



OTC MEDICAL OFFICER'S REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

NDA #:	21-229
Drug name:	Prilosec1 (omeprazole magnesium)
Sponsor:	AstraZeneca LP Procter&Gamble Company
Pharmacologic Category:	Proton Pump Inhibitor
Proposed Indications:	For Prevention of Frequent Heartburn
Dosage Form:	20 mg Tablet
Route of Administration:	Oral
Submission dates:	February 12, 2002
Review date:	April 16, 2002
Reviewer:	Daiva Shetty, MD

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Executive Summary:

I. Recommendations

Recommendation on Approvability

Experience with the already approved Prilosec1 does not suggest an unusual pattern of toxicity, either in terms of frequency or severity of adverse reactions reported.

The target population and indication for use, as well as the risk-benefit assessment of Prilosec1 as an OTC product for the treatment of frequent long standing heartburn, warrant further discussion with members of the Nonprescription and Gastrointestinal Drugs Advisory Committees.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Omeprazole (Prilosec1) is a proton-pump inhibitor (PPI) approved for prescription use in 1989. The original NDA requesting to switch Prilosec1 (omeprazole magnesium, Ome-Mg) from Prescription (Rx) to over-the counter (OTC) status was submitted on January 27, 2000. The data was presented at the joint meeting of the Nonprescription Drugs Advisory Committee and Gastrointestinal Drugs Advisory Committee on October 20, 2000. The original NDA was found to be non-approvable because of the following deficiencies:

- The efficacy, appropriate dose and duration of therapy, and use of Prilosec1 in the OTC setting have not been adequately established. The ability of the consumer to appropriately self-select and to use Prilosec1 safely and effectively in the OTC setting has not been demonstrated.
- The data have not adequately demonstrated the ability of consumers to comprehend the risks associated with concomitant use of Prilosec1 with potential drugs having significant interactions without the intervention of a physician.
- The sponsor did not provide adequate safety information to support OTC omeprazole use in individuals under the age of 18 years, or the risks to women who are pregnant or of childbearing potential.
- The sponsor also was requested to establish that consumers would not use Prilosec1 for extended periods of time without contacting a health care provider.

In support of the current resubmission, requesting to switch Prilosec1 marketing from Rx to OTC status, the sponsor provided results of one Actual Use study, three Label Comprehension studies, safety update, and proposed OTC labeling. This review covers the results of the Actual Use study (#007) and the safety update.

B. Efficacy

No new efficacy data was presented in this NDA resubmission. A new proposed target population and directions for use will be addressed by reviewers in HFD-180. A summary of data from the Actual Use Trial #007 is presented below.

The objective of the Actual Use study was to investigate how consumers use omeprazole magnesium (Ome-Mg) in naturalistic OTC conditions following proposed labeling instructions. This was a multi-center, open-label consumer use study. A total of 1301 subjects participated in the self-selection part of the study, and of those 1251 (96%) stated that Prilosec1 is appropriate for them to use. A total of 863 subjects agreed to participate in the study; 854 bought the study medication; and 782 completed the study. The treated population (subjects who purchased and used the drug) consisted of 758 subjects. Demographically, the enrolled population (N=1301) was reasonably balanced in terms of age and ethnicity, and representative of the general U.S. population. There were 60% female and 40% male, ranging in age from 18 to 91 years, with a mean age of 48 years. The majority (65%) of the subjects were Caucasian, 18% were Black, 11% were Hispanic, and 6% made up other races. The low literacy group (REALM \leq 60) consisted only 9.9% of the enrolled and 7.9% of the treated populations.

Overall, the correct self-selection rate was 83% for the primary population (self-selected to participate in the study and to use the drug) and 76% for the secondary population (self-selected the drug is appropriate for their use). The correct self-selection rates were higher overall and by subgroups in primary vs. secondary population. Lower correct self-selection rates were seen in non-Caucasians and low literacy group. There were a total of 13.5% of self-selection (secondary) and 9% of treated (primary) population that suffered from infrequent heartburn (\leq 1 day a week), who inappropriately self-selected themselves. This shows that Prilosec1 is likely to be used for episodic occasional heartburn. Data from the study also suggest that it is likely that Prilosec will be used by subjects with contraindicated symptoms, with 8.2% of the total treated population selecting to use Prilosec1 despite the warnings on the label that they should not.

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 (N=758). Twenty-three (3%) subjects exceeded 14 consecutive days of treatment, and 249 (33%) took for less than 14 days.

The study results show that majority of the consumers who self-selected and used the product, suffered from long-standing and frequent heartburn. The proposed label states: "Notify your doctor if you have had heartburn for 3 months or longer without talking to your doctor". The results showed that majority of the subjects (98%) who used the drug had heartburn symptoms for more than 3 months. Only half of them (48%) had spoken to their physician within the last year, and 265 (35%) subjects had not spoken to a health care provider at all. Seven percent (7%) of subjects purchased more than one carton of Prilosec1 during the study, which may be an underestimate of use. The responses to the

follow-up questionnaire (3 months after the study) showed that more than half (58%) of the subjects available for follow-up had their heartburn return, and only 20% of those contacted their health care provider. If Prilosec1 will be available for OTC purchase and use, this subgroup of consumers may be migrating from the other OTC heartburn medications to Prilosec1 use, without consultation with a physician. Given current medical practice, in which most practitioners recommend an initial empirical trial of 4-8 weeks of PPIs for the treatment of frequent heartburn prior to invasive procedures, 2-week duration of OTC treatment may be acceptable.

C. Safety

Integrated review of safety of omeprazole for the Rx-to-OTC switch has been reviewed at the time of the original NDA submission on January 27, 2000. Safety data submitted to the current application consisted of safety data gathered from the Actual Use Study #007 and international post-marketing experience with Ome-Mg from January 1, 2000 through June 30, 2001.

The extent of exposure to Prilosec1 in the Actual Use study was relatively short (mean of 14.2 days). Safety data from the actual use trial are consistent with Rx Prilosec and safety profiles from previous actual use trials. The most common adverse event reported in this study was headache (17.9%), followed by diarrhea (3.8%), and abdominal pain (3.2%). There were no unexpected or unlabeled adverse events (AEs) reported during this study.

For the reporting period of January 1, 2000 through June 30, 2001, 27 million patient treatment courses of omeprazole magnesium MUPS (multiple unit pellet system) tablets were distributed; 109 serious AEs among 63 (60 non-fatal and 3 fatal) users and 430 non-serious adverse events among 257 users were reported to AstraZeneca. The most common serious adverse events (SAEs) reported were dyspnea (4 cases), hepatic function abnormal (4), and 3 cases of each: abdominal pain upper, angioneurotic edema, dermatitis, liver function tests abnormal, pancytopenia, Stevens Johnson syndrome, toxic epidermal necrolysis, and vomiting. The five most common non-serious AEs reported were: drug ineffective, dyspepsia, dermatitis, abdominal pain and nausea. All of the reported adverse events are currently listed on Prilosec prescription label.

Safety of Prilosec has been well established by clinical trials supporting its approval as a prescription product. The safety data presented in this NDA resubmission show that Prilosec1 is a relatively safe drug, with a safety profile that is acceptable for OTC marketing. No new signals have appeared in the course of post-marketing surveillance attributable to either labeled use or misuse of the prescription product. Post-marketing surveillance has limitations related to the nature of the reporting system. The rate of adverse events, however, may increase after the Rx-to-OTC switch, when a large uncontrolled population will be exposed to the drug (purchasing and using the drug) without a learned intermediary.

D. Dosing

The dosing regimen is acceptable as proposed: take one tablet every day for 14 days.

The label should not state that this drug could be used for the prevention of symptoms of frequent heartburn for 24 hours. The first bullet in the "Uses" section should state that this drug is for prevention of frequent heartburn. The label should also clearly state that Prilosec1 is not for people with episodic (less than twice a week) heartburn.

E. Special Populations

Prilosec1 is a pregnancy category C drug. Use of Prilosec1 by pregnant women has been addressed by HFD-180. Only one pregnant female tried to purchase and use Prilosec1 in the Actual Use Study. The product should carry a pregnancy warning as specified in 21 CFR 201.63.

Clinical Review:

I. Introduction and Background

Omeprazole is a proton-pump inhibitor approved for prescription use in 1989. It is currently marketed for the following indications:

1. For the treatment of active duodenal and gastric ulcer.
2. For the treatment of heartburn and other symptoms associated with GERD.
3. For the treatment of erosive esophagitis which has been diagnosed by endoscopy.
4. For the maintenance of healing of erosive esophagitis.
5. For the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).
6. In combination with clarithromycin and amoxicillin, it is indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease

The original NDA requesting to switch Prilosec1 from Rx to OTC status was submitted on January 27, 2000. The data was presented at the joint meeting of the Nonprescription Drugs Advisory Committee and Gastrointestinal Drugs Advisory Committee on October 20, 2000. The original NDA was found to be non-approvable for the following reasons:

- The efficacy, appropriate dose and duration of therapy, and use of Prilosec1 in the OTC setting were not adequately established. The ability of the consumer to appropriately self-select and to use Prilosec1 safely and effectively in the OTC setting had not been demonstrated.
- The data had not adequately demonstrated the ability of consumers to comprehend the risks associated with specific drug interactions, nor the ability of consumers to avoid concomitant use of specific interacting drugs without the intervention of a physician.

- The sponsor did not provide adequate safety information to support OTC omeprazole use in individuals under the age of 18 years, or the risks to the fetus of potential Prilosec1 use in the OTC setting by women who are pregnant or of childbearing potential.
- The sponsor also was requested to establish that consumers would not use Prilosec1 for extended periods of time without contacting a health care provider.

The differences between the original submission and current resubmission are listed in Table 1 below.

Table 1. Differences in the Original Submission (1/27/2000) and Resubmission (2/12/2002)

	Original	Resubmission
Dose	10 mg	20 mg
Target population	> 12 years old Anybody with heartburn (HB) symptoms	> 18 years old HB \geq 2x/week
Directions for use	For relief and prevention of HB symptoms. Use no more than 10 days.	For prevention of frequent HB 1 tab QD for 14 days fixed regimen
Efficacy	6 controlled trials	Summary of the same data: AMI 171 AMI 183
Safety	Integrated summary of safety from controlled trials. Global post-marketing data up to 12/31/1999	Safety from the actual use trial (#007). Global post-marketing data 1/1/2000-6/30/2001
Label Comprehension Studies	1 Label Comprehension Study (LCS)	02255: LCS in five cohorts, n=684 12179: LCS in n=145 with HB+other warning symptoms 17859: De-selection study in n=97 with infrequent HB
Actual Use Trials	Total of 4 actual use studies for 20 mg and 1 for 10 mg Ome-Mg tablets.	007: n=759, 8-12 week duration, usage patterns, selection criteria, MD contact, efficaciousness

The use directions proposed for OTC status of Ome-Mg are as follow:

Adults 18 years of age and older:

- for prevention of frequent heartburn, swallow 1 tablet with a glass of water in the morning
- take every day for 14 days
- do not continue beyond 14 days unless directed by your doctor. If your frequent heartburn continues or returns, it could be a sign of a serious condition.
- do not take more than 1 tablet per day
- do not chew or crush the tablets

There are two classes of drugs available OTC for heartburn relief: antacids and histamine-2 receptor antagonists (H₂RA, acid reducers). They are indicated for relief of

heartburn symptoms. In addition, H₂RAs are approved for prevention of heartburn symptoms induced by meal. The list of currently available OTC drug products for the treatment and prevention of heartburn symptoms is presented in Table 2 below.

Table 2. List of Currently Available OTC Products for Relief or Prevention of Heartburn Symptoms

Proprietary (pharmacological) Name	NDA/ANDA Number*	Pharmacological Category
Zantac 75 (ranitidine HCl)	20-520	H ₂ RA
Tagamet HB (cimetidine)	20-951	H ₂ RA
Pepsid AC (famotidine)	20-325	H ₂ RA
Axid AR (nizatidine)	20-555	H ₂ RA
Pepsid Complete (calcium carbonate, famotidine, magnesium hydroxide)	20-958	Combination Product
Gaviscon (aluminum hydroxide, magnesium trisilicate)	18-685	Antacid Combination
Various trade names (Calcium carbonate; Aluminum hydroxide; Magnesium salts; Sodium bicarbonate, in combination or as single ingredients)	Final Monograph for Antacid Products for OTC Human Use	Antacids

* Only reference listed drugs are listed in the table. There are multiple generic drugs for each of the original NDA drug products.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consult Reviews

Refer to the original NDA for prescription omeprazole approval reviews. There is no new nonclinical information contained in this supplemental New Drug Application.

III. Human Pharmacokinetics and Pharmacodynamics

Refer to the original NDA for prescription omeprazole approval reviews. There is no new human pharmacokinetics and pharmacodynamics information contained in this supplemental New Drug Application.

IV. Description of Clinical Data and Sources

In support of this application, the sponsor has submitted the following information:

1. Results of the Actual Use Trial (#007),
2. Results of three Label Comprehension studies (#02255, #12179, #17859),
3. Proposed OTC labeling for 20 mg omeprazole magnesium tablet, and
4. Safety update.

V. Clinical Review Methods

This review will address the Actual Use Trial (#007) and the safety update data. The Division of Coagulation and Gastrointestinal Drug Products (HFD-180) will review the new target population, directions for use, and efficacy for omeprazole 20 mg tablets. In addition, the Division of Surveillance, Research, and Communication Support (HFD-410) will review the three Label Comprehension studies.

Adverse event reports submitted by the sponsor were gathered from the sponsor's postmarketing surveillance system for Prilosec 20 mg tablets for the time period from January 1, 2000 through June 30, 2001.

