

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

---

Date: May 17, 2002

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

To: Gastrointestinal and Nonprescription Drug Advisory Committee Members, Consultants and Guests

Through: Division of Gastrointestinal and Coagulation Drug Products  
Division of Over-the-Counter Drug Products

Subject: NDA: 21-229: Prilosec 1 (omeprazole magnesium) for OTC Use

**Background**

Omeprazole, a proton-pump inhibitor, was approved for prescription use in 1989 and is currently marketed for the following indications:

- For the treatment of duodenal and gastric ulcer;
- For the treatment of gastroesophageal reflux disease (GERD);
- For the maintenance of healing of erosive gastritis;
- For the long-term treatment of pathological hypersecretory conditions.

The recommended dose and treatment duration range from 20 mg daily for up to 4 weeks for short-term symptomatic GERD to 20 mg daily for up to 12 months (for maintenance of healing of erosive esophagitis).

Currently there are two classes of drug products available OTC for use in heartburn: antacids and acid reducers also known as histamine-2 receptor antagonists (H2AR). Both of these classes of drugs are indicated for the treatment of acute occasional heartburn symptoms. The acid reducers have the additional claim for the prevention of meal-induced heartburn at specified times depending upon the product. The 24-hour prevention claim is one not currently available in the OTC market.

The switch of Prilosec from Rx to OTC was previously discussed on October 20, 2000 at a joint advisory committee composed of individuals from the two committees represented today. Originally, the sponsor sought to market Prilosec 1 OTC for the same indications for which OTC antacids and OTC H2-receptor antagonists are approved: "relief of heartburn, acid indigestion and sour stomach; and prevention of these symptoms brought on by consuming certain foods and beverages; and the prevention of symptoms for 24 hours." During that meeting efficacy, safety, pharmacokinetic issues, and consumers' ability to understand and use the product correctly without a learned intermediary were discussed. The Committees felt that adequate data had not been presented to support these indications for Prilosec OTC and approval was not recommended. However, the Committee indicated that the safety profile was such that Prilosec could be switched OTC if a suitable population could be identified that could use this product safely and effectively.

Based on the committee opinion, as well as subsequent discussions with the Agency, the sponsor submitted their completed response to the Agency in February 2002. In that response, the sponsor stated that the target OTC population are those suffering from "frequent heartburn. As such they modified the indication to: "for the prevention of frequent heartburn," "intended for those who suffer heartburn two or more days a week." In addition, they proposed modified versions of the directions for use. In support of these modifications, the sponsor submitted data obtained from an actual use and two label comprehension trials to address appropriate selection/deselection, expectation of benefits, and how this product would fit into the armamentarium of OTC "heartburn" therapy. In addition, to support the proposed 20.6 mg omeprazole magnesium dose, the sponsor relied on pharmacodynamic data showing more consistent acid

suppression at 20 mg than at 10 mg and that 20 mg provided a directionally higher level of prevention across all temporal variables than 10 mg, which was the dose previously proposed for OTC use. This data was discussed at the advisory committee meeting in October 2000. Further, the proposed 14-day duration of consecutive daily doses is proposed based on the efficacy data from the OTC trials and from the Actual Use trials.

## **FDA Reviews**

### *24-h Prevention: Results of Studies 171 and 183*

These studies were randomized, double blind, multicenter, placebo-controlled trials to assess the efficacy of Prilosec 10mg and 20mg OTC in the prevention of further heartburn episodes. Entry criteria consisted of having heartburn of greater than 1-month duration, with a frequency of at least 2 heartburn episodes per week. An antacid or OTC H2RA responsive population was recruited. The results of the primary efficacy variable, the proportion of subjects with no heartburn over 24h, and at 14 days (secondary variable) are as follows:

- A substantial proportion of subjects experienced no heartburn on Day 1 or Day 14 in the placebo group.
- The therapeutic gain with Prilosec, although statistically significant, is only modest on Day 1.
- The therapeutic gain increases on Day 14, confirming that the maximum benefit of treatment relies on consecutive dosing.
- Approximately 30% of participants experience “breakthrough” heartburn on Day 14. This is defined as having an episode of heartburn despite using the medication according to directions.
- The proportion of responders is higher in subjects with low frequency heartburn at baseline versus high frequency; although the therapeutic gain is small.
- There is approximately a 40% treatment failure rate after 14 Days in subjects with high frequency heartburn at baseline, with the benefit being lost within 3 days of discontinuation of therapy.

