MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: September 19, 2000

FROM: OTC Omeprazole Magnesium (Prilosec 1™) Review Team

TO: Gastrointestinal and OTC Advisory Committee Members, Consultants and Guests

THROUGH: Division of Gastrointestinal and Coagulation Drug Products
Division of OTC Drug Products

SUBJECT: October 20, 2000 Advisory Committee Meeting to Discuss NDA 21,229, Prilosec 1™ (omeprazole magnesium) for OTC use

Background

Omeprazole (Prilosec™) was initially approved as a prescription drug in 1989. Prilosec™ Delayed Release Capsules are currently marketed for the treatment of duodenal and gastric ulcer, the treatment of gastroesophageal reflux disease (GERD), the maintenance of healing of erosive esophagitis, and the long-term treatment of pathological hypersecretory conditions. Omeprazole magnesium (OM) is a new formulation of omeprazole. The sponsor, AstraZeneca LP, has proposed OTC marketing of OM 20 milligrams once daily, the prescription dose, for: 1) the relief of heartburn, acid indigestion and sour stomach; 2) the prevention of heartburn, acid indigestion and sour stomach brought on my consuming food and beverages (or associated with events such as stress, hectic lifestyle, lying down or exercise; and 3) the prevention of symptoms for 24 hours. The core support for this program consists of six efficacy and safety studies, an analysis of the postmarketing safety experience with omeprazole, one label comprehension study for OM, and four additional actual use studies examining potential consumer usage patterns in an OTC setting among adults and adolescents. During the course of our review, we have identified a number of issues and concerns that are detailed in the reviews and summaries that follow in this briefing document. These issues are briefly summarized below.

Efficacy

The six controlled efficacy trials designed to support the proposed indications are 092 and 095 (2-week, multi-dose heartburn treatment); 005 and 006 (single-dose, meal-induced heartburn prevention); and 171 and 183 (2-week, multi-dose studies of heartburn prevention). Our concerns include the following:

- Neither studies 092 or 095 show the superiority of a single dose of omeprazole magnesium 20 milligrams over placebo for the treatment of episodic heartburn as a symptom.
- Study 006 supports the efficacy of OM for the 4-hour prevention of meal-induced heartburn, however, results in this study are not adequately replicated in study 005, which demonstrated a statistically borderline difference between OM and placebo. In addition, there does not appear to be a meaningful differentiation between the 10 milligram and 20 milligrams doses of OM in either of these studies.

- Studies 173 and 183 demonstrate the efficacy of OM 10 or 20 milligrams for the prevention of heartburn over a 24-hour period. However, efficacy increases with repeated daily dosing and it is again unclear whether the recommended dose should be 10 or 20 milligrams. Additionally, this proposed use does not clearly differentiate between the prevention of episodic occasional heartburn, the symptom – for which antacids and H2 receptor antagonists have been approved for OTC marketing – and the prevention of chronic heartburn linked to GERD conditions, either symptomatic GERD or erosive esophagitis.

Safety

There is a substantial prescription marketing experience with omeprazole, especially the 20 milligram-per-day dose, and much is known about the safety of this product. Our analysis of adverse events associated with short-term drug exposure (less than 4 weeks) has revealed that omeprazole may be causally linked to several events:

- Liver toxicity in a small percentage of patients. This is usually mild, self-limited and reversible with drug withdrawal; however, rare cases of hepatocellular necrosis requiring liver transplantation and/or associated with hepatic failure and death have been reported.
- Toxic epidermal necrolysis and Stevens-Johnson syndrome. Although very rare, cases have been reported, including fatalities.
- Rare instances of agranulocytosis and other manifestations of bone marrow suppression, usually, but not always, reversible with drug withdrawal.
- Anaphylaxis/Angioedema. The incidence of hypersensitivity symptoms is high enough to have been detected in clinical trials and be as high as 0.5 per 1000 users of omeprazole.
- Drug-Drug Interactions. Omeprazole is a potent acid reducing agent that is metabolized via the cytochrome P-450 system. As such, the potential exists for interaction with the metabolism of other drugs that are metabolized via the same hepatic isoenzymes (e.g., theophylline, propranolol, benzodiazepines). In addition, due to its potent antisecretory effects, omeprazole may interfere with the absorption of other drugs that are dependent on gastric pH (e.g., ketoconazole, iron salts).

Actual use data (see below) suggest that OTC consumers may use OM either beyond 10 days or take repeated courses of omeprazole over time. Our analysis of potential safety concerns associated with long-term drug exposure (more than 4 weeks) raises concerns which include:

- Masking of disease. If individuals with GERD will comprise a significant element of the consumer population, a diagnosis may be delayed and/or significant disease complications may be pharmacologically masked. Literature reports also suggest a potential masking effect of proton pump inhibitors in patients with underlying gastric adenocarcinoma.
- Length of treatment. The sponsor has provided 2-week efficacy data, whereas GERD should be treated for at least 6 to 8 weeks. Although OM is effective in healing esophageal lesions and relieving symptomatic GERD, there is a high recurrence rate of both symptoms and inflammatory disease within a short time after cessation of therapy. For GERD, antisecretory therapy may be needed for months or years.
- Drug-induced hypergastrinemia may occur in a small percentage of omeprazole users. In addition to its gastric effects, gastrin may also have trophic effects on certain epithelial cells in the GI tract, such as the colon, and possibly other organs.
- Omeprazole is genotoxic in several test systems and tumorigenic in animals.