VI. Integrated Review of Efficacy

Since the sponsor did not conduct new efficacy trials, an efficacy supplement was not required for this application. A new proposed target population and directions for use will be addressed by reviewers in HFD-180.

Review of the Actual Use Trial #007. A Multi-Center, Open-Label, Actual-Use Study to Investigate How OTC Consumers Use Omeprazole Magnesium, 20.6 Mg

Study Objective

The objective of this observational study was to investigate how consumers used omeprazole magnesium under proposed label instructions in naturalistic OTC conditions. The following endpoints of consumer behaviors were examined:

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

If a subject took more than 14 doses of study medication, they must have consulted a healthcare provider within the study period to be considered compliant with dosing directions.

Study Design

This study was a multi-site, multi-dose, open-label, observational study of OTC consumers ("all-comers"). The study was conducted in the United States at five retail sites in five cities:

1. Vernon, CT
2. Fayetteville, GA
3. West Palm Beach, FL
4. Norwalk, CT
5. Modesto, CA

Visit 1

Potential subjects were recruited via broad-based advertising through radio and/or print material, as well as from spontaneous intercept at shopping centers. Advertising indicated, “if you get frequent heartburn, male and female volunteers are needed to participate in a research study”. Subjects’ data were collected by non-healthcare professionals. These sites were set up to simulate a naturalistic OTC setting where consumers could purchase an OTC heartburn remedy.

All consumers presenting to the shopping centers were assigned an identification number and were asked:

“We are conducting a research study to determine consumer’s reactions to a proposed new over-the-counter heartburn medication. Do you get heartburn?”

Those who answered “yes” were given an opportunity to participate in a 20 minute interview for which they were offered to be paid \$20. Those who agreed to participate were shown a market-ready carton of Prilosec1 and asked the following questions: “Please read the information on this package to determine if this is a medication you yourself could use for your heartburn. Take as much time as you need. Here is the package for a proposed new over-the-counter product.”

When they had finished examining the package, subjects were then asked:

“Do you think Prilosec1 is a medication you could use for your heartburn?”

After the self-selection decision had been made, study personnel captured each consumer’s decision (yes, no) and reasons word-for-word (verbatim). Subjects who self-selected that the study medication was one they could use for their heartburn were then asked:

“You indicated that Prilosec1 is a medication you could use for your heartburn. We are looking for people to participate in a research study to learn how people use this new heartburn medication. To be in the study you must:

- 1) buy the study medication today which sells for \$12.00 for 14 tablets,*
- 2) write down in a diary each time you take the medication,*
- 3) when finished, mail the dairy back to us in a postage-paid envelope, and*
- 4) return for an end-of-study visit.*

You will be given \$100 for completing the study in addition to the \$20 for today’s interview.

Would you like to participate in this study?”

All subjects responding ‘yes or no’ had their reasons recorded verbatim. All subjects responding ‘yes’ had the purpose and procedures of the Actual Use Study explained to them. All subjects interested in participating in the study were required to provide a full written informed consent prior to enrollment in the Use phase of the study. Female subjects must also agree to take two urine pregnancy tests (one on the first day of the study, the second after the last dose of study medication was taken/before end-of-study visit). Female subjects also provided consent to a Birth Control Agreement during the study.

Subject enrollment ceased when approximately 850 subjects had purchased study medication. Pricing was representative of proposed market prices (\$12.00 for a 14-count carton). Study medication was supplied as a carton of pink/rust tablets packaged in blister cards, each carton containing 14 tablets. The carton simulated the proposed OTC market-ready packages of Prilosec1 and contained proposed OTC use directions on the back carton panel as well as the package insert. The retail display of Prilosec1 also contained both educational materials specific to Prilosec1 and heartburn. These materials were available for the subjects to pick up if they chose, but were not distributed by the study staff.

Comments:

The actual use study protocol has not been reviewed by the Agency prior to initiation of the study. Concerns about the overall design of an actual use study for Prilosec1, that were conveyed to the sponsor prior to the onset of this study, are listed below:

- 1. Heartburn is a condition of a long standing duration. Therefore, an actual use study should be of sufficient length to demonstrate compliance with the labeled warnings and instructions about repeated use, and physician contact.*
- 2. Sample size should be large enough to provide information for different demographic subgroups, those with low literacy, those with alarm symptoms, and those with frequent heartburn of longstanding duration. Subjects should be allowed to purchase drug throughout the duration of the study.*
- 3. Data analysis should include an assessment of whether or not subject self-selection decisions are appropriate based on subject specific information.*

The sponsor is separating 3 parts of the label directions into independent compliance endpoints. The compliance with all three dosing directions (take one tablet per day, one tablet per dose, and no more than 14 days of duration) should be addressed together. As a secondary endpoint, compliance should be analyzed with each part of the directions separately. One important piece of information that was collected in the previous actual use studies, the reason for use of Prilosec1 (for relief or prevention), was not collected in this trial. The sponsor assumes that consumers understand from the label, that this product is to prevent heartburn in the future, not in an acute setting. This is an important deficiency of the study.

The 4th endpoint of the study is the percentage of subjects who took between 11–14 doses of study medication in an 11–17 day period (80%–120% of dosing directions). The sponsor did not provide any reason why those particular numbers were chosen. Previous actual use trials did not have this range of acceptable treatment duration. The primary endpoints of the study should have been correct self-selection, and compliance with all three label use directions.

The carton of Prilosec1 used in this study simulated the proposed OTC package. The label and additional educational materials used in the study have been reviewed and were found to be acceptable.

The informed consent form was given after the self-selection decision has been made. The consent form has been reviewed and was found to be acceptable. The fact that

subjects were aware that they would be paid prior to their enrollment may have influenced their responses to the subsequent questionnaires.

Continuance Criteria

To be allowed to continue the study, subjects must have been 18 years of age or older.

Purchase Criteria

To be allowed to purchase study medication, subjects must:

- Have provided a full written informed consent, and
- After reading the label of Prilosec1, determine that the study medication was appropriate for them to use, be willing and able to purchase the study medication, complete the diary, return for a second visit to review the diary and complete a post-study questionnaire, and answer a 3-month post-initial visit telephone questionnaire.

Subjects who self-selected to participate in the study were not permitted to purchase study medication if they:

- had participated in this study, any other clinical study within the past 30 days, or either of the previous two Prilosec1 actual-use studies,
- stated they were pregnant or lactating, or
- stated they were allergic to omeprazole.

After her self-selection choice was made, every woman was asked if she thought she was pregnant or if she was nursing an infant. Each of these interventions served to identify a pregnant or lactating woman from the study. If a woman thought she was pregnant or tested positive for pregnancy but elected to continue, she was noted as a self-selection failure and was excluded from purchasing study medication for safety considerations. Additionally, a urine pregnancy test was performed on the first day of the study, and if the test result was positive, the subject was (instructed not to take the study medication and was terminated from further participation) excluded from the study. If the woman was of child-bearing potential, she signed the informed consent which included a birth control agreement indicating that she would use adequate contraception during her time in the study. All female subjects were given two take-home urine pregnancy tests. The subject was instructed to complete one pregnancy test at home on the first day of the study. She documented the result of the pregnancy test in her diary. If the test result was positive, she was instructed not to take the study medication and to call the telephone number for the physician-investigator listed in the diary. A second urine pregnancy test was done before the end-of-study visit (Visit 2) to indicate whether a pregnancy occurred during the study period. If she became pregnant during the study, she was to immediately inform the investigator via the provided telephone number and was discontinued from participation in the study. Her pregnancy would then be followed to term and beyond as appropriate.

Comments:

Inclusion and exclusion criteria were minimized and were applied after the self-selection was made. It is reasonable to exclude from the study, subjects who are at risk, after the

self-selection was determined. Those who were excluded by the investigator because of their risk should have been counted as a self-selection failures.

Table 3 lists the schedule of events of the study.

Table 3. Study-Specific Procedures Performed at Each Visit

Procedure	Visit 1	Interim	End-Of-Study Visit (Visit 2)	3-Month Post-Study
Subject Number Assigned	X			
Examine Package/Self-Select	X			
Reason(s) for Self-Selection	X			
Demographics	X			
Continuance Criterion	X			
REALM Test (if appropriate)	X			
Heartburn History	X			
Medication History	X			
Explain Study/Interest in Purchasing Prilosec1/Willingness to Participate	X			
Informed Consent – Subject Enrolled	X			
Purchase Criteria	X			
Pregnancy Test (if appropriate)	X		X	
Study Medication Available for Purchase	X	X		
Diary Dispensed	X	X (with each repurchase)		
Diary mailed to study coordinator		X		
End-of-Study Visit (Visit 2) Scheduled (by telephone on or after study day 57)		X		
Diary Reviewed (Collected if not previously mailed)			X	
Overall Assessment of Study Medication			X	
Concomitant Medication Review			X	
Adverse Event Monitoring/ Brief Medical Exam			X	
Post-study Questionnaire			X	
3-Month Follow-Up Telephone Questionnaire				X

After the self-selection decision had been made (yes, no), study personnel asked all subjects the reason(s) for their decision, which were recorded verbatim. The Rapid Estimate of Adult Literacy in Medicine (REALM) Test was performed on subjects who indicated that their highest education level was equal to or less than high school graduation or equivalent, in order to identify subjects with low reading ability (a score of ≤ 60). Demographics, heartburn history, and medication history were collected for all

subjects participating in the self-selection process (i.e., subjects who self-selected in and self-selected out of the study).

Eligible subjects were given the opportunity to purchase additional cartons of the study medication (limit 4 cartons). Subjects were not told of the 4-carton limit until such time that they requested to purchase more than 4 cartons (56 tablets). Should subjects wish to purchase additional study medication after the first visit, they may have done so during retail hours at the same location, and were asked about contact with medical personnel at the time of repurchase.

A diary was dispensed to all subjects eligible for the actual-use phase of the study and they were shown how to use it. Subjects were asked to provide the following information in the diary each time they used Prilosec 1: the date of the dose, the time of the dose, and the number of tablets taken. If subjects returned to purchase additional product, a new diary was issued. Throughout the study period, information was also recorded on concomitant medications, which subjects may have taken (including other heartburn medications); whether there were any adverse experiences; and (for women) the results of the pregnancy tests.

Subjects were called by telephone on or after study day 57 and scheduled to return to the same retail location within approximately 2 weeks.

End-of-Study Visit (Visit 2)

Subjects had the following procedures performed during this visit:

- Diaries were collected and reviewed. If the diary had not been previously mailed, it was collected at the end-of-study visit (Visit 2). The diary was reviewed during this visit to address any missing, incomplete, inconsistent, or confusing entries with each subject and to ensure a timely analysis of data.
- Concomitant medications were reviewed.
- Adverse event monitoring and brief physical exam were performed.
- Subjects were asked to provide overall assessment of the study medication.
- After all Visit 2 procedures had been performed, subjects were asked to answer questions from a post-study questionnaire. These questions addressed whether they were currently under the supervision of a physician for their heartburn or had received advice from a physician or a healthcare professional (e.g., physician, nurse, nurse practitioner, physician assistant, pharmacist) regarding their heartburn and use of the study medication. Additionally, data were captured on contraindicated medications. If subjects were taking a contraindicated medication, they were asked if they discussed this with a healthcare provider.

3-Month Follow-up Telephone Questionnaire

Those subjects who completed the actual-use portion of the study (returned a diary), were telephoned by study personnel approximately 3 months after the initial visit. They were asked whether or not they had spoken with a physician, a nurse in a physician's office, a nurse practitioner, or a physician's assistant about their heartburn since their end-of-study visit, and whether they had received any advice or recommendations for heartburn treatment (verbatim responses collected). Subjects were also asked if they had a (future)

scheduled appointment with their physician, and if so, whether they planned to discuss their heartburn at that visit. Subjects were also asked if their frequent heartburn returned since stopping the study medication, and, if it did, what they did about it.

Consumer Behavior Endpoints

The following endpoints were summarized to characterize correct self-selection and consumer behavior relative to labeled directions for subjects taking the study medication:

1. The percentage of subjects that correctly self-selected that the study medication was a drug that they could use, and
2. If the subject reported that the medication was one they could use for their heartburn, then they were considered correct if they:
 - reported a history of two or more days of heartburn per week or reported taking heartburn medications two or more days per week,
 - were at least 18 years of age,
 - were not pregnant or nursing,
 - were not allergic to omeprazole,
 - did not report any alarm symptoms,*
 - were not taking any contraindicated medications*

* However, note that if a subject had consulted a physician, physician's assistant, or a nurse practitioner about the alarm symptom(s) or taking any of the contraindicated medications with Prilosec1, then the subject was considered as having correctly self-selected.

Usage patterns, related to labeled directions, were determined using the following measures:

- The percentage of doses where no more than one tablet of study medication was taken per dose.
- The percentage of subjects who took no more than one tablet per dose on all doses.
- The percentage of subjects who took no more than one dose and no more than one tablet on all days.
- 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). If a subject took more than 14 doses of study medication, they must have consulted a healthcare provider within the study period to be considered compliant with dosing directions.

Physician Advice and Supervision

Physician's advice and supervision were summarized using two scenarios (relative to consistency with the dosing instructions). The first scenario was limited to the physician and/or the other healthcare provider (e.g., physician's assistant, nurse practitioner, or nurse in the physician's office) contact during the 2-month use period. While the first scenario assessed physician consultation during the 2-month use period, the second

scenario was expanded to include the subject's overall experience obtaining medical advice or supervision, which included:

- advice from a physician or supporting healthcare provider as recorded in the 3-month post initial visit telephone questionnaire concerning their heartburn,
- advice from a physician or supporting healthcare provider about their heartburn (within the past year and/or at any time prior to the study),
- a prescription medication for their heartburn (within the past year and/or at any time prior to the study), or
- a scheduled appointment with a physician or supporting healthcare provider to discuss their heartburn.