### *Biopharm Issues*

The pharmacokinetic profile of Prilosec is useful in understanding its efficacy. The half-life of omeprazole is short, 0.5-1 hour. There is also a slow pharmacodynamic onset, with acid inhibition only 50% of maximum at 24 hours, and a long-acting pharmacodynamic effect of acid secretion reduction to baseline over 3-5 days. It is these effects that make Prilosec ineffective in acute relief and make it beneficial for 24-hour prevention.

With regard to drug-drug interactions, there is the potential of Prilosec to reduce the clearance of drugs that are metabolized by CYP2C19, such as diazepam, phenytoin, R-warfarin, and tolbutamide. These effects may be clinically significant in susceptible individuals, such as those having liver disease. Thus, caution, in general, needs to be exercised when co-administering the above drugs with omeprazole.

### *Safety*

The frequency of adverse events (AE) reported in the clinical trials were similar to those known for the prescription products, with regard to headaches (5%), infection (2%), and diarrhea (2%), without dose-related differences. The frequency of AEs reported in the Actual Use study was similar: headache (17.9%), diarrhea (3.8%), and abdominal pain (3.2%). Most of these reactions were not dose-dependent, and were transient in nature. The Safety Update did not reveal any new safety areas of concern.

### *Actual Use Trial (#007)*

This was a multi-site, multi-dose, open-label, observational study of OTC consumers (‘all-comers’), conducted in 5 different cities in the United States. Potential subjects were recruited from a variety of advertising media. The objectives of this study were to determine:

- The percentage of subjects who correctly self-selected that the study medication was a drug that they could or could not use;
- The percentage of doses where no more than one tablet of study medication was taken per dose;
- The percentage of dosing days where no more than one dose and no more than one tablet of study medication was taken per day;
- The percentage of subjects who took between 11-14 doses of study medication in an 11-17 day period (80-120% of dosing directions).

A total of 1301 consumers participated in the self-selection portion of the study. Of those, 1251 (96%) stated that Prilosec1 was appropriate for them to use and 863 agreed to participate in the study. Of these, 854 purchased the study medication; 782 completed the study; and 758 actually purchased and used the drug. Overall, 83% of the primary population (those treating themselves with the drug) and 76% of the secondary population (those making a determination that the drug was appropriate to use) correctly self-selected. (Of note, the primary population is composed of people who had gone through 2 screening processes; whereas, the secondary population had undergone only one screening process.) Lower correct self-selection rates were seen in non-Caucasians and in the low literacy group. In addition, 13.5% of the self-selection (secondary) and 9% of the treated (primary) population who had infrequent heartburn ( $\leq 1$  day a week) and 8.2% has contraindicated conditions, classifying them as inappropriately self-selecting. Overall, compliance with the three-labeled directions (take 1 tablet a day, every day for 14 days) was achieved by 63% of the treated population. Compliance increased to 79% if the sponsor analyzed compliance as subjects taking between 11 to 14 doses of study medication in an 11-17 day period. Three percent exceeded 14 consecutive days of treatment and 33% took the drug for less than 14 days. The study showed that the majority of those using Prilosec1 have long-standing heartburn. However, only 48% of those had spoken to their physician within the last year, and 35% had not spoken to a health care provider at all. The responses to the follow-up questionnaire (3 months after the study) showed that 58% of the consumers available for follow-up had their heartburn return, ; 46% took an antacid heartburn medication; 27% took a prescription heartburn medication; 21% took an OTC acid reducer; 20% of those contacted their health care provider; 10% changed life-style; 8% did something else (not specified); and 6% did nothing.

#### *Pregnancy Category*

Pregnancy Category C is the recommended designation; based on the effects on the human fetus, especially developmental and behavioral, which have not been adequately defined. Based on the mechanism of action of the drug and the consistent results amongst several animal species, exposure to pregnant women should be limited.