The OTC availability of omeprazole also raises important concerns in two special populations:

- Pediatric subjects. Omeprazole is not currently approved for prescription use in adolescents. Limited exposure data precludes a rigorous assessment of its safety profile in this age group.
- Pregnancy. Omeprazole exhibits fetal and developmental toxicity and contragestational effects in animal models. Available human data do not suggest omeprazole-linked loss of fertility or teratogenicity; however, to date this has not been studied prospectively.

Actual Use Studies

Actual use study #003 and global safety for omeprazole magnesium tablets have been reviewed by Dr. Ling Chin. Actual Use studies #067, 014 and 022 are covered by this summary. A brief overview of study #091 is also included.

The results of four Actual Use trials were submitted in support of this application. Table 1 displays some of the similarities as well as differences observed among these four studies.

Table 1. Overview of Actual Use Trials

	003	067	014	022
Design	Multi-center, multi-dose, open-label, at-home study			
1-mary objective	Usage pattern/ Dosing compliance			
2-dary objective	Effectiveness/safety	Effectiveness/safety	Only Safety	Effectiveness/safety
Recruited/screened	1514	100	1516	923
Enrolled	1093	100	1440	596
ITT	825	92	939	489
Ages (mean)	13-84 (47)	12-17 (14)	18-82 (43)	13-87 (46)
Male Female	328 (40%) 497 (60%)	36 (39%) 56 (61%)	333 (35%) 606 (65%)	200 (41%) 289 (59%)
Caucasian Non-Caucasian	621 (75%) 204 (25%)	88 (96%) 4 (4%)	789 (84%) 150 (16%)	418 (85%) 71 (15%)
REALM <60	84 (10%)	N/A	N/A	N/A
Centers (N)	7	2	61	5
Dose	20.6 mg	20.6 mg	20.6 mg	10.3 mg

Three out of four studies evaluated omeprazole-magnesium 20.6 mg-strength tablet, and one (#022) 10.3 mg-strength tablet. The primary objective of all four studies was to evaluate consumer usage pattern and dosing compliance. As a secondary endpoint, all four studies evaluated safety profile for the dosage studied. In addition, effectiveness of omeprazole in OTC consumer population was addressed in studies #003 and #067. Study #022 used lower dose (10.3 mg) of omeprazole-magnesium. Study #091 was called a marketing study, and used different formulation of omeprazole – 20 mg capsules. A brief review of this study is included because of certain consumer behavior aspects addressed.

Summary of Acutal Use Studies

Four out of five studies evaluated omeprazole-magnesium 20.6 mg-strength tablet, and one (#022) used the 10.3 mg-strength tablet. The primary objective in all of these studies was to evaluate consumer usage pattern and dosing compliance, as well as safety. Two studies,#014 and #091, were marketing studies. None of these studies were all-comer studies. Each had defined heartburn histories and specific inclusion/exclusion criteria, which selected for individuals with no conditions that would pose a risk for taking omeprazole. All of these studies evaluated consumer behavior regarding the labeled directions. None included an assessment of the appropriateness of self-selection or whether physician consultation was sought.

The overall consistency with all 3 labeled directions ranged from 58% to 84%. Study #014 had the best results but only 12 tablets were dispensed per volunteer for use. In trials #003, #067, and #022, 36 tablets per volunteer were dispensed. Twenty tablets, per volunteer, were dispensed in trial #091.

Subjects across studies who used study drug for Prevention Only consistently used the product for a longer duration (Number of sequential days) than in the Relief Only users.

Conclusion:

Approximately 3500 subjects were enrolled into the 5 actual use studies. In general, the following conclusions can be made from these studies:

1. Overall consistency of subjects with dosing directions was <80% (except for Study #014 in which fewer tablets were dispensed).
2. Relief Only users were more compliant with the dosing directions than the Prevention Only users.
3. Overall consistency by dosing occasions were higher, i.e. each non-compliant subject is not non-compliant all of the time.
4. The majority of subjects took 1 tablet per dosing occasion and per dosing day.
5. Relief Only users were more compliant with the dosing day restriction.
6. The majority of Prevention Only users exceeded the 10-day use limit.
7. Correctness of subjects' self-selection was not assessed.
8. Performance of subjects with respect to certain risk conditions cannot be assessed
    a. pregnancy
    b. difficulty swallowing
    c. persistent stomach pain (>10 days)
    d. use of concomitant drugs.
9. Performance of subjects with respect to contacting a doctor or health care professional cannot be assessed.
10. Safety profile is unremarkable from these trials.

The subjects targeted for these studies may not be representative of the general OTC population who would use this drug once it is available OTC. Thus, concerns about whether or not consumers can adequately self-select and use the product appropriately, in the OTC setting, are not fully answered by these trials.

Points to Consider

The sponsor has proposed making omeprazole magnesium (Prilosec 1™) 20 milligrams available as an OTC product. Omeprazole (Prilosec™ Delayed Release Capsules) 10, 20 and 40 milligrams would remain a prescription product for its currently approved indications. Whether the overall benefit of OTC marketing of this proton pump inhibitor outweighs the potential risk is unclear. Our review of this application raises concerns relating to the lack of efficacy of OM for the treatment of episodic heartburn; the appropriate dose for OTC use; and the inadequacy of a 2-week course of treatment for patients with underlying GERD. Although there has been considerable prescription marketing experience with omeprazole 20 milligrams, there are a number of safety concerns related to use and/or misuse of OM in an OTC setting. Additional questions raised by OTC availability include whether consumers will accurately self-select for (or against) this treatment; their ability to understand and adequately monitor the proposed regimen; and their ability to understand when they should use this product as opposed to an OTC antacid or H_2-blocker.

###