NDA: 21-229
Product: Prilosec (omeprazole magnesium tablets 20.6 mg)
Sponsor: Astra Zeneca/Proctor & Gamble
Indication: Relief and prevention of heartburn
Marketing: OTC
Submission: Actual Use Study 1998003
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Medical Reviewer: Ling Chin. M.D., M.P.H.

A MULTI-CENTER, OPEN-LABEL, ACTUAL USE STUDY TO INVESTIGATE THE CONSUMER USAGE PATTERNS/DOSING COMPLIANCE OF OMEPRAZOLE MAGNESIUM, 20.6 MG, WHEN USED BY OTC CONSUMERS

I. SPONSOR'S STUDY REPORT

1. Study Description

1.1. Primary Objective: characterize the usage patterns/dosing compliance of omeprazole magnesium when used ad libitum according to proposed label instructions under naturalistic over-the-counter (OTC) conditions.

1.2. Secondary Objective: investigate the effectiveness of omeprazole magnesium in a naturalistic setting.

1.3. Study Design: multi-center (7 centers in 6 cities), multi-dose, open-label, at-home study

1.4. Duration Of Treatment: Dosing according to proposed label instructions occurred ad libitum during the approximate 4-week evaluation period.

1.5. Criteria For Inclusion: Subjects of either sex, any race, 12 years of age or older, who "self-selected" to use the study medication (i.e., determined for themselves whether or not the study medication was appropriate for them to use) after reading the proposed package labeling. Specific targeted subgroups were people with low reading ability (as determined by a standardized literacy test) and poorly educated people (e.g., adults who did not enter or complete high school).

To be considered eligible for enrollment into this study, subjects:
1. provided written informed consent (co-signed by parent/guardian if subject was 12–17 years of age),
2. after reading the label, determined that the study medication was appropriate to use,
3. were male or non-pregnant, non-lactating female, of any race, and at least 12 years of age,
4. if female, were willing to complete both at-home urine pregnancy tests (one before taking the initial dose of study medication, the second after taking the last dose of study medication), and not use the study medication if either test was positive,
5. if female of child-bearing potential, were willing to sign a birth control agreement and use an acceptable form of contraception (including abstinence) as determined by the Investigator or study staff, and
6. were willing and able to complete the Product Use Journal during the study period, willing to answer a telephone interview, and willing to return at the end of the study period (Visit 2) with any unused study medication, the study medication package, and the Product Use Journal.

1.6. Criteria For Exclusion: Subjects were excluded from the study if they:
1. were pregnant or lactating,
2. had active peptic ulcer disease currently being treated with prescription H2RAs or PPIs,
3. were currently taking phenytoin (Dilantin), warfarin (Coumadin), diazepam (Valium), or clarithromycin (Biaxin),
4. had known hypersensitivity to omeprazole or omeprazole magnesium,
5. experienced continuous abdominal pain ³ 10 days in duration,

6. had dysphagia (difficulty swallowing), or
7. had previously participated in this study.

2. Study Methodology:

The purpose and procedures of the study were explained to potential subjects prior to enrollment. All subjects who agreed to participate provided written informed consent and, if female, took two urine pregnancy tests (one prior to dosing and one after the last dose). Eligible subjects were supplied with 36 tablets of omeprazole magnesium 20.6 mg (labeled Prilosec 1™). Subjects were to use the study medication for the labeled indications as needed for a period of approximately 4 weeks.

2.1. Read Label/Self-Select

Consumers were intercepted at malls/shopping centers and asked, "Do you get stomach problems?" Those responding positively were invited to participate in a research study about a proposed new OTC medication for stomach problems. They were given a proposed market-ready package of omeprazole magnesium and instructed: "Examine this medication as if you were looking to buy it off the shelf in a drug store or supermarket." After the subject had as much time as necessary to read the label, the interviewer asked the subject: "Do you think this is an appropriate medication or not an appropriate medication for you to use?" The interviewer did not interpret the label for the subjects nor in any way assist the subjects in determining if it was appropriate for them to use the study medication. The interviewer did not offer any advice or counsel the subjects. If asked about how to use omeprazole magnesium, "refer to the label" was the response to any question about the study medication or how to use it.

2.2. Question Reason For Self-Selection

After the self-selection decision was made, study staff asked subjects the reason for their decision. Subjects who indicated that the study medication was inappropriate for them were discharged. Subjects who indicated the study medication was appropriate for them were screened for willingness to participate in the actual use phase of the study (i.e., complete the Product Use Journal, be contacted by phone for a brief interview, and return for a second visit in approximately four weeks).

After the self-selection decision was made, study staff captured the reasons for each subject's decision. Those subjects who elected to participate in the study were screened by study staff for willingness to: complete the Product Use Journal, be contacted by phone at pre-determined time points for a brief interview, and return to the Investigator's study center for a second visit in approximately 4 weeks. Subjects underwent additional screening by study staff to determine eligibility for entry into the study.

2.3. Heartburn History

Subjects answered a questionnaire to characterize their heartburn condition (duration and frequency of heartburn symptoms) and collect prescription and non-prescription medications used to treat the heartburn condition during the past 30 days. Subjects were also questioned: "Over the past month, which of the following factors typically caused you to have heartburn?" The responses available for the subject to select were the following (subjects were to select all that applied):

- Hectic Lifestyle
- Stress and/or Anxiety
- Food and/or Beverages
- Physical Activity (e.g., exercise, bending over)
- Lying down
- Medication

2.4. Medical/Medication History

Subjects provided an abbreviated Medical and Medication History. Prior therapy for any stomach or digestive disorder was documented by the subjects using a brief medication history at Visit 1. Concomitant medication between Visit 1 and Visit 2 was documented using the Product Use Journal.

2.5. Urine Pregnancy Test/Birth Control Agreement

All female subjects were given two take-home urine pregnancy tests. Subjects were instructed to complete one urine pregnancy test at home before taking the initial dose of the study medication. Female

subjects documented the result of the urine pregnancy test on their Product Use Journal. If the test result was positive, subjects were instructed not to take the study medication and to call the 24-hour telephone number given in the Product Use Journal.

Female subjects continuing in the study completed the second urine pregnancy test after they had taken their last dose of study medication (prior to Visit 2). The result of the second test was also recorded in the Product Use Journal. If the result of the second test was positive, subjects were instructed to report the pregnancy to the Investigator via the 24-hour telephone number given in the Product Use Journal.
All females of child-bearing potential (i.e., from puberty until two years post-menopausal, or not surgically sterile) signed a birth control agreement indicating they would use adequate contraception during the study.

2.6. Product Use Journal

A Product Use Journal was dispensed to all subjects eligible for the actual use phase of the study, along with training to complete it. The subject was asked to provide the following information in the Product Use Journal:

For each time they dosed:
- date of the dose,
- time of the dose,
- total number of tablets taken,
- if taken for prevention (any time during the day or 1 hour before events) or relief,
- the severity of each heartburn episode (when study medication was taken),
- assessment of study medication effectiveness, and
- whether another heartburn medication was also taken to treat symptoms.

Throughout the study period:
- other concomitant medications (including name, dose, etc. of any other heartburn medications),
- any adverse events, and
- urine pregnancy test results.

The Product Use Journal provided a chronicle of the subject's self-treatment for heartburn symptoms and was considered part of the case report form (CRF).

2.7. Study Medication Dispensed

Eligible subjects were supplied with 36 tablets of study medication (i.e., more than the number of tablets which would be consumed if one tablet were taken each day for four weeks) supplied in a proposed OTC market-ready package (labeled Prilosec 1). Each subject who agreed to take the study medication used it as needed over a period of approximately four weeks according to the label dosing instructions. Subjects were reminded that the study medication could not be shared with other family members or friends. Subjects were reminded that all study medication and the package, whether full, partially full, or empty, were to be returned to the study centers at the completion of the study period.

2.8. Interim Phone Interview

Two weeks after enrollment (study mid-point), subjects were phoned to inquire about:
- how they were completing the Product Use Journal and if they were using it correctly,
- any complications which had occurred while dosing with the study medication, and
- for females, the result of their urine pregnancy test.

2.9. Visit 2 (End Of Study)

Subjects were scheduled to return to the designated Investigator's study center in approximately four weeks, with the study medication packages, the Product Use Journal, and any unused study medication. The journals were reviewed during this visit to address any missing, incomplete, inconsistent, or confusing journal entries with each subject. Changes made to the journal at this time were initialed by the subject. Each subject was asked: "Did you give the medication to anyone else?" (yes/no) Study staff

compared the amount of study medication returned to the journal entries for study medication consumption and resolved any inconsistencies at that time with the subject. The actual amount of study medication returned was recorded on the Drug Accountability Log.

Subjects were asked to provide their Overall Assessment of omeprazole magnesium as a medication for heartburn. Subject journals provided a history of any AEs experienced since they ingested their first dose of study medication. If necessary, the Investigator examined the subject. All AE data were documented on the appropriate Case Report Forms (CRFs).

3. STATISTICAL METHODS:

3.1. Sample Size Determination:

An 85% return rate on the Product Use Journal information was expected, which equated to a total sample size of approximately 850 subjects. Thus, assuming the study population consisted of 70% who used the study medication for relief of heartburn symptoms and 30% who used the study medication for prevention of heartburn symptoms, a worst case scenario of 50% compliance rate would yield a ± 4.0% error rate for relief users and a ± 6.1% error rate for the prevention users. In other words, with a sample size of 850, we can be at least 95% confident that our estimate of compliance would not differ from the true compliance rate by more than 0.040 for relief users and 0.061 for prevention users. If the true compliance rate was 90% or greater, a sample size of 850 would yield at least 95% confidence that our estimate of compliance was within 0.024 of the true rate for relief users and within 0.037 of the true rate for prevention users.

3.2. Primary Endpoint: The percentage of subjects who used the study medication according to the three label use directions:

(1) take only one tablet per dose,
(2) take no more than one dose per day,
(3) take for no more than 10 consecutive days.

Dosing behaviors were summarized for all subjects who returned the Product Use Journal at Visit 2 regardless of whether or not a dose was taken by the subject.

3.3. Evaluation of Usage Patterns: Demographic characteristics, heartburn history, factors contributing to heartburn, prior and concomitant drug therapies, usage patterns including consistency with the three label use directions, efficacy, and concomitant use of other heartburn medications were summarized over all subjects and also by the following five types of users:

(1) Prevention-Any-Time-Only users,
(2) Prevention-1-Hour-Before-Only users,
(3) Dual-Prevention-Only users,
(4) Relief-Only users,
(5) Prevention-And-Relief users.

Usage patterns were summarized using descriptive statistics by type of user and across all users by pooling across study centers and at each individual study center. In addition, subjects' dosing behaviors over the study period were summarized.

3.4. Evaluation of Efficacy: Study medication effectiveness assessments were recorded for each dose on the Product Use Journal. The study medication effectiveness assessment was taken in the evening just prior to bedtime. If the study medication was taken for nighttime heartburn, or if the subjects forgot to fill out the evaluation in the evening, then subjects were instructed to fill it out the following morning. Subjects answered the following question for each dosing episode:
"Did the medication work for your heartburn?" (yes/no)
Subjects were also asked if any other medication was needed for relief of heartburn:
"Did you have to take any other medication for your heartburn?" (yes/no)

For each dosing episode that the subject dosed with study medication to relieve symptoms, the subject rated the severity of his/her baseline heartburn symptoms using the following scale:

Mild = 1
Moderate = 2
Severe = 3

At Visit 2, subjects rated the Overall Assessment of the study medication by answering the following question: "Overall, how would you rate the medication?"

Poor = 0
Fair = 1
Good = 2
Very Good = 3
Excellent = 4

Study medication effectiveness and Overall Assessment of study medication were summarized using descriptive statistics. For doses where the study medication was taken to relieve heartburn symptoms, the percentage of effective dosing occasions was summarized by baseline heartburn severity.

The number and percentage of subjects and dosing occasions where antacids, H2RAs, or PPIs were used on the same day after study medication was taken were summarized by type of user and across all users.

3.5. Evaluation of Safety: Safety was investigated by evaluating all voluntarily reported 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 voluntarily reported AEs were summarized by the number of subjects reporting AEs, intensity, relationship to study medication, and body system. Safety information were summarized over all subjects and by the following three types of users:

Prevention-Only users,
Relief-Only users, and
Prevention-And-Relief users.

Medical Officer's Comments:

Methodology

This study allows for the use of drug product without physician intervention. Subjects are exposed to the label and have to make a decision about whether or not the product is appropriate or not appropriate for them to use. They are then prompted for the reason for their decision in an open-ended question, after which they can select from a list all the reasons they elected to use or not to use the product. The standard questionnaire is administered by study personnel. Following the list of reasons for self-selection, study inclusion exclusion criteria are then applied.

Inclusion/Exclusion Criteria

The extensive list of inclusion and exclusion criteria detracts from a key aspect of Actual Use Studies; i.e. the all-comers nature of subject enrollment. For OTC use, all consumers who think they have the targeted indication for the product is free to walk up to the counter and buy the product. The purpose of this study would be to demonstrate that the product label is adequate in guiding consumers through appropriate self-selection and use. This study can not demonstrate how consumers would do if they had any of the contraindicated conditions (e.g. difficulty swallowing, abdominal pain, pregnancy/nursing) or contraindicated medications (e.g.

current Rx H_2RA or PPIs, phenytoin, warfarin, diazepam, clarithromycin) since consumers with any risk for use of this product were excluded.