Consumer Reasons for Self-Selection

After the subjects self-selected (i.e., determined for themselves whether or not the study medication was one they could use), they were asked the reason(s) for their decision. These reasons were recorded verbatim. Verbatim responses were classified by the sponsor into response categories after the consumer's self-selection decision had been made. The categories were pre-specified as follows:

- Consumer Reasons Why Not Appropriate to Use
 - “I don't get heartburn.”
 - “I don't get heartburn more than once a week.”
 - “I am pregnant or nursing a child.”
 - “I am currently taking a medication I shouldn't take with Prilosec1.”
 - “I have a condition mentioned on the label warning.”
 - “I am under 18 years of age.”
 - “Other.”
- Consumer Reasons Why Appropriate to Use
 - “I get frequent heartburn.”
 - “I want to prevent heartburn.”
 - “I'm familiar with this medication and/or have tried Prilosec.”
 - “Other heartburn medications are not effective enough.”
 - “It has convenient dosing/24-hour duration.”
 - “Other.”

Participation Status

Those subjects who self-selected Prilosec1 as a medication they could use for their heartburn were asked if they were willing to participate in the study. Subjects who responded “no” had their reason(s) recorded verbatim. Verbatim responses were classified by the sponsor into response categories after the consumer's self-selection decision had been made. The categories were pre-specified as follows:

- “I don't like to try new medications without my physician's approval.”
- “The product is too expensive.”
- “I don't use medications or I only use natural remedies.”
- “Study participation would not be convenient.”
- “I am happy with my current heartburn medication.”
- “Other.”

Physician Consultation

Subjects may have contacted a physician (study or personal), nurse practitioner, physicians assistant, or nurse in a physician's office prior to enrollment or at anytime during this study. Further, approximately 3 months after the initial visit, all subjects participating in the actual-use phase of the study were to be contacted by telephone to answer a questionnaire to determine whether or not over the past month they had spoken with a physician, a nurse in a physician's office, a nurse practitioner, or a physician's assistant about their heartburn, and whether they had received any advice or a recommendation for heartburn treatment. The subject was also asked if they had a (future) scheduled appointment with their physician, and if so, whether they planned to discuss their heartburn at that visit.

Comments:

The information on consultation with a physician or other health care provider was collected from the subjects, but was not confirmed by the study personnel. This is a deficiency of the study.

Safety Measures

Subjects were asked to record in their diary any other adverse effects (AEs) that occurred after taking their first dose of study medication and throughout the study period. A physician/investigator telephone number was provided in the subject's diary to call in the event of an emergency. All AEs noted or reported after taking the first or any subsequent dose of study medication, were to be recorded on the appropriate case report form (CRF).

Statistical Methods and Analysis Plans

Demographic and Baseline Characteristics

The demographic parameters and heartburn history information were summarized using descriptive statistics. These summaries were carried out for 3 populations:

- 1) those who took the study medication,
- 2) all those who participated in the self-selection interview and selected the drug as appropriate to use, and
- 3) those who stated intent to purchase study medication.

Self-Selection and Consumer/Dosing Behavior

The percentage of subjects (and 95% confidence interval) that correctly self-selected that the study medication was one they could use was computed separately for each self-selection criterion. In addition, an overall correct self-selection was computed that utilized all self-selection criteria.

Correct self-selection was computed for two populations:

1. Primary Population: all subjects who used study medication plus all the available information from the 12 subjects who were precluded from participation (N=770).
2. Secondary Population: all those subjects who participated in the self-selection process and selected the drug as appropriate to use (N=1251).

Overall, correct self-selection was summarized by demographic characteristics such as gender (female vs. male), race (Caucasian vs. non-Caucasian), age (< 65 years vs. > 65 years), study center and literacy level (REALM).

Comments:

The sponsor elected to use, as the primary self-selection population, those subjects who selected to use the product. This was a population, that had already gone through the self-selection phase, and not only self-selected to buy and use the drug, but actually made a decision to agree to participate in the study. In order for subjects to participate in the study, they had to meet the 4 prespecified conditions listed below:

- *to pay \$12 for 14 tablets of the study medication,*
- *agree to fill in a diary,*
- *mail in a diary, and*
- *return for the end-of-study visit.*

This population is acceptable for the analyses of safety and compliance with dosing directions, but not as a primary population for the analyses of self-selection. The primary self-selection population should be those subjects who participated in the self-selection interview, prior to actually using the product.

The consumer reasons for why the study medication was appropriate/not appropriate to use, and participation status, were summarized using descriptive statistics.

The following separate elements of consumer behavior relevant to the dosing directions were summarized:

- The percentage of doses (and 95% confidence interval) where no more than one tablet of study medication was taken per dose.
- The percentage of dosing days (and 95% confidence interval) where no more than one dose and no more than one tablet of study medication was taken per day.
- The percentage of subjects (and 95% confidence interval) who took between 11–14 doses of study medication in an 11–17 day period (80%–120% of dosing directions). If a subject took more than 14 doses of study medication, they must have consulted a healthcare provider within the study period to be considered compliant with dosing directions.
- The percentage of subjects who took no more than one tablet per dose on all doses.
- The percentage of subjects who took no more than one dose and no more than one tablet on all days.

The first three endpoints above were summarized by demographic characteristics such as gender (female vs. male), race (Caucasian vs. non-Caucasian), age (< 65 years vs. > 65 years), study center, literacy level (REALM), and by clinical characteristics such as heartburn frequency and duration, use of prescription heartburn medications, and OTC-only heartburn medications. In addition, consumer behavior relative to the dosing directions was assessed based on contact/no contact with a healthcare provider and evidence of healthcare/prescription insurance.

Dosing behaviors, such as total number of dosing days, total number of tablets taken, dosing duration, and maximum and minimum consecutive dosing days were also summarized as frequency distributions in tabular and/or graphical fashion. Subjects who agreed to participate in the study and returned a diary, but decided not to use the study medication, were not included in the analyses/summaries of dosing since no drug usage behavior was available. All subjects who returned their diary had all available data included in the consumer behavior measures. The diary was the definitive source of data about consumer behavior and study medication usage. A subject was considered “complete” if they returned one or more diaries.

Overall Assessment of Study Medication

The overall assessment of study medication was summarized by reporting the percentage of subjects who evaluated the study drug as Poor, Fair, Good, Very Good, or Excellent.

Comments:

Consumer behavior relevant to the dosing directions was analyzed by separate label elements: on per dosing day, per dosing occasion, and per total number of days basis. All label use directions should have been counted together for the evaluation of compliance.

Sample Size Considerations

A sample size of 758 subjects who took study medication, conformed to a 95% confidence limit that the estimate of complying with individual dosing direction would not differ from the true compliance rate by more than 3.6%.

Changes to the Analysis Plans

In addition to all of the endpoints provided in the Statistical Analysis Plan, two more endpoints were computed.

- The percentage of subjects who took no more than one tablet per dose on all doses.
- The percentage of subjects who took no more than one dose and no more than one tablet on all days.

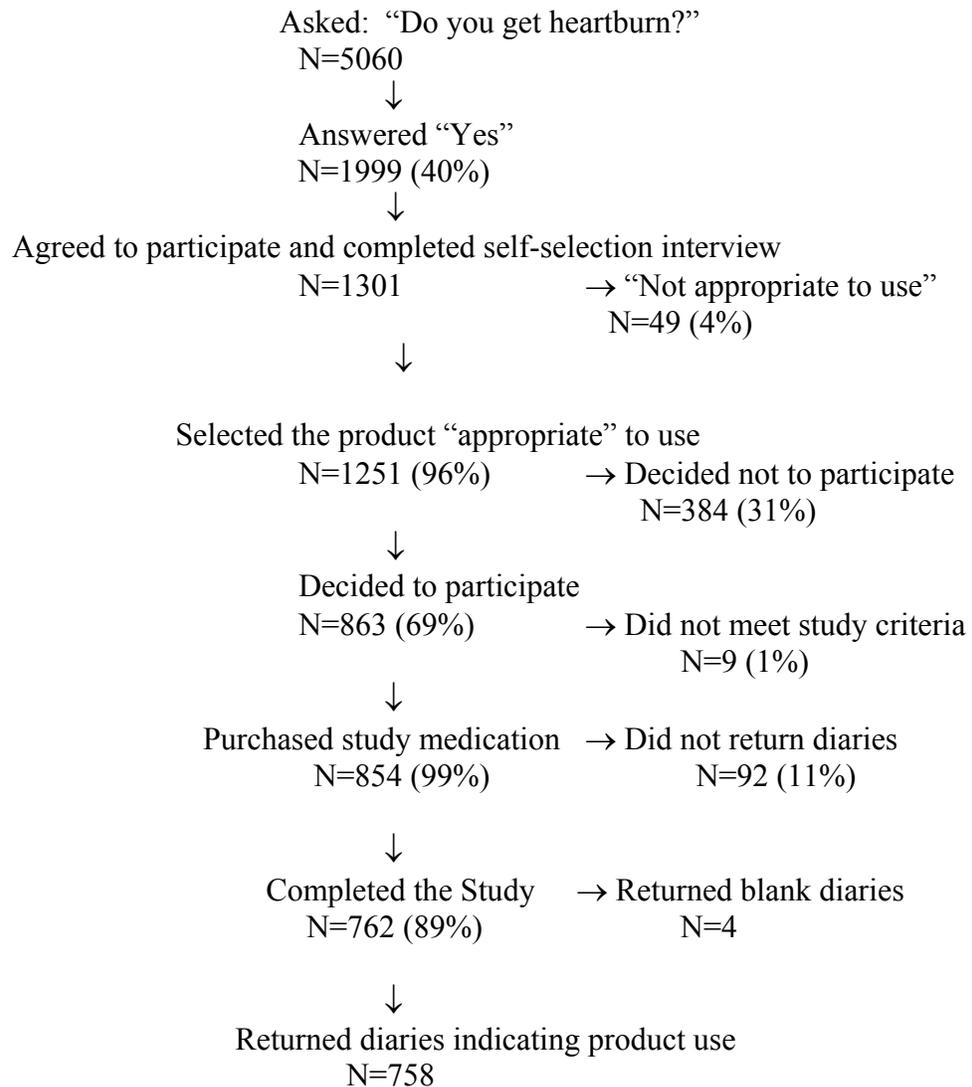
In order to obtain a more accurate measure of the subjects’ heartburn frequency, frequency of taking heartburn medication was utilized in addition to the subjects’ reported heartburn frequency. This was done because some subjects take heartburn medications in a preventive manner, and thus, do not report an accurate measure of heartburn frequency. There was a slight change from the analysis plan in the secondary population for measuring self-selection. Those subjects who selected the drug “not appropriate” to use were not included (as originally planned) in the secondary population because this group of subjects would never have purchased or used Prilosec1. Thus, it would not be accurate to include them as “correct” or “not correct” in self-selection.

Comments:

A statistical consult is pending, from HFD-725, which will comment on the statistical analysis plan, methods, sample size, and endpoints.

Results

The following chart displays a disposition of the subjects.



The reasons for 49 subjects who stated that Prilosec 1 is not appropriate for them to use are listed below:

- 14 (28.6%) do not get heartburn more than once a week,
- 2 (4.1%) pregnant or nursing a child,
- 12 (24.5%) taking a contraindicated medication,

- 7 (14.3%) had a condition mentioned on the label warning, and
- 14 (28.6%) other reasons.

Of the 863 who chose to participate, 9 did not meet study criteria:

- 4 subjects would not provide consent,
- 1 subject was pregnant, and
- 4 subjects had previously participated in a Prilosec1 study.

Of the 854 subjects who received study medication, 762 (89%) completed the study by returning one or more diaries.

For the 92 subjects who did not return one or more diaries, 82 (89%) were lost to follow-up, 8 (9%) reconsidered or withdrew consent, 1 (1%) experienced an AE (Subject 010016 experienced “stomach pains” and discontinued study medication after three doses), and 1 (1%) was withdrawn due to an investigator decision (Subject 030222 reported “burning in chest, dizziness, nausea/vomiting, fever sensation and chills” and was discontinued from the study).

Out of 82 lost to-follow-up subjects, contact with 59 was unsuccessful, and 23 subjects stated that they would not send in the diary. A minimum of 5 attempts were made by phone in addition to at least 1 letter/postcard per subject to gain a follow-up information.

Comments:

It is not clear from the protocol if the study was considered completed when the subject returned at least one or all of the diaries given to him/her. There was a relatively reasonable rate (89%) of study completion. The most common reason for discontinuation (9.6% of the purchase population) from the study was lost to follow-up. Sufficient attempts were made to reach those subjects.

Protocol Deviations

Minor protocol deviations were found but were deemed unlikely to bias the study outcome. Therefore, no data exclusions resulted from these deviations.

Study Centers 2 and 3 (Drs. Moore and Senzatimore, respectively) exceeded the protocol-stipulated recruitment limit of 180 subjects, but did so with the permission of the sponsor and coordinating investigator.

Comment:

Most of the deviations included follow-up visit (Visit 2) earlier (1 to 20 days) or later (1 to 13 days) than specified (14 days after the 56 day use period) under the protocol.

Data Sets Analyzed/Determination of Product Appropriateness to Use

All subjects who took at least one dose of study medication as indicated in their returned diaries were used in the analyses/summaries of dosing behavior. This included the consumer behavior summaries relative to dosing instructions as well as number of dosing days, tablets taken, etc. Of the 762 subjects who returned one or more diaries, 4 subjects

returned blank diaries while 758 returned diaries indicating product usage. Thus, the analyses summarizing behavior related to dosing instructions is based on these 758 subjects.

