptomatic treatment; 2) prevention for up to 10 days.

In responding, consider these factors:

a) The ability of consumers to appropriately self-select.
b) The ability of consumers to use the correct dosage and for the period of time specified in the label.
c) The ability of consumers to identify when they should see a physician before using the product and once they have begun using the product.
d) The ability of consumers to identify serious adverse events.
e) The ability of consumers to avoid interacting drugs.
f) Use in women of childbearing age or in the pediatric population.

I. Has the sponsor provided sufficient evidence to support the approval of omeprazole 10 mg and/or 20 mg for use in the OTC setting for:

1. Acute symptomatic heartburn? Please explain.
2. Prevention of episodic or chronic heartburn? Please explain.
   a) If yes to either, are there any additional studies or risk management programs needed post-approval?
   b) If no, what additional studies or risk management programs are necessary to support approval for OTC marketing?

J. If the Committee recommends approval of omeprazole for use in the OTC setting, please discuss any recommendations regarding information to be conveyed in labeling (e.g., to help consumers select between omeprazole and other currently available OTC products, and to help consumers use omeprazole safely and effectively).