Statistical Methods

The sample size of 850 was intended to yield a compliance rate of ± 4.0% error rate for relief users and ± 6.1% error rate for the prevention users with 95% confidence. The assumption was made that in this study population, 70% of subjects would use the drug for relief, and 30% for prevention. However, in this study, 38% of subjects used the drug for relief only, 10% for prevention only and 52% for relief and prevention. Thus the error rate for the compliance rate may be different from that expected. Compliance with the label is measured by consistency with 3 labeled dosing directions, and point estimates for these 3 primary endpoints were provided. However, the confidence intervals around these estimates were not provided. Since the expected distribution by usage of the subjects in the study turned out to be different (much smaller group) than predicted, the actual 95% confidence intervals around these estimates will be much larger.

II. SPONSOR'S DATA ANALYSIS:

1. Summary Data

1.1. Subject Disposition:

Table 1

SUBJECT DISPOSITION	Ref: TABLE 8.1.1
Number of Subjects Recruited to Participate in the Study	1514
Decided not to participate after reading label (not appropriate to use)	213
Product appropriate to use but decided against participation	164
Self-selected to participate in study after reading label	1137
Did not meet inclusion and Exclusion criteria at Visit 1	13
Subject reconsidered/withdrew consent	23
Investigator/Sponsor decision to withdraw subject(s	8
Received study medication and Product Use Journal at Visit 1	1093
Did not complete study	219
Completed study	874

A total of 1514 subjects were recruited, with 84 consumers of low reading ability. Of these, 1093 participants received medication, and 874 subjects completed the study (returned Product Use Journal). 825 subjects took at least one dose of study medication as indicated in their returned Product Use Journal and they were included in the ITT analysis set. The 825 ITT subjects included 3 subjects who did not complete the study (reason not stated) and 822 who did complete the study. (There were a total of 52 subjects who completed the study but did not dose with study medication.)

Eight hundred thirty-three subjects were included in the summary of safety, which included subjects who reported an adverse event (AE), regardless of returning their Product Use Journal.

Medical Officer's Comments:

Subject Disposition

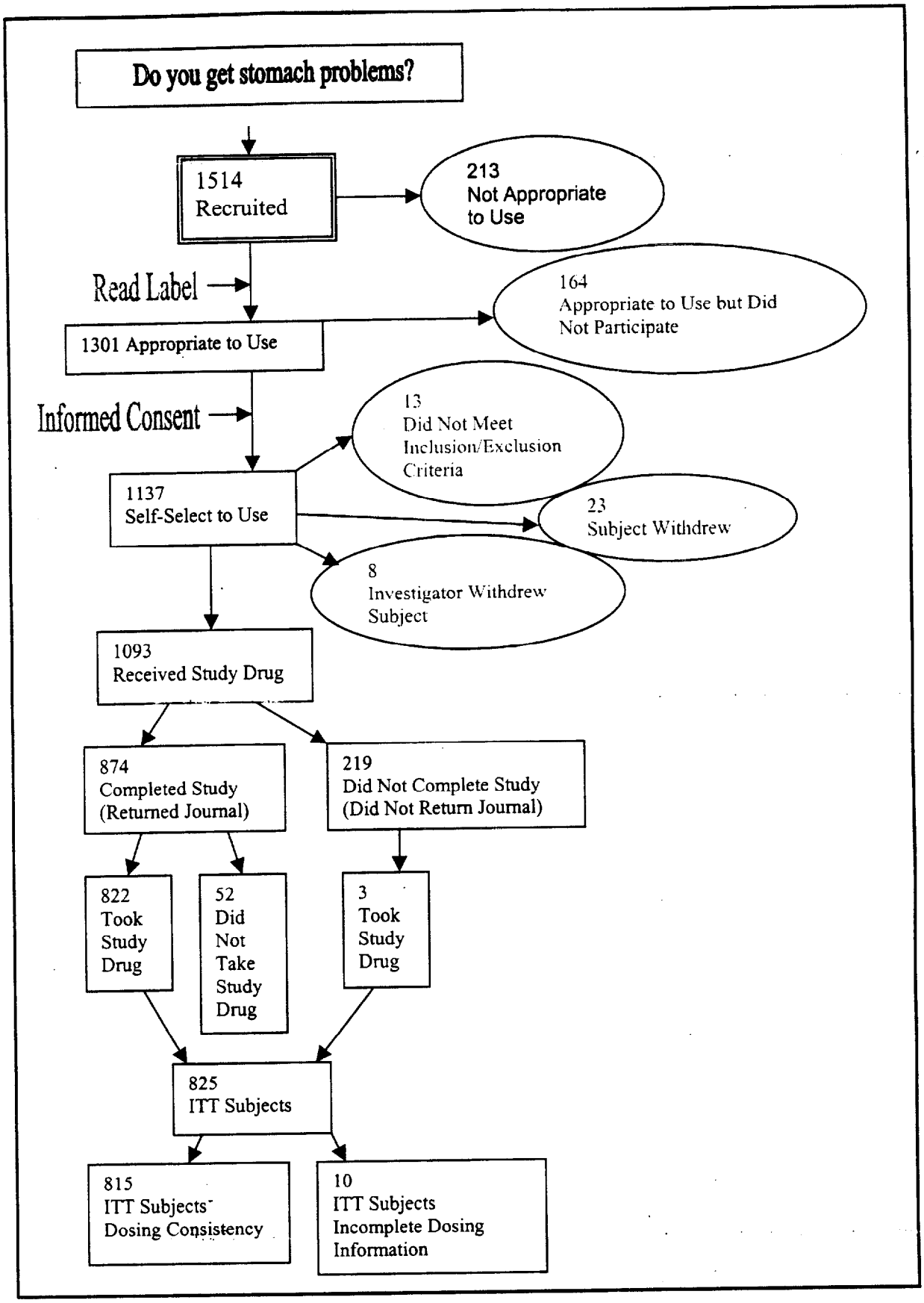
A graphical representation of subject disposition is provided. As can be seen in Fig.1, from approximately 1500 subjects enrolled, only about 50% subjects made it to the ITT population for a variety of reasons. This raises the question as to the biases introduced via selection and

exclusion of subjects, and whether or not the group participating is different from the group not participating or evaluated, and how representative the participants are of the general OTC population.

Areas where information would be useful but were not provided by the sponsor include the following:

1. reasons for non-participation by the 164 subjects
2. reasons for investigator exclusion of 8 subjects
3. reasons for withdrawing consent by the 23 subjects
4. accounting of each subject who received study drug as to what they did with the drug
5. all available information, including demographics, of 219 subjects who did not complete the study (did not return Product Use Journal)
6. all available information, including demographics, of the 52 subjects who did not take study drug
7. clarification of the ITT population: why were 3 subjects who were designated as not completing the study included in the ITT population?
8. All available information, including demographics, of the 10 subjects further excluded from the ITT population on the basis of incomplete data

Figure 1: Subject Disposition



1.2. Breakdown of the reasons for self-selecting and not self-selecting:
Subjects may select more than one reason. Reasons were provided in the questionnaire.

Table 2

SUMMARY OF CONSUMER REASON FOR SELF-SELECTING (Subject may select more than one reason for self-selecting)		Ref: TABLE 8.1.5
Reason for Self-Selecting	**N = 1301**	**%**
I get heartburn	1050	81
I want to prevent heartburn	524	40
It would allow me to sleep through the night	191	15
I'm familiar with the product	114	9
Other heartburn medications are not effective enough	149	11
Other	283	22

Table 3

SUMMARY OF CONSUMER REASON FOR NOT SELF-SELECTING (Subject may select more than one reason for not self-selecting)		Ref: TABLE 8.1.4
Reason for not Self-Selecting	**N = 213**	**%**
I don't get heartburn	45	21
My heartburn isn't that bad	48	23
I am pregnant, or nursing a child	3	1
I am currently taking a contraindicated medication	15	7
I am happy with my current heartburn medication	23	11
I don't like to try new medications without my doctor's approval	29	14
I have a contraindicated condition	14	7
Other	56	26

Medical Officer's Comments:

Self-Selection

After reading the label, 1301 subjects stated that it was appropriate for them to use the drug. From a list of 6 choices, the major reasons given were that they get heartburn (81%), and they want to prevent heartburn (40%). Of the 213 subjects who responded that the drug was inappropriate for them, 26% did not pick a specific reason, 23% selected "My heartburn isn't that bad" as a reason, and 21% selected "I don't get heartburn as a reason". See Tables 2 and 3 for a breakdown of all the reasons.

From the verbatim responses to the open-ended question about the reason for their decisions, the product appealed to some for the expanded claim of relief for heartburn due to stress and exercise, and the 24-hour relief. Concerns raised from the verbatim responses include the following: frequency of heartburn more than occasional (e.g. everyday), heartburn may be severe (nothing else works), have ulcers, have esophagitis, already taking prescription H_2RAs. There were also subjects who were cautious about using study drug: do not use new medications without checking with doctor first, already taking medications such as Biaxin, Dilantin, Coumadin, already pregnant, already using mediations that work.

Unfortunately, there was no correlation of subjects' verbatim responses and medical history to their decisions about drug use appropriateness, so that an assessment of whether or not subjects made the correct decision could not be determined. Information on the subject such as educational level, occupation, heartburn history, and medical history are collected after screening for inclusion/exclusion criteria and informed consent is completed. It would have been useful to have obtained the information on other medications taken, heartburn history and medical history prior to the exclusion of subjects, so that subjects' decisions to use/not use the study drug could be validated; i.e. assessed as being correct or incorrect by study personnel.

1.3. Demographic Characteristics:

Table 4

DEMOGRAPHIC CHARACTERISTICS BY USAGE **Intent-To-Treat Subjects**		**Ref: TABLE 8.1.6**
Gender	**N = 825**	**%**
Female	497	60
Male	328	40
Race	**N = 825**	**%**
American Indian	12	1
Asian	4	<1
Black	113	14
Caucasian	621	75
Hispanic	56	7
Multi-Racial/Other	19	2

Among the ITT subjects, 40% were male and 75% were Caucasian. Subjects averaged 47 years in age (range 13–84 years). Over half (59%) of the subjects had at least some college education. Eighty-eight percent of subjects did not take any prescription heartburn medication, and 73% took non-prescription heartburn medication during the month prior to study participation.

Fifty-nine percent of the subjects indicated they had completed at least some college. Three hundred sixteen subjects who were ages 18 and over and who indicated their highest education level did not include college were administered a REALM test. Of these, 84 subjects scored 60 or below, indicating low reading ability. Two hundred and six (25%) of the ITT subjects indicated their occupation was professional or technical. The remaining occupations are listed by decreasing order of frequency: other (14%), service worker or private household worker (14%), clerical worker (13%), manager or administrator (12%), sales worker (10%). The remaining occupations occurred at a rate of less than 10%.

1.4. Factors Contributing to Heartburn:

Subjects were permitted to select as many factors that contributed to their heartburn over the past month. Food and/or beverage was found to be the most typical contributing factor (93% of subjects) of heartburn over the month prior to Visit 1, followed by stress and/or anxiety (52%) and lying down (26%). See Table 5.

Table 5

SUMMARY OF FACTORS CONTRIBUTING TO HEARTBURN Intent-To-Treat Subjects		Ref: TABLE 8.1.8
Factors Contributing to Heartburn	**N = 825**	**%**
Hectic Lifestyle	156	19
Stress and/or Anxiety	426	52
Food and/or Beverage	764	93
Physical Activity	58	7
Medication	25	3
Lying down	218	26

1.5. Prior and Concomitant Drug Therapies:

Table 6

MOST COMMON PRIOR DRUG THERAPIES WITH INCIDENCE ≥5% Intent-To-Treat Subjects			Ref: TABLE 8.1.9
Prior Drug Therapy	**N = 825**	**Concomitant Drug Therapy**	**N = 825**
Tums	254 (31%)	Tums	240 (29%)
Rolaids	139 (17%)	Rolaids	119 (14%)
Pepcid AC	98 (12%)	Pepcid AC	76 (09%)
Zantac	55 (07%)	Tylenol	63 (08%)
Maalox	53 (06%)	Multivitamins	56 (07%)
Multivitamins	51 (06%)	Maalox	54 (07%)
Mylanta	43 (05%)	Ibuprofen	52 (06%)
Premarin	43 (05%)	Zantac	49 (06%)
Tagamet HB	38 (05%)	Premarin	45 (05%)
Vitamin E	35 (04%)	Aspirin Grain V	44 (05%)

Prior to enrollment, the most common prior drug therapies were Tums, Rolaids, Pepcid AC, and Zantac (≥7% overall). During the study, subjects were allowed any concomitant medication, which was not specifically prohibited in the Exclusion criteria of the protocol. The most common concomitant medications were similar to the prior drug therapies and included Tums, Rolaids, Pepcid AC, and Tylenol (≥8% overall).

1.6. Usage Patterns:

Table 7

USAGE GROUPS Intent-To-Treat Subjects		Ref: TABLE 8.1.6
Type of User	**N = 825**	**%**
Prevention-Any-Time-Only	38	5
Prevention-1-Hour-Before-Only	28	3
Dual-Prevention-Only	14	2
Relief-Only	317	38
Prevention-and-Relief	428	52

Medical Officer's Comments:

Demographics, Heartburn Precipitants, Concomitant Medications, and Usage Pattern

The majority of subjects in this study were female (60%), Caucasian (75%), had some college education (59%), with an average age of 47 (range 13-84 years). Most of the subjects (88%) did not take any prescription heartburn medications, and 73% took non-prescription heartburn medications in the month prior to the study; predominantly Tums (31%), Rolaids (17%), and Pepcid AC (12%). Factors contributing to heartburn included food/beverage (93%) and stress/anxiety (52%). By usage pattern as defined by sponsor, the majority of subjects took study drug for both prevention and relief (52%), followed by relief only (38%), and prevention only (10%).