For the self-selection summaries, the **primary population** (N=770) consisted of those subjects who used study medication (N=758) plus those subjects who did not participate based on study-related criteria (N=12) (i.e., providing consent, underage, pregnant, and previous study participation). The **secondary population** for the self-selection summaries is comprised of all subjects who participated in the self-selection interview and selected the drug as appropriate to use, whether or not they purchased Prilosec1 (N=1251). The consumer reasons for self-selecting the drug “appropriate” to use were classified by the sponsor into pre-specified non-inclusive response categories. Table 4 shows a distribution of subjects in primary and secondary populations by the reason for self-selection categories:

Table 4. Summary of Consumer Reasons Why Appropriate to Use

Reasons Why Appropriate to Use	Primary Population N=770	Secondary Population N=1251
	N (%)	N (%)
I get frequent heartburn	102 (13%)	161 (12.9%)
I want to prevent heartburn	68 (9%)	122 (9.8%)
I'm familiar with the drug and/or had previously tried Prilosec1	179 (23%)	261 (20.9%)
Other heartburn medications are not effective enough	104 (14%)	147 (11.8%)
It has convenient dosing / 24-hour duration	151 (20%)	235 (18.8%)
Other	272 (35%)	475 (38.0%)

Total of 384 (31%) subjects elected not to participate in the use portion of the study even though they had determined the product was appropriate for them to use. The following are the reasons (subjects could list multiple reasons) for declining the participation:

- 115 (30%) study participation would not be convenient,
- 104 (27%) I don't like to try new medications without my doctors approval
- 32 (8%) I am happy with my current medication,
- 19 (5%) the product is too expensive,
- 5 (1%) I don't use medications or only use natural remedies, and
- 113 (29%) had other reasons for not participating.

The one subject who attempted to enter the trial while pregnant (Subject 020138) was a 34-year-old Black female who is a manager/administrator with a college degree. She had a history of frequent heartburn (4–5 days per week) for greater than 5 years, and had been in contact with her doctor and received a prescription for Prevacid within the past year. She had a history of taking Prilosec, and listed Prevacid and Synthroid as her current medications. She listed one contraindicated condition (sweating, shortness of breath or lightheadedness) for which she had consulted her doctor and received a prescription. She was also currently under evaluation by her doctor for unexplained nausea. When study

personnel asked the subject if she was pregnant, she answered ‘yes’. This is the first pregnant female that has attempted to enter a use study/take Prilosec1 in the all of the previous use studies, totaling approximately 2000 subjects.

Demographic and Baseline Characteristics

Table 5 summarizes demographics for those subjects who agreed to participate (enrolled population, N=1301) and for those who used the study medication (treated population, N=758). Table 6 summarizes demographics for the secondary population by the study center.

Table 5. Demographic Characteristics of Treated and Enrolled Populations

		Treated (N=758)	Enrolled (N=1301)*
Gender	Female	449 (59%)	775 (60%)
	Male	309 (41%)	524 (40%)
Age	Mean	49	48
	St. Dev.	17.3	17.8
	Range	18-91	18-91
Race	American Indian	8 (1.1%)	15 (1.2%)
	Asian	14 (1.8%)	26 (2.0%)
	Caucasian	530 (69.9%)	849 (65.3%)
	Black	105 (13.9%)	234 (18.0%)
	Hispanic	78 (10.3%)	139 (10.7%)
	Multi-Racial/Other	23 (3.0%)	35 (2.7%)
Literacy Level	REALM ≤60	60	129
	REALM >60	163	307
	Not tested	535	865

* Gender was not known for 2 subjects, age for 4 subjects, ethnicity for 3 subjects, literacy level for 4, and education for 3 subjects.

Table 6. Demographics of the Secondary Population by the Study Center*

		Center #1 N=207 (%)	Center #2 N=243 (%)	Center #3 N=273 (%)	Center #4 N=299 (%)	Center #5 N=279 (%)
Race	American Indian	2 (1.0%)	1 (0.4%)	0 (0.0%)	3 (1.0%)	7 (2.5%)
	Asian	4 (1.9%)	8 (3.3%)	3 (1.1%)	4 (1.3%)	11 (3.9%)
	Caucasian	144 (69.6%)	120 (49.4%)	253 (92.7%)	211 (70.6%)	101 (36.2%)
	Black	45 (21.7%)	104 (42.8%)	3 (1.1%)	51 (17.1%)	65 (23.3%)
	Hispanic	10 (4.8%)	4 (1.6%)	10 (3.7%)	25 (8.4%)	74 (26.5%)
	Other	2 (1.0%)	5 (2.1%)	3 (1.1%)	5 (1.7%)	20 (7.2%)
Education	< 8 grades	2 (1.0%)	1 (0.4%)	5 (1.8%)	4 (1.3%)	3 (1.1%)
	Some College	75 (36.2%)	105 (43.2%)	107 (39.2%)	82 (27.4%)	136 (48.7%)
	College	53 (25.6%)	59 (24.3%)	45 (16.5%)	58 (19.4%)	40 (14.3%)
	Grad. Degree	10 (4.8%)	9 (3.7%)	18 (6.6%)	22 (7.4%)	5 (1.8%)
	Some HS	11 (5.3%)	10 (4.1%)	13 (4.8%)	30 (10.0%)	8 (2.9%)
	HS Diploma	56 (27.1%)	54 (22.2%)	77 (28.2%)	94 (31.4%)	83 (29.7%)
	Post Graduate	0 (0.0%)	4 (1.6%)	7 (2.6%)	9 (3.0%)	3 (1.1%)
Literacy Level	REALM ≤ 60	13 (6.3%)	19 (7.8%)	23 (8.4%)	42 (14.0%)	32 (11.5%)
	REALM > 60	55	41	69	86	56
	NA	138	182	180	171	190

* A total number in each column does not add up to 100% because some of data were missing

Of the total treated subjects 449 (59%) were female and 309 (41%) were male, ranging in age from 18 to 91 years with a mean age of 49 years. The majority (70%) of the subjects

were Caucasian, 14% were Black, 10% were Hispanic, and 6% made up other races. Of the subjects who dosed, 228 (30%) indicated that their highest education consisted of a high school diploma, GED or below, and 530 (70%) subjects indicated that they had completed at least some college. The REALM test scores revealed that of those subjects that were tested (n=223), 60 were categorized as low literate (scored ≤ 60). In terms of occupations, 29% indicated their occupation was technical or professional, 15% were managers or administrators, 10% were sales workers, and all other occupations occurred at a rate of less than 10%.

Comments:

Low literacy population consisted only 7.9 % (n=60) of the total treated population. There were some demographic differences between the centers. In particular, the study center #2 (Atlanta, GA) had the highest number of African Americans (43%), and study center #3 (West Palm, FL) had the highest number of Caucasians (93%). Recruitment of the subjects with a low literacy level (REALM ≤ 60) also differed (6.3 to 14%) by the center, with the highest being at the center #4 (Trumbull, CT) and the lowest at the center #1 (Vernon, CT).

Heartburn History

Table 7 shows a summary of heartburn history for treated (primary) and self-selection (secondary) populations. Most subjects who used the study medication experienced more than one year of heartburn (91%). Three hundred and forty-seven (46%) subjects experienced heartburn for longer than 5 years. A total of 327 (43%) subjects experienced heartburn 6–7 days per week (n=327), while 67 (9%) subjects had heartburn one or less days per week.

Table 7. Summary of Heartburn History (Primary and Secondary Populations)

Heartburn History		Primary Population N=758	Secondary Population N=1251*
Duration	≤ 3 months	15 (2.0%)	29 (2.3%)
	Over the past 4-12 months	57 (7.5%)	99 (7.9%)
	Over the past 1-2 years	137 (18.1%)	238 (19.0%)
	Over the past 3-5 years	202 (26.6%)	314 (25.1%)
	Longer than for the past 5 years	347 (45.8%)	567 (45.3%)
Frequency	≤ 1 day a week	67 (8.8%)	169 (13.5%)
	2-3 days a week	257 (33.9%)	425 (34.0%)
	4-5 days a week	107 (14.1%)	164 (13.1%)
	6-7 days a week	327 (43.1%)	489 (39.1%)
At any time over the past year have you talked to a HCP about how to treat your heartburn?	Yes	367 (48.4%)	578 (46.2%)
	No	391 (51.6%)	669 (53.5%)
If “No”, when was the last time, if ever, you talked to a HCP about how to treat your heartburn?	1-2 years	62 (15.9%)	98 (14.6%)
	3-5 years	33 (8.4%)	57 (8.5%)
	> 5 years	31 (7.9%)	53 (7.9%)
	Never	265 (67.8%)	461 (68.9%)

* Some numbers in the Secondary Population were missing, therefore, percentages in a certain subgroups do not add up to 100%.

Prior Therapies

Six hundred eighty six (91%) of the subjects who took the study medication had used an OTC heartburn medication within the past year. Out of the subjects who took study medication, 367 (48%) had contacted their healthcare provider within the past year concerning treating their heartburn. An additional 17% (n=126) of subjects had contacted their healthcare provider at anytime prior to one year ago about heartburn.

Overall, 303 (40%) of subjects indicated having used a prescription medication for their heartburn within the past year, and another 87 (11%) subjects had been given a prescription for heartburn at any time longer than one year ago. Of those with prescriptions, 129 (43%) had used Prilosec within the past year; other PPIs prescriptions cited were Prevacid (86 subjects (28.4%)), and Protonix (18 subjects (5.9%)). Of the subjects who previously had used a prescription medication for their heartburn, 150 (50%) had used the medicine 6–7 days per week.

Comments:

The study results show that the majority of consumers who self-selected and used the product, suffered from long-standing and frequent heartburn.

The label used in the study states: “Notify your doctor if you have had heartburn for 3 months or longer without talking to your doctor”. The results of the study show that 98% of subjects (743 out of 758) who used the drug had heartburn symptoms for more than 3 months, and less than half of them (367, 48%) have spoken to their physician within the last year, and 265 (35%) subjects haven’t spoken to a health care provider at all.

The data of the study show that Prilosec1 is likely to be used for episodic heartburn. There were total of 67 (9%) subjects of the primary population with episodic heartburn (≤ 1 day a week). This number is even higher in the secondary population, where 169 (13.5%) subjects were having infrequent heartburn. These subjects should have been treated as self-selection failures.

Contraindicated Symptoms

A total of 62 (8.2%) out of 758 treated subjects stated that they have at least one of the contraindicated symptoms that they did not report to a healthcare provider. Table 8 summarizes subject responses regarding the presence of the nine contraindicated symptoms on the label. The three symptoms with the highest incidence of occurrence not previously reported to a healthcare provider (HCP), include “sudden increase in heartburn with sweating, shortness of breath, or lightheadedness” (8%), “sudden increase in heartburn with nausea/vomiting” (4%), and “chest pain” (2%).

Table 8. List of the Contraindicated Symptoms Not Previously Reported to a HCP

Symptom/Condition not previously reported to a HCP	N (%)
Trouble swallowing	8 (1.1%)
Unexplained weight loss	2 (0.3%)
Wheezing, chronic cough or hoarseness	10 (1.3%)
Chest pain	16 (2.1%)
Tarry/black bowel movement	2 (0.3%)
Vomiting blood	0 (0.0%)
Sudden increase in heartburn with nausea/vomiting	29 (3.8%)
Sudden increase in heartburn with pain spreading to arms, neck or shoulder	13 (1.7%)
Sudden increase in heartburn with sweating, shortness of breath, or lightheadedness	60 (7.9%)

Concomitant Medications

The majority (n=686, 90.5%) of the treated subjects used some kind of OTC heartburn medication within a year prior to the participation in the study, and 40% (n=303) used a prescription heartburn medication. Therapies taken during the course of the study as well as those medications listed as “ongoing” from the pre-study medications are included. This assumes a worst-case scenario because all “ongoing” medications were assumed to have been taken throughout the course of the study. The medications with the highest subject incidence included Tums (30%), Rolaids (13%), aspirin (12%), and Tylenol (12%). All other concomitant medications occurred at a reporting rate less than 10% (including all H2RAs).

Comments:

Data from the study suggest that it is likely that Prilosec will be used by subjects with contraindicated symptoms. A total of 8.2% (n=62) of the total treated population had those symptoms and selected to use Prilosec despite the warnings on the label.

The proposed label states: “Do not use with other acid reducers.” The information on the use of concomitant medications is not useful. It does not provide any information who needed to take a back up medication or why. Medications used prior to the enrollment into the study as well as during the study were lumped together. Four out of five previously conducted actual use studies by the sponsor had collected information on concomitant use of other heartburn medications. Data from those studies showed that, in

addition to omeprazole, 11-20% of people were taking antacids, 2-19% H2RAs, and up to 3% PPIs.

Self-Selection

The pre-specified primary parameter for determining correctness of self-selection was to meet all 6 individual criteria (i.e., experienced heartburn ≥ 2 days/week, were ≥ 18 years old, were not pregnant/lactating, were not allergic to omeprazole, had no contraindicated symptoms that were not reported to a healthcare provider, and were not taking any contraindicated medications without notification to a healthcare provider). Using this definition, 642 (83%) out of 770 subjects in primary population and 961 (76%) out of 1251 subjects in secondary population selected the study medication as “appropriate” to use. Summary of correct self-selection rates by demographics and study centers is presented in Table 9.