#### *Labeling Comprehension*

Two label comprehension trials were undertaken to address the issue of whether consumers could understand the distinction between Prilosec1 and the currently marketed antacids and H2RA. Of note, the label used in both studies was not the same one used in the Actual Use Study, as these studies were conducted simultaneously. However, the label used in the Actual Use trial was similar to those being tested in the label comprehension trials.

Study 2255 suggests that the tested label does not adequately convey to consumers that the product is not for episodic use and that it is only for prevention. Further, the study also indicates that many who may choose to take this product are also using contraindicated medications or have contraindicated conditions, and may not check with a health care provider prior to taking Prilosec 1.

Study 12179 was conducted among persons who should consult a physician before using Prilosec 1 due to medical conditions. The results suggest that most people who should consult a physician before using the product may not understand that they should do so. Among participants, there was a good understanding of the use for frequent heartburn, but a low demonstration of understanding that the use is limited to prevention. After the study, the label was not substantially changed to improve the understanding in these areas.

## Discussion

There are some very specific issues that need to be addressed in considering the safe and effective use of Prilosec 1 in the OTC setting. Despite a relatively short half-life of 2 hours, the pharmacodynamic effect can be measured for 3-5 days after initial administration. The mechanism of action, which has been described as an irreversible inhibition of the proton pump, has a half-life of 50 hours. These characteristics make the product less effective for relieving acute heartburn pain. However, the prolonged pump inhibition that makes this a successful product for repeated (chronic) administration, which is consistent with the new indication sought.

In light of the pharmacological characteristics, one of the questions to be addressed was whether consumers will accurately self-select for (or against) the prevention of frequent heartburn occurring two or more times per week. Overall, the Actual Use study showed that 76% correctly self-selected that the product was appropriate for them to use. This percentage is based on initial self-selection after picking up the product and reading the label. The percentage of correctly self-selecting is higher (83%) if the population that actually self-selected to participate and use the product is used. The majority of those enrolled (87%) and the majority of those treated (91%) had frequent heartburn as defined by having  $\geq 2$  episodes per week. Thus, the self-selection rate was better in those who actually chose to use the product.

The data from the Actual Use study also showed that the majority (98%) of those using Prilosec 1 had heartburn symptoms for more than 3 months; 48% of those had spoken with their physician or health care provider within the past year; and 35% had not spoken to a health care provider about their heartburn ever. This raises an issue that, if available OTC, consumers might not appropriately follow-up with a health care practitioner to identify and treat their underlying condition and may, simply choose to continue treatment if symptomatic relief is afforded.

As studied in the Actual Use trial, the duration of treatment for OTC use was 14 days of continuous use. The majority (97%) of the treated population did not exceed 14 consecutive days of therapy. Overall compliance with all three labeled directions: one tablet a day, every day, for 14 days, was achieved by 63% of the treated population. The difference in the percentages are due to the fact that: not all consumers took only one tablet of Prilosec 1 per dose, not all used just one tablet a day; or not all took medication continuously for 14 days. The responses to the 3-month follow-up questionnaire showed that 58% of the available participants had their heartburn return. Of these, 46% took an antacid heartburn medication; 27% took a prescription heartburn medication; 21% took an OTC acid reducer; 20% of those contacted their health care provider; 10% changed life-style; 8% did something else (not specified); and 6% did nothing.

The label comprehension trials showed that approximately 80% of the participants understood that Prilosec 1 was for frequent heartburn. It was unclear from these studies, due to the way the questions were worded, if consumers understood that Prilosec 1 was intended for prevention only and not for acute or episodic relief.

An additional issue to be addressed is the consequences of long-term and/or chronic intermittent treatment without physician oversight and whether any of the more significant conditions may be masked as a result of consumers choosing to continue to medicate rather than follow-up with a health care provider. Given the targeted population for use (those with frequent heartburn), the issue remains as to whether the proposed duration of therapy (14 continuous days) should be influenced by the likelihood that patients with GERD (having a minimum duration of prescription therapy of 4 weeks) might purchase the medicine.

In summary, when reviewing the data presented in the briefing package consideration should be given to the following issues:

- Has the sponsor identified an acceptable target population?
- What is the appropriate duration of therapy ?
- How should acute and episodic, as well as long-term intermittent use be addressed?