1.7. Heartburn History:

Table 8

SUMMARY OF HEARTBURN HISTORY Intent-To-Treat Subjects		Ref: TABLE 8.1.7
Duration	**N = 825**	**%**
1 month or less	12	1
1-6 months	43	5
6-12 months	44	5
1-2 years	111	13
2-5 years	161	20
5 years or more	454	55
Frequency - daytime		
Rarely	143	17
once a week	160	19
2-3 times a week	315	38
4-5 times a week	100	12
6 or more times a week	107	13

Eighty-eight percent experienced more than one year of heartburn symptoms, and 63% had heartburn ≥2 times per week. About 33% rarely experienced heartburn at night. Seven hundred thirty subjects (88%)

did not take any prescription heartburn medication and 601 subjects (73%) took non-prescription heartburn medication during the month prior to study participation.

Medical Officer Comments:

Heartburn History

A majority of subjects in this study have significant heartburn histories. Only 36% of subjects report heartburn occurring rarely or once a week. Sixty-three percent experience heartburn more frequently (38%: 2-3 times a week, 25%: ≥4 times a week). By duration of heartburn, only 6% of subjects report less than 6 months' duration, 18% report 6 months to 2 years, while 20% report 2-5 years. Fifty-five percent reported heartburn duration of ≥5 or more years, while another 33% had 1-5 years of heartburn. Thus the majority of subjects had heartburn 2-3 times or more per week, and duration of >6 months. The majority of subjects (73%) was already taking non-prescription heartburn medication and had more than a rare occurrence of heartburn at night (67%). The concern is that these subjects may be experiencing more than episodic (occasional heartburn), and may in effect be self-treating for GERD. These subjects may not be the best representation of the OTC intended population for self-medication for episodic heartburn.

1.8. Maximum Sequential Dosing Days:

Table 9

MAXIMUM NUMBER OF SEQUENTIAL DOSING DAYS PER SUBJECT BASIS **Intent-To-Treat Subjects**		**Ref: TABLE 8.2.14**
Number Sequential Dosing Days	**N = 825**	**%**
1-2	423	51
2-4	124	15
5-6	38	5
7-8	29	4
9-10	24	3
11-12	23	3
13-16	18	2
17-20	19	2
21-24	19	2
25-28	40	5
≥29	68	8

A total of 638 (77%) of subjects took medication for up to 10 sequential dosing days. 187 (23%) took medication beyond 10 sequential dosing days.

1.9. Maximum Number Tablets Taken:

Table 10

MAXIMUM NUMBER OF TABLETS TAKEN PER SUBJECT BASIS Intent-To-Treat Subjects		Ref: TABLE 8.2.15
(* Data for 10 subjects excluded because of incomplete data)	N = 815*	%
Per Dosing Occasion		
1	699	86
2	114	14
≥3	2	<1
Per Dosing Day		
1	634	78
2	155	19
≥3	26	3

The majority of subjects took 1 tablet per dosing occasion (86%) or per dosing day (78%). More subjects took >1 tablet by Dosing Day, than by Dosing Occasion.

1.10. Maximum Sequential Dosing Days by Usage Group:

Table 11

MAXIMUM NUMBER OF SEQUENTIAL DOSING DAYS PER SUBJECT BASIS Intent-To-Treat Subjects			Ref: TABLE 8.2.14
	Prevention* N=80	Relief N=317	Total N=825
1-2 Days	16%	80%	51%
3-4 Days	5%	12%	15%
5-6 Days	4%	2%	5%
7-8 Days	4%	1%	4%
9-10 Days	6%	1%	3%
11-12 Days	0%	1%	3%
13-16 Days	5%	1%	2%
17-20 Days	5%	1%	2%
21-24 Days	4%	1%	2%
25-28 Days	20%	<1%	5%
≥29 Days	31%	1%	8%

* The subjects in the 3 prevention groups, Prevention Any Time Only, Prevention 1-hr Before Only, and Dual Prevention Only, were added and considered together.

The majority of Relief-Only subjects (92%) had four or less maximum sequential dosing days. Over half of Prevention users took medication for more than 24 days sequentially.

1.11. Maximum Number Tablets Taken By Usage Group:

Table 12

MAXIMUM NUMBER OF TABLETS TAKEN PER SUBJECT BASIS Intent-To-Treat Subjects			Ref: TABLE 8.2.15
	Prevention* N=77	**Relief N=317**	**Total N=825**
Maximum Number Taken Per Dosing Occasion			
1 Tablet	95%	89%	86%
2 Tablets	5%	11%	14%
≥3 Tablets	0%	0%	<1%
Maximum Number Taken Per Dosing Day			
1 Tablet	90%	82%	78%
2 Tablets	10%	17%	19%
≥3 Tablets	0%	1%	3%

* The subjects in the 3 prevention groups, Prevention Any Time Only, Prevention 1-hr Before Only, and Dual Prevention Only, were added and considered together.

Most of the subjects took 1 tablet per dosing occasion (86%) and took 1 dose per day (78%). The Prevention Only and Relief Only usage groups showed similar results. When examined by actual subgroups, for maximum number of tablets per dosing occasion, 1 subject (3%) in the Prevention-Any-Time-Only group, 2 subjects (7%) in the Prevention-1-Hour-Before-Only group, 1 subject (8%) in the Dual-Prevention-Only group, and 35 subjects (11%) in the Relief-Only group took two tablets on one dosing occasion. For maximum number of tablets taken per dosing day, 3 subjects (8%) in the Prevention-Any-Time-Only group, and 3 subjects (11%) in the Prevention-1-Hour-Before-Only group, took two tablets in one day. For the Relief-Only group, 54 subjects (17%) took two tablets per dosing day and 2 subjects (1%) took ≥3 tablets per dosing day. More subjects in the Relief Only usage group took 2 tablets per dosing occasion or day than those in the Prevention Only usage group.

2. Study Results:

2.1. Consistency With Labeled Use Directions:

Consistency with the three labeled dosing directions is evaluated via the frequency and percentage of subjects who used the study medication according to label instructions over the 4-week usage period. Label use direction consistency is summarized on a per subject basis, per dosing day basis, and per dosing occasion basis.

Subjects were considered consistent with the labeled use directions if they consumed only one tablet per dose, took no more than one dose per day, and dosed for no more than 10 consecutive days. A dosing day was considered consistent with the label use directions if only one tablet per dose was taken and no more than one dose was taken per day. A dosing occasion was considered consistent if only one tablet per dose was taken.

Table 14

LABEL USE DIRECTION CONSISTENCY PER SUBJECT BASIS Intent-To-Treat Subjects	Ref: TABLE 8.2.1
(* Data for 10 subjects excluded because of incomplete data)	N = 815*
Consistent	507 (62%)
Not Consistent	308 (38%)
Exceeded one tablet per dose	116 (14%)
Exceeded one dose per day	106 (13%)
Exceeded 10 consecutive dosing days	181 (22%)

Overall, 507 of 815 subjects (62%) were consistent with all three labeled use directions. Across all subjects who were not compliant, 116 (14%) took more than one tablet per dose, 106 (13%) took more than one dose per day, and 181 (22%) exceeded 10 consecutive days of dosing.

General Medical Officer Comments:

Consistency with the 3 label dosing directions were assessed by subgroups such as literacy level, ethnicity, investigator/site, and drug effect and by the following subsets:

1. per subject
2. per dosing occasion
3. per dosing day
4. per usage (Prevention-Any-Time, Prevention-1-hr-Before, Dual Prevention, Relief, Prevention and Relief)
5. per predominant use

The Agency's statistical reviewer provided a summary table (Table 13) of results for the 5 usage groups. Confidence intervals (95% level) were calculated for each of sponsor's point estimates. As revealed by the table, the numbers of subjects in each usage group is small, especially the 3 prevention groups, and the confidence intervals are much larger than specified, which calls to question the validity and usefulness of these results. That said, and because there is some value to assessing the behaviour of the subjects by their usage pattern, sponsor's results will be presented not for all 5 usage groups, but for 3 groups only, i.e. Prevention only users, Relief only users, and Total users. The numbers of subjects in the 3 prevention groups (Prevention any time, Prevention 1-hr before, Dual Prevention) will be added together and considered as a Prevention Only group.

Table 13. Point Estimation and Confidence Intervals for Consistency Rate (Study 003)

	Prevention Any Time (N = 36)	Prevention 1 hr Before (N = 28)	Dual Prevention (N = 13)	Relief (N = 316)	Prevention And Relief (N = 422)	Overall (N = 815)
Consistency (n (%))	9 (25%)	9 (32%)	7 (54%)	254(80%)	228 (54%)	507 (62%)
95% Confidence Interval	(11%, 39%)	(15%, 49%)	(27%, 81%)	(76%, 84%)	(49%, 59%)	(59%, 65%)

The primary endpoints specified a-priori are the percent of subjects who take only one tablet per dose, take no more than one dose per day, and take for no more than 10 consecutive days. This review will therefore focus only on these primary endpoints, and separate them out whenever possible by the 3 groups specified above (Prevention, Relief, and Total). Sponsor's post-hoc analyses will not be included.

2.2. Label Consistency by Dosing Occasions and Dosing Days:

Table 15

LABEL USE DIRECTION CONSISTENCY PER SUBJECT BASIS Intent-To-Treat Subjects	Ref: TABLE 8.2.3
(* Data for 10 subjects excluded because of incomplete data)	N = 815*
Total Number Dosing Days	**10376**
Consistent	9611 (93%)
Not Consistent	765 (7%)
Exceeded one tablet per dose	463 (4%)
Exceeded one dose per day	340 (3%)
Total Number Dosing Occasions	**10734**
Consistent	10263 (96%)
Not Consistent	471 (4%)
2	24 (3%)
3	15 (2%)
≥4	77 (9%)

Based on dosing days, consistency with label use directions was 93% overall. Similarly, based on dosing occasions, consistency with the label use directions was 96%.

2.3. Label Consistency By Usage Group:

Table 16

LABEL USE DIRECTION CONSISTENCY PER SUBJECT BASIS BY USAGE Intent-To-Treat Subjects			Ref: TABLE 8.2.1
	Prevention* N=77	**Relief N=316**	**Total N=815**
Consistent	25 (32%)	254 (80%)	507 (62%)
Not Consistent	52 (68%)	62 (20%)	308 (36%)
Exceeded one tablet per dose	4 (4%)	35 (11%)	116 (14%)
Exceeded one dose per day	4 (4%)	26 (8%)	106 (13%)
Exceeded 10 consecutive dosing days	49 (64%)	13 (4%)	81 (22%)

* The subjects in the 3 prevention groups, Prevention Any Time Only, Prevention 1-hr Before Only, and Dual Prevention Only, were added and considered together.

Thirty-two percent of Prevention Only users and 80% of Relief Only users were consistent with all three label use directions. Relief users were more complaint. The most inconsistency with label directions was seen among the Prevention users, with 72% in the Prevention Any Time users, 64% in the Prevention 1-hr Before users, and 38% in the Dual Prevention users.

Medical Officer's Comments:

Overall Consistency

This study has demonstrated that a significant number of people did not completely follow the dosing directions on the label. Overall, 62% subjects were found to be consistent with all 3

labeled dosing directions, and 38% were not. Among those who were not consistent, 22% exceeded the 10-day limit, followed by those that exceeded one tablet per dose (14%), and exceeded one dose per day (13%).

Per Dosing Occasion and Dosing Day

When examined by dosing occasions, the data showed that the subjects were consistent over most of the dosing occasions and dosing days. Of 10,734 dosing occasions, subjects were consistent 96% of the time. Of 10,376 dosing days, subjects were consistent 93% of the time. Thus, while only 62% of subjects were consistent overall, this data provides some sense of comfort in the knowledge that subjects were consistent for most of the dosing occasions and dosing days.

The majority of subjects did not take more than 2 tablets per dosing occasion; <1% exceeded 2 tablets per dosing occasion. The majority of subjects also did not exceed more than 2 dosing occasions per day; only 3% did.

Per Usage

The majority of subjects took study drug for both prevention and relief. The subjects (316) who took study drug for Relief Only were more consistent with the dosing directions (80%). Only 32% of those in the Prevention Only group were consistent. Among the Relief only users, the highest inconsistency (11%) occurred with exceeding one tablet per dose.

Among the Prevention Only users, the highest inconsistency occurred with exceeding the 10-day limit (64%). In Table 11, 80% of the relief only users took study drug for a maximum number of 1-2 sequential dosing days, while only 16% of the Prevention Only users did likewise. Of the Prevention Only users, a total of 35% took drug for up to10 sequential dosing days, and 65% took drug for over 10 sequential dosing days. Of the Relief Only users, 96% took drug for up to 10 sequential dosing days.