Table 9. Summary of Corrects Self-Selection Rates by Subgroups

		Primary Population (N=770) N (%)	Secondary Population (N=1251) N (%)
Gender	Female	386/457 (85%)	577/740 (78%)
	Male	256/313 (82%)	384/511 (75%)
Race	Caucasian	461/538 (86%)	653/815 (80%)
	Non-Caucasian	181/232 (78%)	308/435 (71%)
Age	< 65 years	485/593 (82%)	742/980 (76%)
	≥ 65 years	157/176 (89%)	218/266 (82%)
Study Center	Vernon, CT	94/121 (79%)	156/203 (77%)
	Atlanta, GA	104/149 (70%)	151/241 (63%)
	West Palm, FL	177/197 (90%)	218/262 (86%)
	Trumbull, CT	134/158 (85%)	206/275 (75%)
	Modesto, CA	132/145 (91%)	224/270 (83%)
Literacy Level	REALM ≤ 60	46/61 (75%)	78/118 (66%)
	REALM > 60	590/703 (84%)	871/1118 (78%)

Comments:

Overall, the correct self-selection rate was 83% for the primary population and 76% for the secondary population. Correct self-selection rates were higher overall in the primary vs. the secondary population, and in subgroups. The sponsor elected to use, as the primary self-selection population, those subjects who selected to use the product. This was a population, that had already gone through the self-selection phase, and not only self-selected to buy and use the drug, but actually made a decision to agree to participate in the study. This population is acceptable for the analyses of safety and compliance with dosing directions, but not as a primary population for the analyses of self-selection. The primary self-selection population should be those subjects who participated in the self-selection interview, prior to actually using the product.

Data also show that correct self-selection rates varied when analyzed by race, literacy level, and study center. Lower correct self-selection rates were seen in non-Caucasians and in the low literacy group. One study center (Atlanta, GA) had the lowest self-selection rate. The only difference in demographics of the enrolled population at this

center was higher percentage of blacks (43%) compared to the other centers (ranged from 1 to 23 %). Literacy level of the participants of the same center was actually higher than that of the other sites. Seventy five (75%) percent of the participant at the center #2 had at least some of the college education compared to the other centers, where subjects with some college education comprised from 57 to 68 %.

Compliance to Dosing Directions and Associated Behaviors

Table 10 shows consumer behavior information relative to dosing instructions for all subjects who took the study medication.

Table 10. Consumer Compliance with the Labeled Directions (Treated Population)

Compliance with Dosing Directions	N=758 (%)
Compliant with 3 label use directions	478 (63%)
Not compliant with 3 label use directions	280 (27%)
<ul style="list-style-type: none"> • Exceeded 1 tablet per dose 	31 (4%)
<ul style="list-style-type: none"> • Exceeded 1 dose per day 	69 (9%)
<ul style="list-style-type: none"> • Exceeded 14 consecutive days 	23 (3%)

Of the total 758 subjects 478 (63%) took study medication as it directed on the label: one dose every day for 14 days.

Subjects were considered compliant with the 14-day dosing regimen if they:

- took between 11 and 14 doses of study medication in an 11- to 17-day period, or
- contacted a physician or supporting healthcare provider if they exceeded 14 doses.

Using these criteria, 586 (79%) of the subjects were compliant with the dosing regimen.

Compliance rates with dosing directions by subcategories are listed in Table 11 below.

Table 11. Compliance with Label Use Directions by Subcategories

		Compliance rates
Gender	Female (N=449)	81%
	Male (N=309)	77%
Race	Caucasian (N=530)	82%
	Non-Caucasian (N=228)	72%
Age	< 65 years (N=594)	79%
	≥ 65 years (N=163)	82%
Study Center	Vernon, CT (N=119)	71%
	Atlanta, GA (N=147)	76%
	West Palm, FL (N=192)	82%
	Trumbull, CT (N=158)	77%
	Modesto, CA (N=142)	88%
Literacy Level	REALM ≤60 (N=60)	73%
	REALM >60 (N=693)	80%
History of HB frequency	≤ 1 day/week (N=67)	51%

	2-3 days/week (N=257)	76%
	4-5 days/week (N=107)	85%
	6-7 days/week (N=327)	85%
History of HB duration	≤ 3 months (N=15)	73%
	4-12 months (N=57)	75%
	1-2 years (N=137)	78%
	3-5 years (N=202)	79%
	> 5 years (N=347)	80%

A total of 744 subjects took study medication and were available for Visit 2. Out of those 680 (91.4%) took one tablet a day, 707 (95%) took for no more than 14 days, and 532 (71.5%) took for less than 14 consecutive days. Reasons why some subjects were not compliant with those dosing directions are summarized in Table 12. Numbers and percentages in each category are out of a total population (N=744). Subjects could have more than one response, therefore, a total number in each column may exceed a number of subjects available for Visit 2.

Table 12. Reasons for Not Following Dosing Directions (N=744)

Reasons	Took more than 1 tablet a day	Exceeded 14 days	Took for less than 14 consecutive days
Not Applicable	680 (91.4%)	707 (95.0%)	532 (71.5%)
Because a physician or nurse told me to use it that way	2 (0.3%)	6 (0.8%)	1 (0.1%)
Because another medical professional told me to use it that way	0 (0.0%)	0 (0.0%)	1 (0.1%)
Because a friend or relative told me to use it that way	2 (0.3%)	0 (0.0%)	1 (0.1%)
Because I'm accustomed to using HB medications that way	14 (1.4%)	11 (1.5%)	38 (5.1%)
Because I know that Prilosec1 is used that way	NA	4 (0.5%)	0 (0.0%)
Because I forgot to take it	NA	NA	24 (3.2%)
Other	49 (6.6%)	17 (2.3%)	161 (21.6%)
Missing	0 (0.0%)	1 (0.1%)	1 (0.1%)

One subject (040099) took one-half tablet in the morning and one-half tablet in the evening on one day. This subject's tablet count was set to one (20.6 mg) taken on one occasion for the purposes of table presentation.

When the subjects who took study medication and were available for Visit 2 (N=744) were questioned about why they used Prilosec1 on more than 14 total days (total of 23 subjects), 11 subjects stated it was because they were accustomed to taking heartburn medications that way; 6 subjects stated because a healthcare provider (HCP) had told them to take it that way; 4 stated because they know that prescription Prilosec1 is taken that way; 17 had other reasons. The question was not applicable for subjects who did not exceed 14 days of dosing (95% of the population). Similarly, when subjects were questioned about taking Prilosec1 on fewer than 14 consecutive days, 38 subjects stated it was because they were accustomed to taking heartburn medications that way; 24 subjects stated because they forgot to take it; 3 stated because someone (friend, HCP, etc.) told

them to take it that way; 161 had other reasons. The question was not applicable for subjects who did not dose less than 14 consecutive days (72% of the population).

Of the 586 (77%) subjects who took between 11 and 14 doses of study medication in an 11–17 day period, 89 (15%) reported consulting HCP during the 2-month use period, 102 (17%) consulted with HCP between the end of the use study period and the 3-month follow-up, 58 (10%) had a scheduled appointment to discuss heartburn, 399 (68%) of these subjects had previously discussed their heartburn with their HCP, and 242 (41%) had prescription heartburn medication experience.

Out of all subjects who dosed with study medication, 69 (9%) took less than 11 total doses. A majority (n=41, 59%) of these subjects took their doses in less than 18 days. Of these 69 subjects, between 6 and 8 (9%–12%) subjects either consulted a healthcare provider during the 2-month study, after the 2-month study, or had an appointment scheduled to discuss heartburn. Forty-four (64%) of these subjects, however, had previously discussed heartburn with their healthcare provider, and 26 (38%) had prescription heartburn medication experience.

Sixty-six (9%) subjects took between 11 and 14 doses across more than 17 days. Most of these (n=47, 71%) subjects took their doses over 30 days. Of these 66 subjects, 6–7 (9%–11%) subjects either consulted a healthcare provider during the 2-month study, after the 2-month study or had an appointment scheduled to discuss heartburn. Forty-five (68%) of these subjects, however, had previously discussed heartburn with their healthcare provider, and 26 (39%) had prescription heartburn medication experience.

Out of the 758 subjects who took study medication, 34 (5%) took more than 14 doses of study medication. Of the 34 subjects who took more than 14 doses, 14 (41%) contacted a healthcare provider within the 2-month study, 10 (29%) contacted a healthcare provider between the 2-month study and the 3-month follow-up, 5 (15%) had an appointment scheduled with their healthcare provider to discuss heartburn, 27 (79%) had previously discussed heartburn with their healthcare provider, and 19 (56%) of these subjects had prescription heartburn medication experience.

Four hundred eighty six (486 (64%)) subjects took study medication for a maximum of 14 consecutive days. Twenty-three (3%) subjects exceeded 14 consecutive days of treatment, and 249 (33%) took for less than 14 days. In terms of minimum number of dosing days, 159 (21%) subjects took at least one isolated dose of study medication through the 2-month study period.

Comments:

The sponsor did not have a prespecified compliance rate prior to the study initiation. Overall compliance with all three labeled directions in this study was 63%. In five previously conducted Prilosec actual use studies, compliance ranged from 58 to 83%. The highest rate was achieved in the study where subjects were dispensed fewer tablets (12 tablets for a 10 day labeled directions of use). The compliance rate in this study increases significantly (from 63% to 79%), when the sponsor analyzes compliance with the 14-day regimen, by subjects taking between 11 to 14 doses of study medication in an

11-17 day period. It is not clear, why the sponsor included this range of “acceptable” dosing duration.

One of the Agency’s concerns raised in the non-approvable action letter was that people would exceed a maximum duration of therapy specified on the label without contacting their physician. The methodology of this study does not allow us to address this concern. The study personnel did not confirm the consultation with a physician or other health care provider. There is no evidence that those subjects talked to their HCP about the duration of Prilosec1 therapy for their heartburn. The sponsor is also trying to imply that the history of use of any Rx heartburn medicine somehow justifies non-compliance with the use of Prilosec1.

The following information would have been useful to obtain: if subjects talked to their HCP about the use of Prilosec1, or if they previously used Prilosec, but not the other Rx heartburn medicine.

The consistency rates for the 14-day regimen varied among subcategories. The rates were lower in non-Caucasians vs. Caucasians, and in subjects with low literacy level vs. higher literacy level. The lowest compliance rate was in subjects with infrequent heartburn. This subgroup should have been treated as a self-selection failure. The warning on the label should clearly state that Prilosec1 is not for people with episodic heartburn. The label also should not state that this drug provides a prevention of symptoms for 24 hours.

Analyses of the data on per dosing day basis and per dosing occasion basis, do not provide any additional consumer behavior information, and therefore, were not included in this review. All three labeled use directions (take one tablet per dose, one dose a day for 14 consecutive days) should be accounted together for the evaluation of compliance.

Purchasing Patterns

In total, 705 (93%) subjects purchased 1 carton of Prilosec1, 19 (3%) purchased 2 cartons, 8 (1%) subjects purchased 3 cartons and 26 (3%) purchased 4 cartons of study medication. Forty-eight subjects (6%) returned to the retail site after the initial visit to buy additional medication. When all subjects are considered, regardless of whether the subjects dosed with study medication (N=854), 799 (94%) subjects purchased only 1 carton, 20 (2%) purchased 2 cartons, 8 (1%) purchased 3 cartons and 27 (3%) purchased 4 total cartons.

Behavior of subjects who purchased >1 carton of medication

Fifty three (53) subjects (7%) purchased more than 1 carton (14 tablets) of study medication during the course of the study. Of these 53 subjects, 35 subjects (66%) took more than 14 tablets: 17 subjects took 15–28 tablets and 18 subjects took 29–56 tablets. All subjects who purchased more than one carton of study medication were subjects with frequent heartburn, many (38) of them reporting daily heartburn (72%). The majority (40) of this population had previously consulted a physician about their heartburn (75%). Additionally, 27 of the 53 subjects (51%) held a current or prior prescription for heartburn medications.

Comment:

Seven percent (7%) of subjects, who purchased more than one carton, may be an underestimate. If Prilosec1 will become available to OTC consumers, there is no safeguard to prevent from repurchasing the drug.

Doctor/Healthcare Provider Consultation and 3-Month Follow-up Questionnaire

Subjects could contact their healthcare provider at more than one point. Of a total of 758 subjects 119 (16%) contacted their healthcare provider during the 2-month study, 126 (17%) contacted them between the end of the 2-month study and the 3-month follow-up, 76 (10%) had a doctor's appointment scheduled to discuss heartburn, 315 (42%) subjects had used a prescription heartburn medication within the past year, 370 (49%) subjects had discussed their heartburn with a healthcare provider within the past year, 87 (12%) had received a prescription medication for heartburn over a year ago, and 126 (17%) subjects had a discussion with their healthcare provider over one year ago. Overall, 565 (75%) subjects had consulted a physician about their heartburn prior to, during, or soon after using Prilosec1.

Comments:

One of the Agency's concerns raised in the non-approval action letter was that people would exceed a maximum duration of therapy specified on the label without contacting their physician.

The rate of consultation with a physician (75%) seems high. However, the methodology of the study for this outcome is deficient. Specific information regarding the nature of the interaction between consumer and HCP was not collected and the contact itself was not confirmed by the study personnel. There were many variables incorporated into this concept of consultation with a physician. Subjects were counted as having had a consultation with HCP if they stated that:

- *they have spoken to their HCP about their heartburn (prior, during or after the study), or*
- *if they have taken any prescription heartburn medication (specific information on the drugs was not collected), or*
- *if they had an appointment scheduled in the future.*

Label states: "Notify your doctor if you have had heartburn for 3 months or longer without talking to your doctor". At the time of enrollment, 265 (35%) subjects out of the total treated population (n=758) stated that they had never spoken to a physician about their heartburn. During the study, 54 (20%) out of those 265 subjects did have doctor consultation. The remaining 211 subjects (28% of the total treated population) did not have a consultation with a health care provider.