2.4. Label Consistency by Reading Level:

Table 17

LABEL USE DIRECTION CONSISTENCY PER SUBJECT BASIS IN SUBJECTS WITH LOW READING ABILITY **Intent-To-Treat Subjects**	**Ref:TABLE 8.2.8**
Subjects with Low Reading Ability (≤60 on REALM test)	**N = 84**
Consistent	48 (57%)
Not Consistent	36 (43%)
Exceeded one tablet per dose	20 (24%)
Exceeded one dose per day	13 (15%)
Exceeded 10 consecutive dosing days	21 (25%)

For all users, consistency was slightly higher for subjects with >8th grade reading ability (63%) compared to subjects with low reading ability (57%). In general, the most noticeable difference between the reading ability groups overall was that a higher percentage of subjects with low reading ability exceeded one tablet per dose (24%) compared to 13% in the >8th grade reading ability group.

Medical Officer's Comments:

Per Literary Level

Among subjects (N=84) with low reading ability (<60 on REALM test), 57% were consistent with all 3 dosing directions, while 43% were not. This compares with 62% consistency for all subjects. Twenty-five percent of these subjects exceeded the 10-day limit, 24% exceeded one tablet per dose, and 15% exceeded one dose per day; the low literacy subjects were more compliant with the 10-day limit and less complaint with the 1-tablet per dose. However, since the total numbers of subjects in this group is small, the confidence intervals (not provided) around these estimates are expected to be larger than predicted, and the usefulness of these results for comparison with the total group may be limited.

3. **Efficacy:**

3.1. Overall Efficacy:

A total of 874 subjects returned the Product Use Journal. Fifty-two subjects (5.9%) were given study medication but did not dose with it over the 4-week usage period. Subjects were asked in the Product Use Journal: "Did the medication work for your heartburn?" The percentage of effective dosing occasions and the percentage of dosing occasions requiring backup medication use over the study period were calculated per subject and then averaged across subjects in each group.

Table 18

MEDICATION EFFECTIVENESS **Intent-To-Treat Subjects**	**Ref: TABLE 8.2.19**
	N = 825
Mean Percent of Effective Dosing Occasions	91%*
Mean Percent of Effective Dosing Occasions on First Dose	90%*
Mean Percent Dosing Occasions with Backup Medication Use	4%*

* Actual numbers for these percentages were not presented

Overall, the mean percentage of effective dosing occasions was 91%, the percentage of effective dosing occasions for the first dose was 90%, and the mean percentage of dosing occasions requiring backup medication use was 4%.

Subjects were also asked in the Case Report Form to provide an overall assessment of the medication. They were asked to rate medication as: Poor, Fair, Good, Very Good, or Excellent. Thirty-five percent (35%) of subjects rated the study medication as Excellent followed by 34% of subjects who rated it Very Good, 21% of subjects who rated it Good, 6% who rated it Fair, and 4% who rated it Poor (no table provided).

3.2. Concurrent Use of Heartburn Medication:

Table 19

CONCURRENT USE OF OTHER HEARTBURN MEDICATIONS **Intent-To-Treat Subjects**	**Ref: TABLE 8.2.25**
	N = 825
Antacid	111 (13%)
H_2RA	17 (2%)
PPI	1 (1%)

These medications were obtained from the medications log if the subject reported they took a backup heartburn medication after dosing with the study medication on the same day. Overall, 111 of 825 (13%) subjects used antacids on the same day as the study medication, while 2% of subjects took H_2RA. The rate of concurrent PPI use was the lowest, consisting of 5 of 825 subjects.

3.3. Efficacy by Usage Group:

Table 20

MEDICATION EFFECTIVENESS **Ref: TABLE 8.2.19**
Intent-To-Treat Subjects

	Prevention* N=80	Relief N=317	Total N=825
Mean % Effective Dosing Occasions	96%	88%	91%
Mean % Effective Dosing Occasions on First Dose	91%	90%	90%
Mean % Dosing Occasions with Backup Medication Use	4%	5%	4%

* The subjects in the 3 prevention groups, Prevention Any Time Only, Prevention 1-hr Before Only, and Dual Prevention Only, were added and considered together. Actual numbers for the percentages were not provided.

The mean percentage of effective dosing occasions was about 96% for the Prevention Only group, and 88% for the Relief Only group. The mean percentage of dosing occasions with backup medication use was minimal in both groups.

For an overall assessment of the medication (no table provided), the three Prevention groups had a greater percentage of subjects (47%–67%) who rated the study medication as Excellent compared to the Relief-Only (25%) and the Prevention-And-Relief groups (39%).

3.4. Efficacy by Usage Group by Dosing Occasions and Dosing Days:

Eighty-eight percent of the subjects had at least 90% effective dosing occasions with an average of 10.6 dosing occasions for prevention by taking any time during the day. Eighty-eight percent of the subjects had at least 90% effective dosing occasions with an average of 6.9 dosing occasions for prevention by taking 1 hour before event. Seventy-seven percent of the subjects had at least 90% effective dosing occasions with an average of 6.6 dosing occasions for relief of symptoms.

3.5. Concurrent Use of Heartburn Medication By Usage Group:

Table 21

CONCURRENT USE OF OTHER HEARTBURN MEDICATIONS **Ref: TABLE 8.2.25**
Intent-To-Treat Subjects

	Prevention* N=80	Relief N=317	Total N=825
Antacid	15 (19%)	24 (08%)	111 (13%)
H_2RA	(0%)	1 (<1%)	17 (2%)
PPI	(0%)	1 (<1%)	5 (1%)

* The subjects in the 3 prevention groups, Prevention Any Time Only, Prevention 1-hr Before Only, and Dual Prevention Only, were added and considered together.

The rate of concurrent antacid use was 18% for the Prevention-Only group, and 8% for the Relief-Only group. No subjects in the Prevention-Only group used H_2RAs or PPIs on the same day as study medication. The rate of concurrent H_2RA use was <1% for Relief-Only group. The rate of concurrent PPI use was <1% for Relief-Only group. Dosing occasions with concurrent use of H_2RAs and PPIs occurred at a rate of 1% or less in all sub-groups.

Medical Officer's Comments:

Efficacy

Only subjective reports of drug effect was obtained in this study. Subjects were asked if the drug worked and for a global rating of the drug as being good or bad, etc. on a 5-point scale. An objective assessment of drug efficacy cannot be made on the basis of this trial. Other clinical trials conducted in support of this application will provide the efficacy data for this product; these will be reviewed by medical officers in the GI review division.

III. SPONSOR'S SAFETY ANALYSIS

1. Extent of Exposure:

One thousand ninety-three subjects were supplied with 36 tablets of omeprazole magnesium 20.6 mg each. Subjects were instructed to use the study medication as needed for a period of four weeks. Eight hundred twenty-five subjects (75%) took at least one dose of study medication and returned the Product Use Journal. Fifty-two subjects (5%) were given study medication but did not dose with it over the 4-week usage period. Dosing information was not available from the remaining 216 subjects (20%).

Table 22

SUMMARY OF EXPOSURE BY DOSING DAYS **Intent-To-Treat Subjects**	**Ref: TABLE 8.3.1**
Mean	12.8 Days
Standard Deviation	9.5 Days
Minimum-Maximum	1-35 Days

The largest percentage of subjects took medication for 3 days (8%). Four to six percent of subjects took drug from 1 to 9 days. Less than 1% to 3% of subjects took drug ranging from 10 to 35 days, except for 12 days (5%).

Adverse events (AEs) that occurred during the study were documented on the Case Report Forms (CRFs), whether or not they were considered study medication related. Descriptions of reactions or complaints included the start and end dates of the AE, intensity of the AE, action taken with respect to study medication, relationship of the AE to the study medication, and whether the AE led to dropout. Eight hundred thirty-three subjects were included in the safety summary, which included subjects who reported an AE regardless of returning their Product Use Journal.

Overall, 203 subjects (24%) reported 292 AEs. Of those who reported AEs, 74% experienced AEs, which were Mild or Moderate in intensity. Thirty-three percent of subjects had AEs considered Possibly or Probably related to study medication. The percentages of AEs, which were Mild or Moderate in intensity were 89%, and 77% for Prevention-Only users, and Relief-Only users, respectively. The percentages of AEs considered Possibly or Probably related to study medication were 21%, and 30%, for Prevention-Only users, and Relief-Only users, respectively.

2. Adverse Events

2.1. Deaths:

Only 1 death was reported.

SUBJECT NUMBER 030046 was a 54 year old white female who took a total of five doses of study medication from 12-Jan-99 to 20-Jan-99. On 30-Jan-99 the subject took an overdose of Vicodin for which she went to a local emergency room. After leaving the emergency room, against medical advice, the subject returned home on 30-Jan-99. The following morning, the police found the subject dead in bed at 2:00 AM. A number of prescription bottles were open at the bedside. These medications consisted of Premarin, nitroglycerin tabs, Vicodin, Prednisone, Valium, and Prozac. An autopsy was performed and

the cause of death was considered to be polydrug intoxication. Underlying medical conditions included systemic lupus erythematosis, heart problems, asthma, and depression.
The Investigator believes this SAE was Unlikely related to study medication.

2.2. Serious Adverse Events (SAEs):

A total of 5 SAEs were reported, including the 1 fatal case #030046.
(1) SUBJECT NUMBER 020089
This subject was a 31 year old Hispanic female who experienced an exacerbation of asthma on 17-Feb-99. The subject was admitted to the hospital and treated successfully with intravenous steroids and fluids. The subject was discharged on 19-Feb-99 and given Prednisone 30 mg per day for three additional days. The subject started study medication on 20-Jan-99. The previous SAE did not recur when the study medication was started. The subject took a total of 33 tablets from 20-Jan-99 to 24-Feb-99. Other concomitant medications included Proventil inhaler which the subject had been using since 1985.
The Investigator believes this SAE was unlikely to be related to study medication.

(2) SUBJECT NUMBER 050196
This subject was a 84 year old white male who took a total of 6 tablets of study medication from 5-Jan-99 to 23-Feb-99. Beginning on 15-Jan-99, the subject developed progressive shortness of breath and productive yellowish sputum. The subject was admitted to the hospital with a diagnosis of pneumonia on 18-Jan-99. The episode completely resolved on 26-Jan-99. Concomitant medications included Eulexin, Lupron, Prevacid, theophylline, and Detrol. The Investigator believes this SAE was Unlikely related to study medication.

(4) SUBJECT NUMBER 050285
This subject was a 78 year old white male who took an unknown number of study medication beginning 23-Jan-99. On 22-Feb-99, the subject experienced a heart attack. The subject had experienced a heart attack five months previous. No other information is available, as the subject's wife refused to provide any additional information. The Investigator believes this SAE was Unlikely related to study medication.

(5) SUBJECT NUMBER 060019
This subject was a 25 year old white male who took the study medication from 15-Jan-99 to 20-Jan-99. It is unknown how many tablets of study medication he took. On 3-Feb-99, the subject noticed "fluid build up" and went to the hospital where he was treated and released on 6-Feb-99. The subject had been previously hospitalized for a similar condition and was diagnosed as having cardiomyopathy in December 1998. The subject's edema subsided and his condition stabilized. The subject refused to answer subsequent inquiries regarding his condition. Concomitant medications included Accupril, Lanoxin, Lasix, and Primatene Mist. The Investigator believes this SAE was Unlikely related to study medication.

2.3. Discontinuation due to Adverse Events:

There were 4 subjects who discontinued study participation due to an AE. Three of these cases have already been discussed in the SAE section. These cases involved Subjects 030046, 050285, and 060019. Subject 020024 discontinued because of skin itching on the chest, neck, arms, and back. This subject took a total of three tablets of study medication from 12-Jan-99 to 20-Jan-99.

2.4. Other Adverse Events:

MOST COMMON ADVERSE EVENTS BY COSTART TERM Safety Subjects			Ref: TABLE 8.3.10
(* Number subjects who reported Adverse Event)	Prevention N=80	Relief N=317	Total N=833*
BODY: Headache	1 (1%)	12 (4%)	47 (6%)
RESP: Infection	6 (8%)	12 (4%)	36 (4%)
DIG: Diarrhea	2 (3%)	8 (3%)	22 (3%)
BODY: Flu Syndrome	1 (1%)	5 (2%)	14 (2%)
DIG: Dyspepsia	0 (0%)	7 (2%)	13 (2%)
DIG: Flatulence	2 (3%)	2 (1%)	13 (2%)
BODY: Pain Abdomen	2 (3%)	2 (1%)	12 (1%)

Overall, the most commonly reported AE was headache (47 subjects, 6%), followed by respiratory infection (4%) and diarrhea (3%). All other AEs had an incidence of 2% or less overall. Overall among all subjects, there appears to be no increase in the percentage of AEs with increasing days of use, increasing number of doses, increasing number of tablets taken, or increasing duration of use. Differences were noted in percentage of AEs among the Prevention Only Users and Relief Only Users, but not in any consistent pattern with increasing the number of doses, days, or duration of use.

The AEs considered probably related to the study medication included headache, malaise, abdominal pain (Body as a Whole), diarrhea, dyspepsia, eructation, flatulence, gastritis, abdominal pain (Digestive System), and nausea. For Prevention Only users, there were no AEs thought probably related to the study medication. AEs thought possibly related include headache, diarrhea, dry mouth, and flatulence. For Relief Only users, AEs thought probably related to study medication include malaise, dyspepsia, eructation, while those possibly related include headache, pain, pain abdominal, constipation, diarrhea, dry mouth, nausea, arthralgia, insomnia, and nervousness.

Medical Officer's Comments

A total of 1093 subjects received study medication, of which 52 were known to not have taken any study drug. Of the subjects who were classified as not having completed the study (219), sponsor did not specify if any of these subjects took study drug and if any AEs were recorded.