3-month Follow-up Questionnaire (Return of Frequent Heartburn)

Out of a total of 649 who were available for 3-month follow-up 276 (43%) subjects did not have their frequent heartburn return after they stopped taking Prilosec1. Of those who did have their frequent heartburn return (n=373), 171 (46%) subjects took an antacid heartburn medication; 99 (27%) took a prescription heartburn medication; 78 (21%)

subjects took an OTC acid reducer; 75 (20%) subjects consulted a healthcare provider; 36 (10%) changed their lifestyle; 29 (8%) did something else; and 22 (6%) did not do anything after their frequent heartburn returned. Subjects' responses could fit into more than one category.

Overall Assessment of Study Medication

Overall, 93% of the study population rated the product as Good, Very Good or Excellent: 48% of subjects rated the study medication Excellent, 34% of subjects rated the study medication Very Good, 12% of subjects rated the study medication Good, 3% rated the study medication Fair, and 2% of subjects rated the study medication Poor.

Comments:

This three-month telephone follow-up was not a part of the original study protocol. The study was initiated in July 2001. Three months into the study, the amendment to the original protocol was made by the sponsor. This amendment allowed the sponsor to gather information on subjects' further interaction with a physician, and about the possible recurrence of heartburn after a discontinuation of the study medication. This amendment is acceptable. The responses to the follow-up questionnaire showed that more than half (58%) of the subjects available for follow-up had their heartburn return, and only 20% of those contacted their health care provider. If Prilosec1 will be available for OTC purchase and use, this subgroup of consumers may be migrating from the other OTC heartburn medications to Prilosec1 use.

Summary:

The objective of the Actual Use study was to investigate how consumers use omeprazole magnesium (Ome-Mg) under proposed label instructions in naturalistic OTC conditions. This was a multi-center, open-label consumer use study. A total of 1301 subjects participated in the self-selection part of the study, and of those 1251 (96%) stated that Prilosec1 is appropriate for them to use. A total of 863 subjects agreed to participate in the study; 854 bought the study medication; and 782 completed the study. The treated population (subjects who purchased and used the drug) consisted of 758 subjects. The demographically enrolled population (N=1301) was reasonably balanced in terms of age and ethnicity, and representative of the general U.S. population. There were 60% female, 40% male, ranging in age from 18 to 91 years with a mean age of 48 years. The majority (65%) of the subjects were Caucasian, 18% were Black, 11% were Hispanic, and 6% made up other races. Low literacy group (REALM \leq 60) consisted only 9.9% of the enrolled and 7.9% of the treated populations.

Overall, the correct self-selection rate was 83% for the primary population and 76% for the secondary population. Correct self-selection rates were lower overall in the secondary vs. the primary population. Data also show that correct self-selection rates varied when analyzed by race, literacy level, and study center. Lower correct self-selection rates were seen in non-Caucasians and in the low literacy group. There were a total of 13.5% of self-selection (secondary) and 9% of treated (primary) population that suffered from infrequent heartburn (\leq 1 day a week), and therefore inappropriately self-selected themselves. This shows that Prilosec1 is likely to be used for episodic occasional heartburn. Data from the study also suggest that it is likely that Prilosec will

be used by subjects with contraindicated symptoms. A total of 8.2% of the total treated population had those symptoms and selected to use Prilosec1 despite the warnings on the label.

Overall, compliance with the three label directions (take 1 tablet a day, every day for 14 days) was achieved by 63% of the treated population (N=758). Twenty three (3%) subjects exceeded 14 consecutive days of treatment, and 249 (33%) took for less than 14 days.

The study results show that the majority of consumers who self-selected and used the product, suffered from long-standing and frequent heartburn. The proposed label states: "Notify your doctor if you have had heartburn for 3 months or longer without talking to your doctor". The results of the study show that even though the majority of the subjects (98%) who used the drug had heartburn symptoms for more than 3 months, only half of them (48%) had spoken to their physician within the last year, and 265 (35%) subjects had not spoken to a health care provider at all. Seven percent (7%) of subjects purchased more than one carton of Prilosec1 during the study, which may be an underestimate of use. The responses to the follow-up questionnaire (3 months after the study) showed that more than half (58%) of the subjects available for follow-up had their heartburn return, and only 20% of those contacted their health care provider. If Prilosec1 will be available for OTC purchase and use, this subgroup of consumers may be migrating from the other OTC heartburn medications to Prilosec1 use, without consultation with a physician. Given current medical practice, in which most practitioners recommend initial empirical trial of 4-8 weeks of PPIs for the treatment of frequent heartburn prior to invasive procedures, 2-week duration of OTC treatment may be acceptable.

Conclusions:

- 1. One of the major deficiencies of the study is that it did not collect information on the reasons why subjects were taking Prilosec1, for prevention vs. relief or other. The second major deficiency of the study was that information on the consultation with HCP was not confirmed by the study personnel.*
- 2. The study was of a short duration and did not address the issues of repeat courses of self-medication, return of the frequent heartburn etc.*
- 3. Overall, the correct self-selection rate was 83% for the primary population and 76% for the secondary population.*
- 4. The label states: "Notify your doctor if you have had heartburn for 3 months or longer without talking to your doctor". The results of the study show that almost all subjects (98%) who used the drug had heartburn symptoms for more than 3 months, and only half of them (48%) had spoken to their physician within the last year, and 265 (35%) subjects had not spoken to a health care provider at all.*
- 5. The data show that Prilosec1 is likely to be used for episodic heartburn. There were total of 9% of subjects of the treated population and 13.5 % of self-selection population with episodic heartburn (≤ 1 day a week), which is an underestimate.*
- 6. Data from the study suggest that it is likely that Prilosec will be used by subjects with contraindicated symptoms. A total of 8.2% of the total treated population had those symptoms and selected to use Prilosec1 despite the warnings on the label.*

7. *At the time of enrollment, 265 (35%) subjects out of the total treated population (n=758 stated that they had never spoken to a physician about their heartburn. During the study, 54 out of those 265 subjects did have doctor consultation. The remaining 211 subjects (28% of the total treated population) never had a consultation with a health care provider.*
8. *Overall compliance with all three labeled use directions (take 1 tablet a day, every day for 14 days) in this study was 63%. The compliance rate in this study increases significantly (from 63% to 79%), when the sponsor analyzes compliance with the 14-day regimen, by subjects taking between 11 to 14 doses of study medication in an 11-17 day period.*
9. *The responses to the follow-up questionnaire showed that more than half (58%) of the subjects available for follow-up had their heartburn return, and only 20% of those contacted their health care provider.*

VII. Integrated Review of Safety

The global post-marketing experience of omeprazole had been reviewed by HFD-180 at the time of original NDA submission. This review will cover safety data submitted by the sponsor in their February 12, 2002 submission. Safety data submitted to this NDA was retrieved from the following sources:

1. Safety data gathered from the Actual Use Study 007.
2. International post-marketing experience with Ome-Mg from January 1, 2000 through June 30, 2001.

Omeprazole was first marketed for clinical use in Europe in 1988, and in the United States in 1989. Currently, the omeprazole magnesium (MUPS) tablet is currently available by prescription in 33 markets globally. To date, the MUPS tablet is available as an OTC product in Sweden only.

1. Review of Safety Data from the Actual Use Trial 007.

Safety was investigated by evaluating all reported adverse events (AEs). Verbatim terms on the CRFs were coded to preferred terms and related body systems using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) mapping system. All reported AEs were summarized by the number of subjects reporting AEs, intensity (where given), relationship to study medication, and body system. Extent of exposure, as characterized by the number of dosing days, was summarized using descriptive statistics. All subjects who took any study medication or who reported an AE were included in the safety analysis.

A total of 759 subjects were exposed to Ome-Mg 20 under actual use conditions. The extent of exposure for the 758 study participants is displayed in Table 13. A total of 37 subjects (4.8%) took more than 14 tablets; 19 subjects took between 15 and 28 tablets; and 18 subjects took between 29 and 56 tablets. Note, 2 subjects (030267 and 020234) are included in these numbers as having taken 18 and 15 tablets, respectively, because that is what was reported in their diary; however, each subject only purchased one carton

(14 tablets) of study medication. Additionally, 56 subjects took a total of 10 tablets or less.

Table 13. Summary of Extent of Exposure

		Treated Subjects (N=758)
Number of Dosing Days	Mean	14.2
	Std. Deviation	6.02
	Minimum-Maximum	1-56
Number of Dosing Occasions	Mean	14.3
	Std. Deviation	5.99
	Minimum-Maximum	1-56
Number of Tablets Taken	Mean	14.4
	Std. Deviation	5.93
	Minimum-Maximum	1-56

Overall, 239 subjects (31.5%) reported 602 adverse events (AEs). Table 14 displays the overall summary of AEs.

Table 14. Summary of Adverse Events

		Subjects who used study medication (N=759)
Subjects	With any AE	239 (31.5%)
	With SAEs	1 (0.1%)
	Withdrawal due to AEs	1 (0.1%)
	Deaths	0
Number of AEs per Subject	Reporting 0 AEs	520 (68.5%)
	Reporting AE	96 (12.6%)
	Reporting >1 AE	143 (18.8%)
AE Relationship to Study Medication	Unlikely	467 (77.6%)
	Possible	107 (17.8%)
	Probable	25 (4.2%)
	N/A	3 (0.5%)
AE Intensity	Mild	194 (32.2%)
	Moderate	292 (48.5%)
	Severe	116 (19.3%)
	Total Number of AEs	602 (100.0%)

Table 15 presents AEs by body system. The most frequently reported AEs in this study were in Body as a Whole category, followed by Digestive and Respiratory systems.

Table 15. Adverse Events by Body System

Body System	Subjects who used study medication (N=759)	
	Subjects N (%)	AEs
Body as a Whole	180 (23.7%)	354
Cardiovascular	7 (0.9%)	10
Digestive	101 (13.3%)	156
Metabolic	5 (0.7%)	6
Musculoskeletal	13 (1.7%)	15
Nervous	19 (2.5%)	22
Respiratory	22 (2.9%)	24
Skin	2 (0.3%)	2
Special Senses	4 (0.8%)	5
Urogenital	7 (0.9%)	8

Table 16 displays the most common AEs by COSTART terms in decreasing order of overall incidence >1%.

Table 16. Most Common Adverse Events by COSTART Term

COSTART Term	Safety Subjects (N=759)		
	N of Subjects	%	N of AEs
Total	239	31.5%	602
Headache	136	17.9%	272
Diarrhea	29	3.8%	41
Abdominal Pain	24	3.2%	29
Pain	19	2.5%	26
Back Pain	16	2.1%	21
Nausea	14	1.8%	25
Infection	13	1.7%	15
Flatulence	12	1.6%	23
Dyspepsia	10	1.3%	10
Constipation	9	1.2%	10

The most commonly reported AE was headache (17.9%), followed by diarrhea (3.8%), and abdominal pain (3.2%).

Deaths

No deaths were reported in this study.

Other Serious Adverse Events

There was one serious adverse event reported. The narrative of the case is given below.

Subject 020173, a 58-year old Caucasian female, had a medical history significant for a dissecting aorta, hypertension, and hypothyroidism. The subject began Ome-Mg 20 therapy on the morning of August 19, 2001 and developed severe chest pain associated with dizziness, nausea/vomiting, and chills on August 20, 2001. The subject was hospitalized on August 20, 2001, to rule-out myocardial infarction. The subject reported intermittent chest pain for 2 weeks prior to the August 20, 2001, episode of chest pain. The subject discontinued study medication during the two-day hospitalization. The subject was discharged on August 22, 2001. All tests conducted in the hospital were negative and there was no change in the subject's medications consisting of Toprol, Zocor, Imdur, Norvasc, and Synthroid. The chest pain AE was determined to be unlikely related to Ome-Mg 20 treatment. The subject resumed study medication on August 23, 2001, after discharge from the hospital.

Other Significant Adverse Events

There were no other significant AEs reported in this trial.

Discontinuation Due to Adverse Events

Three subjects had AEs that resulted in discontinuation from the study.

Subject 030222 (37-year-old Caucasian male) experienced severe burning in the chest, dizziness, nausea/vomiting, fever, and chills following two days of therapy. The subject discontinued study medication the next day. All AEs resolved without intervention. The AEs were considered unlikely to be related to treatment.

Subject 010016 (47-year-old Hispanic female) initially experienced mild stomach pain, then three days later experienced a second episode of severe stomach pain. The subject discontinued treatment following the second occurrence upon the recommendation from her personal physician. The second episode of severe stomach pain resolved the same night. The AEs were considered probably related to treatment.

Subject 050194 (34-year-old Caucasian male) experienced moderate headache, diarrhea, and nausea. Two days after the AEs started treatment was discontinued. The diarrhea became severe one day after stopped treatment. All AEs were considered possibly related to treatment and resolved within seven days.

Clinical Laboratory Tests

The only clinical laboratory tests performed for this study were two self-administered urine pregnancy tests for female subjects. One test was performed on the first day of the study and the last test before the end of the study at Visit 2. One female subject who was pregnant was excluded prior to entering the study.

The subject who attempted to enter the trial while pregnant (Subject 020138) was a 34-year-old Black female who is a manager/administrator with a college degree. She had a history of frequent heartburn (4–5 days per week) for greater than 5 years, and had been

in contact with her doctor and received a prescription for Prevacid within the past year. She had a history of taking Prilosec, and listed Prevacid and Synthroid as her current medications. She listed one contraindicated condition (sweating, shortness of breath or lightheadedness) for which she had consulted her doctor and received a prescription. She was also currently under evaluation by her doctor for unexplained nausea. When study personnel asked the subject if she was pregnant, she answered 'yes'. This is the first pregnant female that has attempted to enter a use study/take Prilosec1 in the all of the previous use studies, totaling approximately 2000 subjects.

Vital Signs, Physical Findings, and Other Safety Observations

No vital signs or physical examinations were performed in this study.

Comments:

The extent of exposure to Prilosec1 was relatively short (mean of 14.2 days). Safety data from the actual use trial are consistent with Rx Prilosec1, and safety profiles from previous actual use trials. The most common adverse event reported in this study was headache (17.9%), followed by diarrhea (3.8%), and abdominal pain (3.2%). There were no unexpected or unlabeled AEs reported during this study.

2. International post-marketing experience with Ome-Mg from January 1, 2000 through June 30, 2001.

The safety data included adverse event reports for key ingredient of omeprazole and a unit dose form of MUPS tablet received by AstraZeneca from January 1, 2000 through June 30, 2001.

From first launch in February 1998 and up to December 31, 1999, 11.6 million patient treatment courses of omeprazole magnesium MUPS tablets were distributed to wholesalers. During that time period, 46 serious AEs among 27 users and 352 non-serious AEs among 192 users were reported to AstraZeneca.

For the reporting period of this safety summary of January 1, 2000 through June 30, 2001, 27 million patient treatment courses of omeprazole magnesium MUPS tablets were distributed; 109 serious AEs among 63 (60 non-fatal and 3 fatal) users and 430 non-serious adverse events among 257 users were reported to AstraZeneca.

Table 17 displays all cases per body system class presented as non-fatal (60), fatal (3), and non-serious (257) cases, respectively. A single person case may have more than one AE occurring within one, or more than one, body system class. Therefore, the numbers of AEs does not coincide with the total number of cases displayed on the table.

Table 17. Adverse Events Reported for MUPS by Body System (1/1/2000-6/30/2001)

Body System	# of Cases	Serious		Non-Serious
		Fatal	Non-Fatal	
Blood & lymphatic system disorders	11	0	4	7
Cardiac disorders	4	0	3	1
Ear & labyrinth disorders	2	0	0	2
Eye disorders	8	0	0	8
Endocrine disorders	1	0	1	0
Gastrointestinal disorders	104	0	12	92
General disorders & administration site conditions	84	0	9	75
Hepato-biliary disorders	12	1	10	1
Immune system disorders	9	0	4	5
Infections & infestations	3	0	0	3
Injury and poisoning	2	0	0	2
Metabolism and nutrition disorders	5	0	1	4
Musculoskeletal, connective tissue & bone disorders	15	0	2	13
Nervous system disorders	51	0	10	41
Psychiatric disorders	21	1	4	16
Renal and urinary disorders	3	0	1	2
Reproductive system and breast disorders	11	0	0	11
Respiratory disorders	17	0	4	13
Skin & subcutaneous tissue disorder	79	1	16	62
Vascular disorders	2	0	0	2
Total Number of Cases	320	3	60	257
Total Number of Events	539	3	106	430

Table 18 in the Appendix 1 is a summary of all non-serious and serious adverse event cases by frequency. The reports are displayed in decreasing frequency for non-serious events.

Serious (Fatal and Non-Fatal) Post-Marketing Adverse Events

A total of 63 serious adverse event (SAE) (60 non-fatal and 3 fatal) cases comprising 109 total AEs were reported for omeprazole magnesium MUPS tablets worldwide during the reporting period. A narrative of each fatal case is given below.

Case # 2000AH00903. A 70-year-old male smoker with a history of chronic obstructive pulmonary disease and decompensated heart failure was hospitalized due to vomiting blood (2-3 days), dyspnea, and progressive weight loss. Concomitant medications included theophylline, amphotericin B, amiodarone hydrochloride, furosemide/spironolactone, isopromethazine hydrochloride, tramadol hydrochloride,

budesonide and formoterol. He was treated with an infusion of omeprazole; the dyspnea continued overnight. The next day an esophago-gastro-duodenoscopy was performed which showed an axial hernia, second-degree reflux esophagitis with signs of bleeding and candida esophagitis. Treatment with amiodarone hydrochloride was maintained and omeprazole magnesium 20 mg daily was added. The next morning, the patient was transferred to the intensive care unit with suspected acute liver failure. The patient died three days later after developing acute liver failure, anuria and worsening cardiopulmonary parameters. The cause of death was reported as cardiovascular arrest due to biventricular heart failure with disseminated infarct-like lesions and extensive centrilobular liver failure. Autopsy showed heart and liver failure were of ischemic origin due to myocarditis. The reporting physician made no assessment of causality.

Case # 2001SE00377. A report of a 68-year-old female with history of a mitral valve replacement, renal insufficiency, epistaxis, pneumonia, and an allergy to nickel was received from the Centre for Documentation of Severe Skin Reaction in Germany. The patient was hospitalized for suspected sepsis and acute renal failure. Fifty-four days later, the patient was treated with omeprazole magnesium for gastric protection at which time she developed a transitional form of Stevens-Johnson syndrome with blisters and generalized, small-spotted partly confluent exanthema. Omeprazole magnesium therapy was stopped. Two days later the patient developed stomatitis, erosive oral and genital mucosa hemorrhage. The patient died 12 days later. During hospitalization, the patient was treated with approximately 30 different medications, including pantozol. The reporter assessed most of the medications, including omeprazole magnesium, as causally related.

Case # 2001SE01028. A 30-year-old male with history of an appendectomy, fracture of femur and no previous history of depression or other concomitant medication treatment was placed on omeprazole magnesium 20 mg daily for gastritis and duodenitis. The patient committed suicide twelve days later. The reporting health professional felt there was a possible relationship to omeprazole magnesium therapy.

The most common SAEs reported were dyspnea nos (4 cases), hepatic function abnormal nos (4), and 3 cases of each: abdominal pain upper, angioneurotic edema, dermatitis nos, liver function tests nos abnormal, pancytopenia, Stevens Johnson syndrome, toxic epidermal necrolysis, and vomiting nos.

Non-Serious Post-Marketing Adverse Events

A total of 430 non-serious adverse events were reported among 257 patients for omeprazole magnesium MUPS tablets

worldwide during the reporting period from January 1, 2000 through June 30, 2001. The five most common AEs reported were drug ineffective, dyspepsia, dermatitis nos, abdominal pain nos and nausea. All of the reported adverse events are currently listed on Prilosec prescription label.

Table 19 displays a dictionary comparison of the most common AEs reported to AstraZeneca as presented in the original Prilosec1 NDA, the 4-month safety update request, the August 28, 2000 Response to FDA's Request for Additional Information and the updated safety information contained in this submission for omeprazole prescription capsules and omeprazole magnesium MUPS tablets during their post-marketing life cycle.

Table 19. Dictionary Comparison of Most Common Worldwide AEs Reported to AstraZeneca for Ome-Mg MUPS Tablets and Omeprazole Prescription Capsules

	Ome-Mg MUPS Tablet 1/1/2000-6/30/2001 (MedDRA Dictionary)	Ome-Mg MUPS Tablet Launch-12/31/1999 (Astra AE Dictionary)	Omeprazole Rx Capsule Launch - 6/30/1998 (Astra AE Dictionary)
Serious (Non-Fatal and Fatal)	Dyspnea nos, Hepatic function abnormal nos, Abdominal pain upper, Angioneurotic edema, Dermatitis nos, Liver function tests nos abnormal, Pancytopenia, Stevens Johnson syndrome, Toxic epidermal necrolysis, Vomiting nos	Nephritis interstitial, Pancytopenia, Stomach pain, Abdominal pain, Abdominal discomfort	Death, Thrombocytopenia, Hepatitis, Nephritis interstitial, Fever, Interaction
Non- Serious	Drug ineffective, Dyspepsia, Dermatitis nos, Abdominal pain nos, Nausea	Lack of efficacy, Nausea, Diarrhea, Stomach pain, Headache	Non-serious AEs not reported in original NDA

There are some differences seen in the safety profile of this summary for the coding of the MUPS tablet AE reports using MedDRA dictionary as compared to the Astra AE dictionary, used for legacy safety data. The sponsor explains that differences are seen because the Astra AE dictionary is comprised of only 1900 preferred terms while the MedDRA dictionary contains over 14,000 preferred terms. In addition, death is no longer coded as an adverse event but considered an outcome, which is why death is only reported for the omeprazole prescription capsules.

Comments:

Prilosec delayed-release capsules were generally well tolerated during domestic and international clinical trials in 3096 patients. The following adverse experiences were reported to occur in 1% or more of patients on therapy with Prilosec: headache, diarrhea, abdominal pain, nausea, upper respiratory infection, dizziness, vomiting, rash, constipation, cough, asthenia, back pain, flatulence, and acid regurgitation.

Additional adverse experiences listed on the current prescription label, occurring in < 1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below for each body system. In many instances, the relationship to PRILOSEC was unclear.

Body as a Whole: Allergic reactions, including, rarely, anaphylaxis, fever, pain, fatigue, malaise, abdominal swelling.

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema.

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), (gamma)-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional: Hyponatremia, hypoglycemia, weight gain.

Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain.

Nervous System/Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia.

Respiratory: Epistaxis, pharyngeal pain.

Skin: Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme; purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis.

Special Senses: Tinnitus, taste perversion.

Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia.

Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The safety data presented in this NDA resubmission show that Prilosec I has a safety profile that is acceptable for OTC marketing. Safety of Prilosec I has been well established by clinical trials supporting its approval as a prescription product. No new

signals have appeared in the course of post-marketing surveillance attributable to either labeled use or misuse of prescription product. Post-marketing surveillance has limitations related to the nature of the reporting system. The rate of adverse events, however, may increase after the Rx-to-OTC switch, when a large uncontrolled population will be exposed to the drug, purchasing and using the drug without a learned intermediary.

VIII. Dosing, Regimen, and Administration Issues

The label proposed for the OTC marketing is presented bellow. The actual package of OTC Prilosec1 is displayed in the Appendix 2.

Active Ingredient (in each tablet) Purpose

Omeprazole magnesium 20.6 mg.
.Acid reducer
(equivalent to 20 mg omeprazole)

Uses

- for **prevention** of the symptoms of frequent heartburn for 24 hours
- only for those who suffer heartburn two or more days a week

Warnings

Allergy alert Do not use if you are allergic to omeprazole
Heartburn Warning. Heartburn can be a sign of a more serious condition. Notify your doctor if you have had heartburn for 3 months or longer without talking to your doctor.

Do not use

- with other acid reducers

Ask a doctor before use if you have:

- any of the following symptoms and have not seen a doctor
 - frequent chest pain
 - chest pain with: shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
 - trouble swallowing food
 - frequent wheezing, particularly with heartburn
 - unexplained weight loss
- These may be signs of more serious conditions. Notify your doctor.

Ask a doctor or pharmacist before use if you are taking

- warfarin (blood thinning medicine)
- phenytoin (seizure medicine)
- ketoconazole (prescription antifungal medicine)

Stop use and ask a doctor if

- stomach pain continues or worsens
- heartburn continues or returns after using this product every day for 14 days

If pregnant or breast-feeding, ask a health professional before use.

Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control center right away.

Directions

Adults 18 years of age or older

- for prevention of frequent heartburn, swallow 1 tablet with a glass of water in the morning

- take every day for 14 days

- do not continue beyond 14 days unless directed by your doctor. If your frequent heartburn continues or returns, it could be a sign of a more serious condition.

- do not take more than 1 tablet a day

- do not chew or crush the tablets

Children under 18 years of age: as a doctor

Comments:

A new proposed target population and directions for use will be addressed by reviewers in the Division of Coagulation and Gastrointestinal Drug Products (HFD-180).

The label should not state that this drug provides prevention of the symptoms of frequent heartburn for the next 24 hours. This statement is misleading. The first statement in the "Uses" section should state that this drug is for prevention of frequent heartburn (two or more days a week).

The label should state: "Do not use if you have heartburn less than twice a week."

The quantitative definition "frequent" on the proposed label, section "Ask a doctor before use...", should be deleted, because word "frequent" may have a different meaning to a different consumer.

The label states that Prilosec1 should not be taken with other acid reducers. Prilosec1 is not a relief medicine; therefore, directing consumers to a physician, if they did not get a relief, should be stated on the label. As an alternative, a statement that Prilosec1 is not intended for acute relief or prevention of heartburn, and the expectation of benefits, should be listed on the label.

IX. Use in Special Populations

The sponsor did not request marketing of Prilosec1 in subjects less than 18 years of age.

Prilosec1 is a pregnancy category C drug. Use of Prilosec1 by pregnant women has been addressed by HFD-180. Only one pregnant female tried to purchase and use Prilosec1 in

the Actual Use Study. The product should carry a pregnancy warning as specified in 21 CFR 201.63.

X. Conclusions

Experience with the already approved Prilosec1 does not suggest an unusual pattern of toxicity, either in terms of frequency or severity of adverse reactions reported.

The target population and indication for use, as well as the risk-benefit assessment of Prilosec1 as an OTC product for the treatment of frequent long standing heartburn, warrant further discussion with members of the Nonprescription and Gastrointestinal Drugs Advisory Committees.

Daiva Shetty, M.D.
Medical Officer, DOTCDP
HFD-560

Concurrence:

Appendix 1.