There were 833 subjects in the safety database. A total of 203 subjects in the safety database reported a total of 292 AEs. There were a total of 5 Serious AEs, of which 1 had a fatal outcome. Thirty-three percent of all subjects had AEs considered Possibly or Probably related to study drug. Seventy-four percent of all AEs were Mild or Moderate in intensity were 74% for all subjects. Four subjects discontinued study because of an AE; 3 of these subjects experienced a SAE, and the fourth discontinued because of skin itching on the chest, neck, arms, and back.

The one death which occurred in a 54 year old white female was presumed due to polydrug intoxication involving Vicodin, Prozac, Valium, and other drugs. All 4 other SAEs were considered unlikely to be related to study drug by study investigator. Of these 4 subjects, one experienced an exacerbation of asthma, one had pneumonia, and two had heart disease (cardiomyopathy, myocardial infarction).

A listing of all AEs were submitted; however, a summary table of all the AEs by number of subjects and frequency of occurrence was not provided. The most frequently reported AEs by body system occurred in the Body as a Whole category, in which 92 subjects (11%) reported 104 AEs. The most common AE experienced was headache (6%), followed by respiratory infection (4%) and diarrhea (3%). All other AEs occurred with 2% frequency or less.

The AEs considered Probably related to study drug were mostly in the Body as a Whole and Digestive Body systems, such as headache, abdominal pain, diarrhea, dyspepsia, flatulence, gastritis, and nausea.

1. Discussion

The decision for whether omeprazole can be approved for OTC use should be based on issues specific to the active ingredient and drug class, such as the following:

(1) Efficacy: that omeprazole at a specific dose is effective for OTC use for relief and prevention of heartburn due to foods, beverages, stress, and other lifestyle factors
(2) Safety: that omeprazole used by consumers without the learned intermediary is safe
(3) OTC considerations: that consumers can self-select and use the product appropriately. These OTC considerations should be driven by the proposed OTC regimen and product labeling, if different from current labeling for this indication.

A determination of efficacy for omreprazole magnesium MUPS tablets will be made on the basis of the pivotal clinical trials submitted and will be reveiwed eslewhere. This study provided a general sense that most subjects felt that the drug was effective. For global assessments, it is interesting to to note that 25% of Relief only users rated study drug as excellent compared to 47-67% of the various Prevention only user groups.

A determination of safety will also be made from the overall package submitted to this NDA. From this study, the adverse event experiences reported were unremarkable. All 5 serious events, including 1 death, were not related to study drug. Discontinuations secondary to an adverse event were minimal; 3 of the subjects were the same subjects who had reported an SAE, and the fourth subject had skin itching. The most common AE is headache which is often reported in drug studies. Other common AEs belong in the Digestive body system, occurring in a targeted study population with self-professed "stomach problems". The safety information will need to be supplemented by the safety information from the controlled trials as well as post-marketing information accumulated for the prescription use of omeprazole.

As to appropriate self-selection and use, this study was not designed to demonstrate how OTC consumers would do with self-selection, since validation of subjects' self-selection decisions was not done. Furthermore, the study population is very restricted such that all subjects with potential risks as designated by the label were excluded, specifically the groups pertinent to this class of drug such as pregnant or lactating females, people already taking certain medications. This information is critical to an assessment of the performance of the OTC label in directing the consumer towards safe and appropriate use of omeprazole. The only assessment of appropriate use in this study is consistency with dosing directions in terms of dose taken per dosing occasion, per dosing day, and total number of days of use. There is no assessment of compliance with label warnings such as absolute contraindications, relative contraindications, when to stop use, and when to have contact with a doctor or health care professional.

In the area of consistency with dosing directions, the overall consistency on a per subject basis is unimpressive, with only 63% overall consistency. This result is improved depending on the subsets used in the analysis, but the fact remains that 38% of subjects do not comply with the

dosing directions at one time or another. It should be noted that there were several exclusions of subjects from the consistency analysis, such as the 10 subjects with incomplete data, and the 219 subjects who did not complete the study. The question is what impact these exclusions would have on the study results.

Dosing consistency on a per dosing day basis is worse in the users who state that they are using the drug for prevention only since the majority of these users took drug for more than 16 days, with up to 39% of them taking for over 29 days. It may be that the subjects in this study have more than occasional heartburn and require much longer use of medication. Heartburn that requires continuous and extended use of medication should be evaluated by a physician so that more serious conditions can be ruled out, and proper treatment plans are implemented. The risk of chronic heartburn and Barrett's esophagus should be addressed by a physician without undue delay.

3. Conclusions:

The information obtained from this study can be summed up as follows:

1. Overall consistency of subjects with dosing directions is 62%.
2. Relief only (80%) users were more compliant with the dosing directions than the prevention only users (25-54%).
3. By dosing occasions, overall consistency is 96%, and 93% by dosing days; i.e. each non-compliant subject is not non-compliant all of the time.
4. The majority of subjects took 1 tablet per dosing occasion (86%) or per dosing day (78%). More subjects took >1 tablet by Dosing Day, than by Dosing Occasion.
5. Relief only users were more compliant with the dosing day restriction; 73% had 8 or less dosing days, compared to 9-21% in the 3 prevention subgroups. Seventy-one to eighty-one percent of Prevention only users (all types) had 13 or more dosing days, compared to 18% in Relief only users.
6. Correctness of subjects' self-selection decision was not assessed.
7. Performance of subjects with respect to certain risk conditions cannot be assessed:
   - pregnancy
   - difficuty swallowing
   - persistent stomach pains (>10 days)
   - use of concomitant drugs.
8. Performance of subjects with respect to contacting a doctor or health care professional cannot be assessed.
9. Safety profile is unremarkable.

Appendix I

Proposed Prilosec Label

- Purpose: Acid preventer
- Uses:
  - for relief of heartburn, acid indigestion and sour stomach
  - for prevention of heartburn, acid indigestion and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise

Allergy alert: Do not use if you are allergic to omeprazole

- Absolute contraindications:
  - do not use if difficulty swallowing
  - do not use with acid reducers
- Ask a doctor or pharmacist before use:
  - If taking ketoconazole or itraconazole, both antifungal medicines
- Stop use and ask a doctor:
  - stomach pain continues for 10 days
- Directions
  - do not use for more than 10 days in a row unless directed by a doctor

Label used in 198003

The carton labels had the following use directions:

Uses:

- for **prevention** of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise
- for **relief** of heartburn, acid indigestion, and sour stomach

Directions: Adults and children 12 years of age and older:

- for prevention of symptoms for 24 hours: Swallow one tablet with a glass of water anytime during the day, or if you prefer, one hour before those events associated with occasional heartburn, such as consuming food and beverages, stress, hectic lifestyle, lying down, or exercise.
- for relief of symptoms: Swallow one tablet with a glass of water.
- do not take more than one tablet a day. Do not use for more than 10 days in a row unless directed by a doctor.
- do not chew or crush tablets.

Children under 12 years of age: Ask a doctor.

NDA #:	21-229
Drug name:	Prilosec 1 (Omeprazole Magnesium) 20.6 mg Tablets
Sponsor:	Procter&Gamble Company 8700 Mason-Montgomery Road Mason, Ohio 45040-9426
Submission date:	January 27, 2000
Review date:	September 12, 2000
Reviewer:	Daiva Shetty, MD

Table of Contents:

Study #067

A MULTI-CENTER, OPEN-LABEL, ACTUAL-USE STUDY TO INVESTIGATE THE CONSUMER USAGE PATTERNS/DOSING COMPLIANCE OF OMEPRAZOLE MAGNESIUM 20.6 MG WHEN USED BY ADOLESCENTS

The **primary objective** of this study was to characterize the usage patterns of omeprazole magnesium when used *ad libitum* according to proposed label instructions under naturalistic OTC conditions in adolescents.

A **secondary objective** of this study was to investigate the effectiveness and safety of omeprazole magnesium in adolescents in a naturalistic setting.

Design
This was a multi-center, multi-dose, open-label, at-home study.

Subjects were recruited through, but not limited to, families who presented at two Pediatric offices. Those subjects who were willing to participate in the actual-use phase of the study were screened by study staff. The Investigator obtained written and signed informed consent for each subject, who elected to participate in this study.

There was no blinding or randomization done due to the single-medication, open-label study design. Subject enrollment began 5-Jan-99 and ceased 15-Feb-99. Sample size calculations were not carried out for this study. A goal of 100 subjects was established for enrollment. Subjects were paid $50.00 upon completion of the study.

Inclusion Criteria

- provided written informed consent (co-signed by legal guardian),
- were male or non-pregnant, non-lactating female, of any race, at least 12 years of age but not older than 17 (12–17 years inclusive),
- if female, were willing to complete three urine pregnancy tests (one at Visit 1 [enrollment], the second before taking the initial dose of study medication, and the third at Visit 2), and not use the medication if any test was positive,
- if female, were either sexually inactive or using an acceptable form of contraception (including abstinence) as determined by the Investigator or study staff,
- had a history of heartburn which they had treated with antacids or histamine-2 receptor antagonists (H2Ras) in the last month, and
- were willing and able to complete the Product Use Journal during the study period, were willing to answer a telephone interview, and were willing to return at the end of the study period (Visit 2) with any unused study medication, the study medication package, and the Product Use Journal.

Exclusion Criteria

- were pregnant or lactating,
- had an active peptic ulcer disease currently being treated with prescription H2RAs or PPIs,
- were currently dosing with phenytoin (Dilantin), warfarin (Coumadin), diazepam (Valium), or clarithromycin (Biaxin),
- had a known hypersensitivity to omeprazole or omeprazole magnesium,
- had experienced continuous abdominal pain >10 days in duration,
- had dysphagia (difficulty swallowing), or
- had previously participated in this study.

Comments

The informed consent used in this study has been reviewed and found to be acceptable. Only two study centers were included in this trial. Even though subject distribution was equal between these centers, both of them were located and recruited subjects in the same state - Utah. Subjects targeted and enrolled into the study were screened for eligibility by the investigator prior to subjects' determination if this product is appropriate for them. Thus, self-selection was not addressed in this study. The expanded list of inclusion and exclusion criteria makes actual use behavior interpretation problematic, especially regarding history and frequency of heartburn, and potential use during pregnancy.

Visit 1 (Screening Visit)

The information on subjects' demographics, heartburn history, medical/medication history, if female, the pregnancy test/birth control agreement was obtained from the subject or her guardian. Eligible subjects were supplied with 36 tablets of omeprazole magnesium 20.6 mg and a Product Use Journal. Subjects were scheduled to return to the study site in approximately 4 weeks.

The carton labels used in this study had the following use directions:

USES: **for prevention** of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, stress, hectic lifestyle, lying down, or exercise.
for relief of heartburn, acid indigestion, and sour stomach.

DIRECTIONS: Adults and children 12 years of age and older:
For prevention of symptoms for 24 hours: swallow 1 tablet with a glass of water anytime during the day, or if you prefer, one hour before those events associated with occasional heartburn, such as consuming food and beverages, stress, hectic lifestyle, lying down, or exercise.
For relief of symptoms: Swallow 1 tablet with a glass of water.
Do not take more than 1 tablet every 24 hours. Do not use for more than 10 days in a row unless directed by a doctor.
Do not chew or crush tablets.
Children under 12 years of age: ask a doctor.

Subjects were asked to record the following information in the Product Use Journal: date and time of each dose, number of tablets taken, if taken for prevention or relief of symptoms, severity of heartburn symptoms, assessment of study medication effectiveness and whether another medication was also taken to treat heartburn symptoms. In addition, urine pregnancy test results, adverse events, and concomitant medications were recorded.

Interim Phone Interview
Approximately 2 weeks after Visit 1, the subjects were contacted by phone to ensure that the Product Use Journal was being filled out correctly and that no complications had occurred from taking the study medication. The female subjects were asked to provide the result of their urine pregnancy test.

Visit 2 (Final Visit)
Subjects returned any unused medication, the medication package and the Product Use Journal. Subjects were asked to provide an overall assessment of study medication they had been using.

Statistical Methods and Analysis Plans
All statistical analyses were performed using SAS® Version 6.04 on a DOS operating system. Descriptive statistics were used to assess baseline comparability of demographic variables between types of users. Usage patterns, including consistency with the three label use directions, were summarized using descriptive statistics by type of user and across all users. Consistency rates were calculated by pooling across study centers and for each individual study center. In addition, subjects' dosing behaviors over the study period were summarized. Study medication effectiveness and overall assessment of study medication were summarized using descriptive statistics. Except for the summary of dosing behaviors, all other statistical summaries were performed on the Intent-to-Treat (ITT) subjects. Dosing behaviors were summarized on all subjects who returned the

Product Use Journal at Visit 2 (regardless of whether or not a dose was taken by the subject).

Demographic characteristics, heartburn history, factors contributing to heartburn, prior and concomitant medication therapies, usage patterns including consistency with the three label use directions, efficacy, and concomitant use of other heartburn medications were summarized by the following five types of users and overall:

- Prevention-Any-Time-Only users (users who recorded this use type exclusively),
- Prevention-1-Hour-Before-Only users (users who recorded this use type exclusively),
- Dual-Prevention-Only users (users who recorded both of the prevention use types but not relief use type),
- Relief-Only users (users who recorded this use type exclusively), and
- Prevention-And-Relief users (users who indicated that one or more doses were taken for prevention and one or more doses were taken for relief of heartburn symptoms).

The label use direction consistency on a per subject basis was additionally summarized by the 'Predominant Use Pattern,' which was defined as > 50% use for any one of the three reasons for use as collected on the Product Use Journal.

Comments
The indications listed on the label were identical to those on the proposed OTC product. Descriptive statistics for evaluation of compliance is acceptable for actual use trials. Data analysis was summarized by five exclusive types of users. In addition, the sponsor reanalyzed the data by the "Predominant Use Pattern." This analysis is considered post-hoc and is not considered as formal evidence. Therefore, the results summarized by the predominant use will not be discussed in this review.

Results
The following chart displays disposition of the subjects.

Screened at Visit 1
N=100
↓
Met Inclusion/Exclusion Criteria
N=100
↓
Completed Study / Did not Complete study
N=98 N=2

Of the 98 subjects who completed the study, 92 subjects consumed at least one dose of study medication, as indicated in their returned Product Use Journals and were included in the Intent-to-Treat (ITT) analysis set. The other 6 subjects did not dose with study medication. Among them, 2 subjects did not experience heartburn during the 4-week usage period and 4 subjects did not have the study medication with them when they experienced heartburn. Out of two subjects who did not complete the study, one was lost to follow-up, and one had difficulty swallowing the medication.

There were twelve protocol violations. Four subjects took study medication prior to administering the home pregnancy test. Three of those got the final pregnancy test done at visit 2, and one subject refused to return for testing (this subject never took study medication). Seven subjects returned product kit with tablets missing or unaccounted for. One subject did not sign revised informed consent.

One case (#002049) where the subject did not comply with the label directions was not considered as protocol violation by the sponsor. This patient took the drug continuously because parent, who was a physician, instructed the subject to take it every day. This was a 17-year-old caucasian female with an almost daily ($\geq$ 6 days a week) heartburn symptoms of 2-5 year duration. She has been treated with OTC, but not Rx heartburn medication. The frequency of intake of OTC medications was not recorded. Her pattern of intake of omeprazole during this study was: one tablet a day, except for 4 days when she took 2 tablets per dose, continuously.

Comments
Behavior of childbearing age women was not addressed in this study. Four subject who did not comply with home urine pregnancy testing represent total of 7% (4/56) of females enrolled. This number greatly underestimates the use of this drug by childbearing potential female.

Demographic and Other Baseline Characteristics and Concomitant Medication
Fifty-six (56) subjects (61%) were female and 36 (39%) were male, ranging in age from 12–17 years, with a mean age of 14 years. The majority (88 of 92) of the subjects (96%) were Caucasian, and the remaining 4 subjects were Hispanic.

Heartburn History
A majority of the subjects [78 out of 92 (85%)] had more than 1 year of heartburn experience. All subjects experienced more than 1 month of heartburn. Frequency of daytime heartburn during a week in the ITT subjects was as follow:

- 32% once a week;
- 45% two to three times a week;
- 16% four to five times a week;
- 3% six or more times a week.

About two-thirds of the subjects (68%) rarely experienced heartburn at night. Three subjects (4%) were taking prescription medication for heartburn at the time of enrollment, of which two were taking Zantac and one Pepcid. Ninety (90) subjects (98%) took non-prescription heartburn medications during the month prior to study participation.

The sponsor asked enrolled subjects about the factors contributing to their heartburn. Subjects were permitted to select as many factors that contributed to their heartburn over the past month. Food and/or beverage was found to be the most typical contributing factor [77 out of 92 ITT population (84%)] of heartburn over the month prior to Visit 1,

followed by stress and/or anxiety [60 subjects (65%)] and hectic lifestyle [27 subjects (29%)].

The most common prior medication therapies for heartburn were TUMS, ibuprofen, Tylenol, Pepto-Bismol, Pepcid AC, Rolaids, and amoxicillin. During the study, subjects were allowed any concomitant medication, which was not specifically excluded in the Exclusion criteria of the protocol. The most common concomitant medications were similar to the prior medication therapies and included TUMS, ibuprofen, Tylenol, Pepto-Bismol, Rolaids, Pepcid AC, and Advil.

Comments
The demographically enrolled population was not representative of the overall U.S. population. The majority of enrolled subjects were Caucasians. There were no African-Americans enrolled in this study. Socio-economic status, which could possibly influence the behavior of adolescents, was not evaluated in this study.

It is not surprising that every subject in ITT population was taking some kind of medication for their heartburn prior to their enrollment, especially given the inclusion criteria. Information about the history of heartburn showed that 45% of the enrolled subjects suffered from it two to three times a week; nineteen percent (19%) had 4 to 6 episodes a week; and 85% had more than one year of heartburn experience, raising a concern if this is the appropriate OTC population with "occasional episodic heartburn."

Summary of Usage Patterns
As mentioned in the protocol design section, subjects were classified into five categories representing usage patterns within the two indications.

The frequency and percentage of the ITT subjects in each of the usage categories were as follows:

- 7 (8%) for the Prevention-Any-Time-Only users,
- 1 (1%) for the Prevention-1-Hour-Before-Only users,
- 3 (3%) for the Dual-Prevention-Only users,
- 34 (37%) for the Relief-Only users, and
- 47 (51%) for the Prevention-And-Relief users.

Consistency with label use directions
The sponsor's rationale to use consistency rather than compliance with the label is based on the fact that this study design did not collect information regarding physician/subject consultation in reference to the use direction 'do not take for more than 10 consecutive days.' To evaluate consistency with the three label use directions, the frequency and percentage of subjects who used study medication according to label instructions over the 4-week usage period were summarized on a per subject basis, per dosing day, and per dosing occasion.

Subjects were considered to be consistent with the three label use directions if they 1)

consumed no more than one tablet per dose, 2) took no more than one dose per day, and 3) dosed for no more than 10 consecutive days. A dosing day was considered consistent with the label use directions if no more than one tablet was taken per dose and if no more than one dose was taken per day. A dosing occasion was considered consistent with the label use direction if no more than one tablet was taken per dose. Summarization of label use direction consistency on a per subject basis can be found in Table 1.

Table 1. Consistency with Label Use Directions (ITT Population)

	Prevention Any Time N=7 (%)	Prevention 1-Hr Before N=1 (%)	Dual Prevention N=3 (%)	Relief Only N=34 (%)	Prevention and Relief N=47 (%)	Overall N=92 (%)
Consistent with Label Use Direction	2 (29%)	1 (100%)	1 (33%)	32 (94%)	33 (70%)	69 (75%)
Not Consistent with Label Use Directions	5 (71%)	0 (0%)	2 (67%)	2 (6%)	14 (30%)	23 (25%)
• Exceeded 1 tablet per dose	1 (14%)	0 (0%)	0 (0%)	1 (3%)	6 (13%)	8 (9%)
• Exceeded 1 dose per day	0 (0%)	0 (0%)	0 (0%)	1 (3%)	2 (4%)	3 (3%)
• Exceeded 10 consecutive dosing days	5 (71%)	0 (0%)	2 (67%)	0 (0%)	9 (19%)	16 (17%)

Overall 69 of 92 subjects (75%) were consistent with all three label use directions, 8 subjects (9%) took more than one tablet per dose, 3 subjects (3%) took more than one dose per day, and 16 subjects (17%) exceeded 10 consecutive days of dosing. Prevention any time and dual prevention groups were less consistent and tended to continue on treatment for more than 10 days.

Consistency with the three label use directions on a per subject basis by investigator showed that investigator Folland had a greater consistency rate (86%) when compared to investigator Gabrielson (65%). Gabrielson's study center had a larger percentage of subjects who dosed for more than 10 consecutive days (27%) than Folland's study center (7%).

Consistency with the three label use directions was similar (75%) in both female and male groups.

Table 2 shows the result of consistency with the three label use directions by number of dosing occasions on a per subject basis for ITT subjects. The consistency was higher in subjects who had fewer dosing occasions over all users. Overall, 75% of subjects were consistent with the three label use directions. For Prevention-Only users, all subjects who had more than 4 dosing occasions were not consistent, but all subjects who had 1–4 dosing occasions were consistent, with all three label use directions.

Table 2. Label Use Direction Consistency by Number of Dosing Occasions in ITT Population (N=92)

Number of Dosing Occasions	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	>32	Overall
Consistency (N)	36/37	21/24	8/10	N/A	N/A	2/7	2/6	0/3	0/5	69/92
Consistency (%)	97%	88%	80%	N/A	N/A	29%	33%	0%	0%	75%

Comments
The number of subjects in some of the five usage pattern groups was too small to make a meaningful conclusions. Therefore, the data discussion will focus on the overall population enrolled into the study.

Primary objective to characterize the usage patterns was achieved by 75% of treated subjects. Even though the number of subjects in some of the five usage pattern groups was too small, a tendency to be non-consistent and to take medication for longer than 10 consecutive days was observed in Prevention-Any-Time and Dual-Prevention groups. Consistency with the label directions in the prevention group was observed only when subjects had not more than 4 dosing occasions. Conclusions could be made that consumers are more familiar and compliant with acute/symptomatic treatment than prevention.

Analysis of the same data on per dosing day basis, and per dosing occasion basis does not give us any additional information. All three label use directions should be accounted for in the evaluation of consistency.

Since there were only 4 non-Caucasian subjects enrolled in to the study, analysis by racial groups is not meaningful.

Product Use Summaries
Table 3 displays the maximum number of sequential days of dosing for ITT subjects. Overall, 67% of subjects had 1–2 maximum sequential dosing days and 17% of subjects had more than 10 maximum sequential dosing days.

Table 3. Maximum Number of Sequential Dosing Days (ITT population)

Maximum Number of Sequential Days	Prevention Any Time N=7 (%)	Prevention 1-Hr Before N=1 (%)	Dual Prevention N=3 (%)	Relief Only N=34 (%)	Prevention and Relief N=47 (%)	Overall N=92 (%)
1-2	2 (29%)	1 (100%)	1 (33%)	33 (97%)	25 (53%)	62 (67%)
3-4	0 (0%)	0 (0%)	0 (0%)	1 (3%)	6 (13%)	7 (8%)
5-6	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6%)	3 (3%)
7-8	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)
9-10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6%)	3 (3%)
11-12	1 (14%)	0 (0%)	1 (33%)	0 (0%)	1 (2%)	3 (3%)
13-14	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
≥15	4 (57%)	0 (0%)	1 (33%)	0 (0%)	8 (17%)	13 (14%)

Overall, 9% of subjects had a maximum number of two tablets taken per dosing occasion and per dosing day. One percent (1%) of subjects had a maximum number of three or more tablets taken per dosing day.

The sponsor also analyzed the minimum number of hours between doses for ITT subjects. Overall, 37 of 92 of subjects (40%) had a minimum interval of less than 20 hours between doses.

Comments
The analysis of the total number of dosing days, total number of dosing occasions, total number of tablets, and the minimum number of hours between the doses for the ITT subjects across the study is not as important as the maximum number of sequential dosing days. Even though the number of subjects in the prevention groups was small, the data gathered in this study raise a concern. Seven out of 11 subjects in the combined prevention groups exceeded 10 sequential dosing days. Behavior of the subjects taking study medication for relief only was much better than other subgroups, since none of the subjects exceeded 10-day dosing. Most of the subjects enrolled in this study were taking one tablet per dose and no more than 1 tablet per day.

Efficacy evaluation
The percentage of effective dosing occasions and dosing occasions with backup medication use over the study period were calculated per subject and then averaged across subjects in each group. Overall, the mean percentage of effective dosing occasions was 92%, the percent of effective dosing occasions for the first dose was 90%, and the mean percentage of dosing occasions requiring backup medication was 3%. The mean percentage of dosing occasions with backup medication use was about 1% or less in any of the three Prevention-Only groups and about 2%–4% in the Relief-Only and the Prevention-And-Relief groups.

Overall, assessment of study medication on a per subject basis for ITT subjects was good (14%), very good (41%), or excellent (43%) except for 1 subject who rated fair.

As part of effectiveness evaluation, the sponsor analyzed the effective dosing occasions by baseline heartburn severity for relief of symptoms among ITT subjects. The percentage of effective dosing occasions were 92% for mild heartburn symptoms, 90% for moderate heartburn symptoms, and 83% for severe heartburn symptoms.

Concurrent Use of Heartburn Medication
These data were obtained from the subjects' Product Use Journals and Concomitant Medications Log. There was no concurrent use of PPIs in this study. Overall, 10 of 92 subjects (11%) used antacids and 7 subjects (8%) used H2RAs on the same day as the study medication. The Prevention-Any-Time-Only and the Prevention-1-Hour-Before-Only groups had no concurrent use of other heartburn medication. Only 1 of the 3 subjects in the Dual-Prevention-Only group used antacids on one occasion. One of 34 subjects (3%) in the Relief-Only group used an antacid and 1 subject used an H2RA each on one occasion. Eight of 47 subjects (17%) in the Prevention-And-Relief group used antacids on a total of 16 occasions, and 6 subjects (13%) used H2RAs, on a total of 8 occasions. Across all groups, 2% of the dosing occasions involved concurrent antacid use and 1% of dosing occasions involved concurrent H2RA use.

Comments
Data to support efficacy of omeprazole magnesium 20.6 mg tablets for proposed indications will be based on the controlled clinical trials, and will be covered by the HFD-180 reviewers. Interpretation of the efficacy data in this actual use study has to be taken with caution. There was no placebo-control group and the efficacy endpoint was subjects' subjective self-evaluation. Overall, most of the subjects rated effectiveness of the study medication as good to excellent. Back-up medications for heartburn relief were mainly used by the subjects in the Relief group. The label used in this study and current label for Prilosec Rx use or proposed OTC use has a statement that this product should not be used with other acid reducers. Despite the label warning, 11% of subjects in this study used these drugs concomitantly with the study medication.