Table 18. Post-Marketing AEs for Ome-mg tablets Reported to the Sponsor from January 1, 2000 through June 30, 2001

	Non-Serious N=430 (%)*	Serious AEs N=109 (%)**
Drug ineffective	42 (9.8)	2 (1.8)
Dyspepsia	27 (6.3)	0 (0.0)
Dermatitis nos	21 (4.9)	3 (2.8)
Abdominal pain nos	18 (4.2)	0 (0.0)
Nausea	16 (3.7)	0 (0.0)
Diarrhea nos	13 (3.0)	2 (1.8)
Therapeutic response decreased	13 (3.0)	1 (0.9)
Urticaria nos	13 (3.0)	1 (0.9)
Dizziness (exc vertigo)	10 (2.3)	2 (1.8)
Myalgia	9 (2.1)	1 (0.9)
Pruritus nos	9 (2.1)	1 (0.9)
Abdominal pain upper	8 (1.9)	3 (2.8)
Headache nos	8 (1.9)	2 (1.8)
Gastro-esophageal reflux disease	7 (1.6)	0 (0.0)
Dyspnea nos	6 (1.4)	4 (3.7)
Flatulence	6 (1.4)	0 (0.0)
Gynecomastia	6 (1.4)	1 (0.9)
Depression nec	5 (1.2)	0 (0.0)
Fatigue	5 (1.2)	0 (0.0)
Hypersensitivity nos	5 (1.2)	1 (0.9)
Paresthesia nec	5 (1.2)	0 (0.0)
Rash pruritic	5 (1.2)	1 (0.9)
Alopecia	4 (0.9)	1 (0.9)
Insomnia nec	4 (0.9)	0 (0.0)
Liver function tests nos abnormal	4 (0.9)	3 (2.8)
Sleep disorder nos	4 (0.9)	0 (0.0)
Burning sensation nos	3 (0.7)	0 (0.0)
Chest pain nec	3 (0.7)	0 (0.0)
Confusion	3 (0.7)	0 (0.0)
Constipation	3 (0.7)	0 (0.0)
Cough	3 (0.7)	2 (1.8)
Malaise	3 (0.7)	1 (0.9)
Edema peripheral	3 (0.7)	0 (0.0)
Pain in limb	3 (0.7)	0 (0.0)
Taste disturbance	3 (0.7)	0 (0.0)
Taste loss	3 (0.7)	0 (0.0)
Vomiting nos	3 (0.7)	3 (2.8)
Agitation	2 (0.5)	0 (0.0)
Alanine aminotransferase increased	2 (0.5)	0 (0.0)
Anorexia	2 (0.5)	0 (0.0)
Arthralgia	2 (0.5)	0 (0.0)
Breast pain	2 (0.5)	0 (0.0)
Bronchospasm nos	2 (0.5)	0 (0.0)
Choking	2 (0.5)	0 (0.0)

	Non-Serious N=430 (%)[*]	Serious AEs N=109 (%)^{**}
Dysphagia	2 (0.5)	0 (0.0)
Face edema	2 (0.5)	2 (1.8)
Gastric polyps	2 (0.5)	0 (0.0)
Gastric ulcer	2 (0.5)	0 (0.0)
Gastrointestinal disorder nos	2 (0.5)	0 (0.0)
Memory impairment	2 (0.5)	0 (0.0)
Nightmare	2 (0.5)	0 (0.0)
Edema nos	2 (0.5)	1 (0.9)
Oral pain	2 (0.5)	0 (0.0)
Pyrexia	2 (0.5)	2 (1.8)
Rash erythematous	2 (0.5)	0 (0.0)
Sweating increased	2 (0.5)	0 (0.0)
Thrombocytopenia	2 (0.5)	0 (0.0)
Tongue edema	2 (0.5)	1 (0.9)
Vision abnormal nec	2 (0.5)	0 (0.0)
Vision blurred	2 (0.5)	0 (0.0)
Accident nos	1 (0.2)	0 (0.0)
Anemia vitamin B ₁₂ deficiency	1 (0.2)	0 (0.0)
Angioneurotic edema	1 (0.2)	3 (2.8)
Aspartate aminotransferase increased	1 (0.2)	0 (0.0)
Asthenia	1 (0.2)	0 (0.0)
Ataxia nec	1 (0.2)	0 (0.0)
Blister	1 (0.2)	0 (0.0)
Blood lactate dehydrogenase increased	1 (0.2)	0 (0.0)
Blood prolactin increased	1 (0.2)	0 (0.0)
Body temperature increased	1 (0.2)	0 (0.0)
Bronchospasm aggravated	1 (0.2)	0 (0.0)
Calculus renal nos	1 (0.2)	0 (0.0)
Chest tightness	1 (0.2)	0 (0.0)
Convulsions nos aggravated	1 (0.2)	0 (0.0)
Cranial arteritis	1 (0.2)	0 (0.0)
Dermatitis exfoliative nos	1 (0.2)	0 (0.0)
Disorientation	1 (0.2)	0 (0.0)
Dry eye nec	1 (0.2)	0 (0.0)
Dry mouth	1 (0.2)	0 (0.0)
Dyspepsia aggravated	1 (0.2)	0 (0.0)
Dysphonia	1 (0.2)	0 (0.0)
Eczema nos	1 (0.2)	0 (0.0)
Eye disorder nos	1 (0.2)	0 (0.0)
Eye hemorrhage nec	1 (0.2)	0 (0.0)
Eye inflammation nos	1 (0.2)	0 (0.0)
Feces discolored	1 (0.2)	0 (0.0)
Fungal infection nos	1 (0.2)	0 (0.0)
Galactorrhea	1 (0.2)	0 (0.0)
Gingivitis	1 (0.2)	0 (0.0)
Glossitis	1 (0.2)	0 (0.0)
Gout	1 (0.2)	0 (0.0)

	Non-Serious N=430 (%)[*]	Serious AEs N=109 (%)^{**}
Hallucination nos	1 (0.2)	0 (0.0)
Hiccups	1 (0.2)	0 (0.0)
Hot flushes nos	1 (0.2)	0 (0.0)
Hypertrophy breast	1 (0.2)	0 (0.0)
Hypochromic anemia	1 (0.2)	0 (0.0)
Hyponatremia	1 (0.2)	1 (0.9)
Impotence	1 (0.2)	0 (0.0)
International normalized ratio increased	1 (0.2)	0 (0.0)
Iron deficiency anemia	1 (0.2)	0 (0.0)
Irritability	1 (0.2)	0 (0.0)
Jaundice nos	1 (0.2)	2 (1.8)
Leukocytoclastic vasculitis	1 (0.2)	0 (0.0)
Lip ulceration	1 (0.2)	0 (0.0)
Loose stools	1 (0.2)	0 (0.0)
Movement disorder nos	1 (0.2)	0 (0.0)
Muscle cramps	1 (0.2)	0 (0.0)
Night sweats	1 (0.2)	0 (0.0)
Esophageal disorder nos	1 (0.2)	0 (0.0)
Esophageal pain	1 (0.2)	0 (0.0)
Pain nos	1 (0.2)	0 (0.0)
Palpitations	1 (0.2)	1 (0.9)
Pancytopenia	1 (0.2)	3 (2.8)
Paresthesia oral nos	1 (0.2)	0 (0.0)
Paresthesia tongue	1 (0.2)	0 (0.0)
Pharyngitis nos	1 (0.2)	0 (0.0)
Photosensitivity reaction nos	1 (0.2)	0 (0.0)
Polyneuropathy nos	1 (0.2)	0 (0.0)
Prothrombin level decreased	1 (0.2)	0 (0.0)
Psychotic disorder nos	1 (0.2)	0 (0.0)
Rash vesicular	1 (0.2)	0 (0.0)
Renal impairment nos	1 (0.2)	1 (0.9)
Skin disorder nos	1 (0.2)	0 (0.0)
Skin hypertrophy	1 (0.2)	0 (0.0)
Skin irritation	1 (0.2)	0 (0.0)
Stomatitis	1 (0.2)	0 (0.0)
Thrombocytopenia aggravated	1 (0.2)	0 (0.0)
Tinnitus	1 (0.2)	0 (0.0)
Tongue papillary atrophy nos	1 (0.2)	0 (0.0)
Tooth loss	1 (0.2)	0 (0.0)
Transaminase nos increased	1 (0.2)	0 (0.0)
Tremor nec	1 (0.2)	2 (1.8)
Unevaluable reaction	1 (0.2)	0 (0.0)
Vaginitis	1 (0.2)	0 (0.0)
Vertigo nec	1 (0.2)	0 (0.0)
Visual disturbance nos	1 (0.2)	0 (0.0)
Weight decreased	1 (0.2)	0 (0.0)
Weight increased	1 (0.2)	0 (0.0)

	Non-Serious N=430 (%)[*]	Serious AEs N=109 (%)^{**}
Hepatic function abnormal nos	0 (0.0)	4 (3.7)
Stevens Johnson syndrome	0 (0.0)	3 (2.8)
Toxic epidermal necrolysis	0 (0.0)	3 (2.8)
Anaphylactic reaction	0 (0.0)	2 (1.8)
Erythema nec	0 (0.0)	2 (1.8)
Hematemesis	0 (0.0)	2 (1.8)
Hepatitis cholestatic	0 (0.0)	2 (1.8)
Hepatitis nos	0 (0.0)	2 (1.8)
Hepatocellular damage	0 (0.0)	2 (1.8)
Aggression	0 (0.0)	1 (0.9)
Anaphylactic shock	0 (0.0)	1 (0.9)
Anxiety	0 (0.0)	1 (0.9)
Atrial fibrillation	0 (0.0)	1 (0.9)
Balance impaired	0 (0.0)	1 (0.9)
Blood sodium increased	0 (0.0)	1 (0.9)
Bone marrow depression nos	0 (0.0)	1 (0.9)
Completed suicide	0 (0.0)	1 (0.9)
Crying	0 (0.0)	1 (0.9)
Delirium	0 (0.0)	1 (0.9)
Depression aggravated	0 (0.0)	1 (0.9)
Depression nec	0 (0.0)	1 (0.9)
Electrocardiogram abnormal nos	0 (0.0)	1 (0.9)
Epilepsy nos	0 (0.0)	1 (0.9)
Gastrointestinal hemorrhage nos	0 (0.0)	1 (0.9)
Hepatic failure	0 (0.0)	1 (0.9)
Hepatic fibrosis	0 (0.0)	1 (0.9)
Leucopenia nos	0 (0.0)	1 (0.9)
Esophagitis nos	0 (0.0)	1 (0.9)
Pancreatitis nos	0 (0.0)	1 (0.9)
Peripheral swelling	0 (0.0)	1 (0.9)
Petit mal epilepsy	0 (0.0)	1 (0.9)
Polyarthralgia	0 (0.0)	1 (0.9)
Proctalgia	0 (0.0)	1 (0.9)
Pulmonary fibrosis	0 (0.0)	1 (0.9)
Rigors	0 (0.0)	1 (0.9)
Sore throat nos	0 (0.0)	1 (0.9)
Speech disorder nec	0 (0.0)	1 (0.9)
Suicide attempt	0 (0.0)	1 (0.9)
Syncope	0 (0.0)	1 (0.9)
Tachycardia nos	0 (0.0)	1 (0.9)
Thyroid disorder nos	0 (0.0)	1 (0.9)
Thyroid nodule	0 (0.0)	1 (0.9)

* Percentage of total non-serious adverse events reported

** Percentage of total serious adverse events reported

Appendix 2.

Label Proposed for the OTC Marketing.

Produced by Pharm & Health, Elmwood, NJ 07033

000000-000000-000000

14 TABLETS

omeprazole tablets 20 mg
acid reducer

Prilosec

NEW!

1 tablet
prevents heartburn
for 24 hours

Prilosec

Safety Feature—Do not use if tablet blister unit is open or broken.

Drug Facts	Drug Facts (continued)
<p>Active ingredient (in each tablet) Purpose Omeprazole (equivalent to 20.5 mg omeprazole) Acid reducer</p> <p>Uses • for prevention of the symptoms of frequent heartburn for 24 hours • only for those who suffer heartburn two or more days a week</p> <p>Warnings Allergy alert Do not use if you are allergic to omeprazole. Heartburn Warning. Heartburn can be a sign of a more serious condition. Notify your doctor if you have had heartburn for 3 months or longer without talking to your doctor.</p> <p>Do not use • with other acid reducers</p> <p>Ask a doctor before use if you have • any of the following symptoms and have not seen a doctor • frequent chest pain • chest pain with shortness of breath, sweating, pain spreading to arms, neck or shoulders, or lightheadedness • trouble swallowing food • frequent wheezing, particularly with heartburn • unexplained weight loss</p> <p>These may be signs of more serious conditions. Notify your doctor.</p> <p>Ask a doctor or pharmacist before use if you are taking • warfarin (blood-thinning medicine) • phenytoin (seizure medicine) • ketoconazole (prescription antifungal medicine)</p> <p>Stop use and ask a doctor if • stomach pain continues or worsens • heartburn continues or returns after using this product every day for 14 days</p>	<p>Directions Adults 18 years of age and older: • for prevention of frequent heartburn, swallow 1 tablet with a glass of water in the morning. • take every day for 14 days. • do not continue beyond 14 days unless directed by your doctor. If your frequent heartburn continues or returns, it could be a sign of a more serious condition. • do not take more than 1 tablet a day. • do not chew or crush the tablets. Children under 18 years of age: ask a doctor.</p> <p>Other information • read the directions, warnings and package insert before use • keep the carton and package insert. They contain important information. • store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). • avoid product exposure to excessive heat and humidity • protect from moisture</p> <p>Inactive ingredients glyceryl monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin, polyethylene glycol 8000, polyisobutyl 80, polyvinylpyrrolidone, sodium stearoyl fumarate, starch, sucrose, talc, titanium dioxide, triethyl citrate</p> <p>Questions or comments? Call toll free</p>