Overview of Safety
One hundred subjects were each supplied with 36 tablets of omeprazole magnesium 20.6 mg to use as needed according to the label for a period of 4 weeks. All of the 92 ITT subjects took at least one dose of study medication and returned the Product Use Journal. Summary of the extent of exposure to study medication is presented in Table 4.

Table 4. Summary of Extent of Exposure

		ITT (N=92)
Number of Dosing Days	Mean	10.1
	Std. Deviation	10.4
	Minimum-Maximum	2-39
Number of Dosing Occasions	Mean	10.2
	Std. Deviation	10.4
	Minimum-Maximum	1-39

Table 5 presents summary of adverse events (AEs) reported for ITT subjects. Overall, 51 of the subjects (55%) reported 94 AEs. More than half of the subjects enrolled into the study experienced at least one adverse event. No AEs were considered probably related to study medication. All the events were considered non-serious, and only 10% were considered possibly related to the study drug.

Table 5. Summary of Adverse Events

		ITT (N=92)
Subjects	With Any AE	51 (55%)
	With SAEs	0 (0%)
	Withdrawals Due to AEs	0 (0%)
	Deaths	0 (0%)
Number of AEs per Subject	Reporting 0 AEs	41 (45%)
	Reporting 1 AE	26 (28%)
	Reporting >1 AEs	25 (27%)
AE Relationship to Study Medication	Unlikely	85 (90%)
	Possibly	9 (10%)
	Probably	0 (0%)
	Total Number of AEs	94 (100%)
AE Intensity	Unknown	0 (0%)
	Mild	21 (22%)
	Moderate	46 (49%)
	Severe	27 (29%)
	Total Number of AEs	94 (100%)

Table 6 presents AEs by body system and COSTART term. The most frequently reported AEs in this study were in Body as a Whole category, followed by Respiratory and Digestive systems.

Table 6. Adverse Events by Body System

	ITT (N=92)	
Body System	Subjects N (%)	AEs N
Body as a Whole	29 (32%)	38
Respiratory	22 (24%)	28
Digestive	12 (13%)	14
Cardiovascular	6 (7%)	6
Musculoskeletal	3 (3%)	3
Urogenital	2 (2%)	2
Special Senses	1 (1%)	1
Nervous	1 (1%)	1
Skin	1 (1%)	1
Endocrine	0	0
Hemic/Lymphatic	0	0

The most common adverse events with overall incidence by COSTART terms are presented in Table 7.

Table 7. Adverse Events by Body System and COSTART Term

	ITT N=92	
Body System	N	%
RES: Infection	13	14%
BODY: Headache	12	13%
BODY: Infection	8	9%
BODY: Flu Syndrome	6	7%
RES: Pharyngitis	6	7%
RES: Cough	5	5%
BODY: Pain Abdominal	5	5%
BODY: Injury Accident	4	4%
CV: Migraine	4	4%
DIG: Dyspepsia	3	3%
MS: Arthralgia	3	3%
BODY: Fever	3	3%
DIG: Nausea	2	2%
BODY: Pain Back	2	2%
BODY: Pain	2	2%
DIG: Diarrhea	1	1%
NER: Dizziness	1	1%

Most commonly reported AE was respiratory infection, followed by headache. There appears to be no increase in the percentage of AEs with increasing days of use, increasing number of doses, increasing number of tablets taken, or increasing duration of use.

Deaths
There were no deaths reported.

Other Significant/Potentially Significant Events
There were no other significant events reported in this study.

Discontinuation Due To Adverse Events
There were no discontinuations from the trial due to AEs.

Vital Signs, Physical Findings, and Other Observations Related to Safety
No vital signs or physical examination was performed during the study.

Laboratory findings, Vital signs
The only clinical laboratory work done for this study was three urine pregnancy tests for women.

Drug-Demographic Interactions/Drug-Drug Interactions

Drug-demographic interactions and drug-drug interactions for Prilosec 1 were not addressed in this actual use study. Subjects taking certain drugs were either excluded from the study or withdrawn later. Currently approved label for prescription Prilosec lists a number of drugs that could cause drug interactions. Proposed label for OTC marketing has only ketoconazole and itraconazole listed.

Summary of Study #067

- *The population enrolled in the study was enriched in terms that all subjects had a heartburn history and have used antacids or H2RAs prior to the enrollment.*
- *Behavior and self-selection by people with certain risks for the use of Prilosec1 (childbearing potential females, persistent abdominal pain, use of concomitant medications) were not addressed in this study.*
- *Demographically enrolled population was not representative of overall U.S. population. All subjects came from the same state, Utah, and the majority were Caucasian (96%).*
- *Forty-five percent (45%) of enrolled subjects suffered from heartburn 2-3 times a week, and 19% - 4 to 6 times a week, raising a concern if this is an appropriate OTC targeted population.*
- *The primary objective to characterize the usage patterns (consistency with three label use directions) was achieved by 75% of treated subjects.*
- *Consistency with the label directions in the prevention group was observed only when subjects dosed themselves not more than 4 occasions. Even though the number of subjects in the prevention groups was small, the data gathered in this study raise a concern. Overall, 7 out of 11 subjects in the prevention groups exceeded 10 sequential dosing days.*
- *Despite the warning on the label, 11% of study population used omeprazole magnesium concomitantly with other antacids or H2RAs.*
- *Safety data gathered from this study confirms overall benign safety profile for omeprazole short term use. There were no unexpected or unlabeled AEs reported during this study.*

Study #014

AN UNCONTROLLED, OPEN-LABEL, MULTI-CENTER STUDY TO INVESTIGATE CONSUMER USAGE PATTERNS OF OMEPRAZOLE MAGNESIUM 20.6 MG AND FORECAST MARKET VOLUME

The **primary objectives** of this study were:

- to evaluate the usage patterns of Ome-Mg, packaged in a carton labeled Prilosec 1, under home-use conditions, and
- to forecast market volume.

A **secondary** purpose of this study was to augment the safety profile for Ome-Mg, packaged in a carton labeled Prilosec 1, under home use conditions.

Design

This was an uncontrolled, open-label, multi-center study. The trial had both clinical and marketing end-points. The marketing aspects of the trial were considered proprietary and were not disclosed in this clinical study final report nor in the NDA. The clinical aspects of the study were coordinated by West Pharmaceutical Services and the marketing aspects by A. C. Nielsen BASES.

A randomization was not generated because of the single-medication, open-label study design. The study took place at approximately 61 study centers located in malls/shopping centers in approximately 41 USA cities. Approximately 4,450 subjects were interviewed, which provided 1,516 subjects who were screened; 1,440 subjects were valid for product placement. The total number of subjects recruited was divided as evenly as possible among the mall/shopping center study centers.

Visit 1

After the questions related to the marketing part of the study, an interviewer asked the subject specific questions regarding purchase intent. Each potential subject read a product concept and indicated their intent to purchase the product. Those subjects who indicated a definitely would buy, probably would buy, or might or might not buy purchase intent or a probably would not buy, or definitely would not buy for reasons related to the value of the product were screened by study personnel for willingness to use the product for 30 days, complete the Product Use Journal, respond to a telephone interview, and return all study-related materials at the end of the 30 days.

Those agreeing to participate in the home-use test signed an informed consent form and underwent additional screening by a health professional. Subjects who satisfied Inclusion and Exclusion criteria were enrolled into the study.

Inclusion Criteria

To be considered eligible for enrollment into this study, subjects:

- provided written informed consent;
- had, after reading the concept and label, self-selected to use the study medication;
- were male or non-pregnant, non-lactating female, of any race, and at least 18 years of age (women of child-bearing potential were to be using an acceptable form of contraception [including abstinence] as determined by the Sub-Investigator or study staff);
- were willing to complete the two at-home urine pregnancy tests: one before taking the initial dose of study medication and the second after taking the last dose of study medication (this was required independent of birth control method being used);
- were willing and able to complete the Product Use Journal during the study period, answer a telephone interview, and return any unused study medication, the study medication package, and the Product Use Journal at the end of the study period; and
- must have used an oral OTC heartburn medication to treat a labeled indication during the past 3 months.

Exclusion Criteria

Subjects were excluded from the study if they:

- were a pregnant or lactating female;
- had an active peptic ulcer disease currently being treated with prescription H2RAs or PPIs;
- were currently taking phenytoin, diazepam, clarithromycin, or warfarin;
- had experienced continuous abdominal pain $\geq$10 days in duration;
- had dysphagia (difficulty swallowing); or
- had known hypersensitivity to omeprazole or Ome-Mg.

Subjects were asked to record the following information in the Product Use Journal for all doses of study medication:

- date and time study medication was taken,
- number of tablets taken, and
- indication/reason study medication was taken.

Subjects were requested to disclose all medications taken within 30 days prior to starting the study period. In addition, subjects were asked to record all other concomitant medications taken for relief of heartburn symptoms and any other effects experienced during the study period.

Study medication was supplied as pink/rust-colored tablets packaged in six-count blister cards packaged two cards to a carton. One carton was dispensed to each subject. All subjects who agreed to take the study medication were to use it for the labeled indications as needed for a period up to 30 days.

The carton labels used in this study had the following use directions:

USES: **for prevention** of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, stress, hectic lifestyle, lying down, or exercise.
for relief of heartburn, acid indigestion, and sour stomach.

DIRECTIONS: Adults and children 12 years of age and older:
For prevention of symptoms for 24 hours: swallow 1 tablet with a glass of water anytime during the day, or if you prefer, one hour before those events associated with occasional heartburn, such as consuming food and beverages, stress, hectic lifestyle, lying down, or exercise.
For relief of symptoms: Swallow 1 tablet with a glass of water.
Do not take more than 1 tablet every 24 hours. Do not use for more than 10 days in a row unless directed by a doctor.
Do not chew or crush tablets.
Children under 12 years of age: ask a doctor.

Interim Phone Interview
All subjects were contacted by telephone by A. C. Nielsen BASES (marketing) interviewers no later than 30 days after their enrollment in the study, and asked marketing questions, such as intent and reasons for purchase, frequency and average number of units the subject would buy on future purchase occasions, and intensity of liking rating. After this information was collected, subjects were reminded to use the postage-paid envelope to return any unused study medication, the study medication package, and the completed Product Use Journal.

Subjects were not allowed to continue the study period for longer than 30 days after enrollment into the study, even if the study medication had not been used. While each subject was encouraged to complete the full course of the study, any participant may have withdrawn from the study at any time and for any reason.

Comments
The indications for use on this label were identical to the label proposed for OTC marketing, and study #067. However, the design of this study differs from the design of Study #067 in the following ways: information was not collected about heartburn history, response/satisfaction with the drug, and back-up treatment required. All other medications, including heartburn medicine, were considered as concomitant medications. The percentage of subjects who used other heartburn medicine at least once on the same day, regardless of the time of the study medication intake, were presented in the data analyses.

There were no self-selection evaluated in this study. Subjects were given only 12 omeprazole magnesium 20.6 mg tablets even though the study duration was 30 days. Analysis of usage pattern for prevention of heartburn symptoms, therefore, is limited.

The study was enriched in terms of population. All subjects enrolled into the study must have used OTC heartburn medication to treat their heartburn during the last 3 months prior to enrollment. If the purpose of this study was to learn how people with heartburn would use this product, then above mentioned behavior aspects (back-up medication use and prevention usage pattern) are even more important.

Design of the study did not have a provision for final follow-up with a study investigator. Data about usage of the study drug, was gathered from the Product Use Journal, which was returned by the subjects by mail. Only the telephone call was made to contact participants.

Seven out of 36 investigators participated in the other actual use study #091, which preceded this study, by almost one year. The exclusion criteria in study #014 did not have a provision to exclude those subjects, who participated in a similar study in the past. It is not known if any of the subjects were enrolled into more than one study.

Results

One thousand five hundred sixteen (1,516) male and female subjects were screened, providing 1,440 subjects who were asked to evaluate Ome-Mg, packaged in a carton labeled Prilosec 1. All eligible subjects were expected to take at least one dose of study medication. The following chart displays a disposition of the subjects.

Interviewed/Targeted for Enrollment
N=4,450
↓
Screened at Visit 1→ Did not meet Enrollment Criteria
N=1,516 N=66
↓
Met Inclusion/Exclusion Criteria→ Withdrew Consent
N=1,450 N=10
↓
Received Study Medication→Dosing Information is not Available
N=1,440 N=417
↓
Took Study Medication & Returned Product Use Journal
N=939
↓
Completed the Study
N=931

One thousand five hundred sixteen (1,516) subjects were screened at Visit 1. Sixty-six (66) subjects did not meet enrollment criteria, leaving 1,450 subjects. Of these, 10 subjects reconsidered, withdrew consent, or the Investigator decided not to enroll them in the study prior to receiving study medication, leaving 1,440 subjects who received study medication and the Product Use Journal. Nine hundred thirty nine (939) subjects returned their Product Use Journal and took at least one dose of study medication, 417

subjects did not have dosing information available (i.e., they did not return their Product Use Journal), and 84 subjects returned their Product Use Journal but did not dose with study medication.

Of the 66 subjects who did not meet enrollment criteria, half of them (n=33) were in the risk category:
17 had peptic ulcer disease;
8 were taking contraindicated drugs;
5 had abdominal pain for more than 10 days;
2 had dysphagia; and
1 had known hypersensitivity to omeprazole.

Of the 1,440 subjects who received study medication, 931 completed the study. The completed subjects consisted of those who were evaluable for the Intent-to-Treat (ITT) population (939) minus 8 subjects who dropped after taking at least one dose of study medication. Six (6) of the subjects were dropped due to an AE, and two of the subjects were dropped by the Investigator.

Table 1 contains the reasons for 509 subjects discontinuating from the study after receiving the Product Use Journal and study medication at Visit 1. Six (6) subjects (006028, 014022, 018019, 026026, 045026, and 051025) withdrew due to AEs which included fever, abdominal pain, chest pain, diarrhea, nausea, shortness of breath, headache, dizziness, and stomach ache. Consent was withdrawn by 87 subjects.

Table 1. Reasons for Discontinuation

	N	(%)
Did not Complete the Study (Total)	509	(100%)
• Adverse Events	6	(1%)
• Consent Withdrawn	87	(17%)
• Lost to Follow-up	413	(81%)
• Investigator/Sponsor Decision	3	(<1%)

Four-hundred thirteen (413) subjects were lost to follow-up. The investigator discontinued 3 subjects (005032, 043001, and 049008). It was discovered that Subject 005032 had an ulcer recorded in his medical history. This subject was withdrawn before using the study medication. As noted above, the other two subjects were withdrawn after taking at least one dose: Subject 043001 was placed on Biaxin for a sinus infection, and Subject 049008 had an active esophageal stricture and intermittent dysphagia.

The ITT population (those subjects used to summarize usage patterns) consisted of 939 subjects who took at least one dose of study medication and had Product Use Journal information available. Summary of dosing behaviors included all 1,023 subjects who returned the Product Use Journal, regardless of whether they dosed. For the purposes of summarizing label use direction consistency, subjects who had missing tablet counts and/or missing dates were excluded, with one exception. Subjects who had a missing date and took only one dose were considered compliant with respect to the criteria 'take

no more than one dose per day.' Data for 43 subjects could not be summarized due to incomplete data; therefore, data displays summarizing label use direction consistency are based on a total of 896 subjects.

Comments
The reasons why 66 subjects did not meet enrollment criteria were not provided by the sponsor. No self-selection for the therapy was addressed in this study. A substantial number [509 (35%)] of the study participants, did not complete the study. The most common reason for discontinuation was lost to follow-up (n=413). It is not clear what attempts were made by the investigator to contact these people. Withdrawal rate due to adverse events for the available subjects was 1.2%, and it may be underestimated because of the high number of subjects lost to follow-up.

Demographic Characteristics and Concomitant Medication
Table 2 displays subject demographics for the ITT population. Six-hundred and six (606) subjects (65%) were female and 333 (35%) were male, ranging in age from 18–82 years with a mean age of 43 years. The majority (789) of the 939 subjects (84%) were Caucasian.

Table 2. Demographics Characteristics (ITT Population)

	Prevention Any Time N=79	Prevention 1-Hr Before N=43	Dual Prevention N=56	Relief Only N=240	Prevention and Relief N=491	Overall N=939
Gender						
Female	52 (66%)	24 (56%)	39 (70%)	151 (63%)	321 (65%)	606 (65%)
Male	27 (34%)	19 (44%)	17 (30%)	89 (37%)	170 (35%)	333 (35%)
Age						
Mean	50.60	40.70	44.29	42.22	42.26	43.08
Std. Dev.	17.97	15.39	15.74	16.40	16.16	16.43
Range	18-77	18-75	18-82	18-77	18-82	18-82
Race						
American Indian	1 (1%)	0 (0%)	1 (2%)	2 (1%)	5 (1%)	9 (1%)
Asian	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (0%)	2 (0%)
Black	6 (8%)	5 (12%)	6 (11%)	26 (11%)	39 (8%)	85 (9%)
Caucasians	70 (89%)	34 (79%)	45 (80%)	200 (83%)	413 (84%)	789 (84%)
Hispanic	1 (1%)	3 (7%)	1 (2%)	10 (4%)	20 (4%)	35 (4%)
Multi-Racial/Other	1 (1%)	0 (0%)	3 (5%)	2 (1%)	13 (3%)	19 (2%)

Prior to enrollment, the most common concomitant medication therapies were TUMS, Tylenol, aspirin, Pepcid AC, and multivitamins (≥8% Overall). During the study, subjects were allowed to take any concomitant medication, as long as it was not specifically prohibited in the exclusion criteria.

The most common concomitant medications were similar to the prior concomitant medication therapies and included Tylenol, TUMS, aspirin, and multivitamins. Use of antacids and H2RAs in different usage groups is displayed in Table 3.

Table 3. Concurrent Use of Other Heartburn Medications

	Prevention Any Time N=79 (%)	Prevention 1-Hr Before N=43 (%)	Dual Prevention N=56 (%)	Relief Only N=240 (%)	Prevention and Relief N=491 (%)	Overall N=939 (%)
Antacids	13 (16%)	6 (14%)	11 (20%)	50 (21%)	102 (21%)	187 (20%)
H2RAs	23 (29%)	9 (21%)	11 (20%)	34 (14%)	94 (19%)	180 (19%)
PPIs	15 (19%)	0 (0%)	1 (2%)	3 (1%)	13 (3%)	32 (3%)

Overall, 187 of 939 subjects (20%) used antacids on the same day as the study medication. Similarly, 180 of 939 subjects (19%) used H2RAs on the same day as study medication. The rate of concurrent PPI use was the lowest, consisting of 32 of 939 subjects (3%). The rate of concurrent PPI use was 19% for the Prevention-Any-Time-Only group.

Comments
Demographics of enrolled subjects are not representative of overall U.S. OTC population. Majority (84%) of the participants enrolled into the study were Caucasian. Literacy level, which is an important factor evaluating consumer behavior, was not evaluated in this study. There were no major differences, in terms of demographics, in all the subgroups by the usage pattern.

Information about the heartburn history was not collected in this study; therefore, it is not known if the population enrolled represents targeted population for Prilosec 1 OTC use.

Concomitant medication usage was collected differently than in Study #067, in that the subjects were required to list only the name of the medication and the reason for use. The time of ingestion was not collected. Thus, it is not clear when the subjects took a particular concurrent heartburn drug as a rescue. Overall, 20% of the participants took antacids, 19% took H2RAs, and 3% took PPIs, in addition to the study drug.

Summary of Usage Patterns
Subjects were classified into the same five categories as in the study #067 representing usage patterns within the two indications. The frequency and percentage of subjects who used study medication in each of the usage categories were as follows:

- 79 (8%) for the Prevention-Any-Time-Only users,
- 43 (5%) for the Prevention-1-Hour-Before-Only users,
- 56 (6%) for the Dual-Prevention-Only users,
- 240 (26%) for the Relief-Only users,
- 491 (52%) for the Prevention-And-Relief users, and
- 30 (3%) did not specify a usage category.

Consistency with Label Use Directions
The t rm 'consistency' is used in this report to describe the subjects' adherence to the label use directions. Subjects were considered consistent with the three labeled

directions if they 1) consumed only one tablet per dose, 2) took no more than one dose per day, and 3) dosed for no more than 10 consecutive days.

Evaluation of the consistency with label use directions did not include all of the 939 ITT subjects, as 43 subjects could not be assessed due to incomplete data. Therefore, total number of subjects included in this analyses is 896. Twenty six subjects had all entries with missing reason for use, therefore they are included only in Overall column, but not in the subgroups. Consistency by usage group per subject basis is presented in Table 4.

Table 4. Consistency with Label Use Directions

	Prevention Any Time N=77 (%)	Prevention 1-Hr Before N=41 (%)	Dual Prevention N=56 (%)	Relief Only N=231(%)	Prevention and Relief N=465 (%)	Overall N=896(%)
Consistent with Label Use Direction	35 (45%)	35 (85%)	40 (71%)	218 (94%)	402 (86%)	754 (84%)
Not Consistent with Label Use Directions	42 (55%)	6 (15%)	16 (29%)	13 (6%)	63 (14%)	142 (16%)
• Exceeded 1 tablet per dose	1 (1%)	2 (5%)	5 (9%)	5 (2%)	20 (4%)	34 (4%)
• Exceeded 1 dose per day	0 (0%)	2 (5%)	4 (7%)	9 (4%)	33 (7%)	48 (5%)
• Exceeded 10 consecutive dosing days	41 (53%)	3 (7%)	8 (14%)	0 (0%)	16 (3%)	69 (8%)

Overall, 754 of 896 subjects (84%) were consistent with all three label use directions. The best consistency results were achieved in Relief Only subgroup (94%), and the worst – in Prevention Any Time Only subgroup (45%). Across all subjects, 34 (4%) took more than one tablet per dose, 48 (5%) took more than one dose per day, and 69 (8%) exceeded 10 consecutive days of dosing.

Table 5 summarizes consistency with label use direction by demographic characteristics on per-subject calculation. Consistency with the three label directions was similar within a gender, race, and age categories.

Table 5. Consistency with Label Use Directions by Demographics

	Female N=577 (%)	Male N=319 (%)	Caucasian N=760 (%)	Non-Caucasian N=136(%)	Age <65 Yrs N=769 (%)	Age >65 Yrs N=122(%)
Consistent with Label Use Direction	493 (85%)	261 (82%)	640 (84%)	114 (84%)	650 (85%)	100 (82%)
Not Consistent with Label Use Directions	84 (15%)	58 (18%)	120 (16%)	22 (16%)	119 (15%)	22 (18%)
• Exceeded 1 tablet per dose	15 (3%)	19 (6%)	21 (3%)	13 (10%)	33 (4%)	1 (1%)
• Exceeded 1 dose per day	33 (6%)	15 (5%)	43 (6%)	5 (4%)	41 (5%)	7 (6%)
• Exceeded 10 consecutive dosing days	42 (7%)	27 (8%)	63 (8%)	6 (4%)	54 (7%)	14 (11%)

Table 6 presents consistency with the three label use directions by number of dosing occasions based on a per-subject calculation. For all categories of users, subjects who had fewer dosing occasions demonstrated better consistency with the label use directions. For Prevention-Any-Time-Only users, consistency with the three label use directions was 100% for all levels, with the exception of those subjects who had 11–12 dosing occasions, where consistency was 24%.

Table 6. Consistency with Label Use Directions by Number of Dosing Occasions

Number of Dosing Occasions/Type of User	Prevention Any Time N=77 (%)	Prevention 1-Hr Before N=41 (%)	Dual Prevention N=56 (%)	Relief Only N=231 (%)	Prevention and Relief N=465 (%)	Overall N=896 (%)
1-2	8/8 (100%)	12/12(100%)	4/4 (100%)	101/102 (99%)	17/18 (94%)	144/146 (99%)
3-4	6/6 (100%)	6/7 (86%)	6/6 (100%)	59/60 (98%)	60/60 (100%)	140/142 (99%)
5-6	3/3 (100%)	3/5 (60%)	2/4 (50%)	29/32 (91%)	54/62 (87%)	95/110 (86%)
7-8	1/1 (100%)	1/1 (100%)	1/3 (33%)	8/9 (89%)	57/66 (86%)	71/84 (85%)
9-10	4/4 (100%)	4/4 (100%)	4/6 (67%)	7/11 (64%)	61/70 (87%)	81/96 (84%)
11-12	13/55 (24%)	9/12 (75%)	23/33(70%)	14/17 (82%)	153/189(81%)	223/318 (70%)
Overall	35/77 (45%)	35/41(85%)	40/56(71%)	218/231 (94%)	402/465(86%)	754/896 (84%)

The maximum number of sequential days of dosing per subject is presented in Table 7. Forty-two (42) of 79 (53%) Prevention-Any-Time-Only users had a maximum number of 11–12 sequential dosing days. The majority of the Prevention-1-Hour-Before-Only users (60%), Relief-Only users (91%), and Prevention-And-Relief users (65%) had at most 1–2 sequential dosing days.

Table 7. Maximum Number of Sequential Dosing Days (ITT population)

Maximum Number of Sequential Days	Prevention Any Time N=79 (%)	Prevention 1-Hr Before N=43 (%)	Dual Prevention N=56 (%)	Relief Only N=240 (%)	Prevention and Relief N=491 (%)	Overall N=939 (%)
1-2	18 (23%)	26 (60%)	26 (46%)	218 (91%)	318 (65%)	621 (66%)
3-4	5 (6%)	8 (19%)	11 (20%)	14 (6%)	95 (19%)	141 (15%)
5-6	7 (9%)	3 (7%)	7 (13%)	3 (1%)	39 (8%)	62 (7%)
7-8	4 (5%)	1 (2%)	4 (7%)	1 (<1%)	10 (2%)	21 (2%)
9-10	3 (4%)	2 (5%)	0 (0%)	0 (0%)	11 (2%)	17 (2%)
11-12	42 (53%)	3 (7%)	8 (14%)	4 (2%)	18 (4%)	77 (8%)

The sponsor also gathered the data about the minimum number of hours between doses for each subject. Overall, 622 out of 939 subjects (66%) had 20 or more hours between doses.

Comments
Half of the subjects who took the drug, used it for relief and prevention, and the other half equally divided between prevention only and relief only usage categories.

Overall, consistency with all three labeled directions was achieved by 84% of subjects. Consistency with all three label directions was achieved by the majority of subjects in the Relief-Only usage category. As seen in the previous study, tendency to be non-consistent in the Prevention groups, was observed in this study as well. More than half (55%) of subjects in Prevention-Any-Time-Only group were non-consistent. And, again, most common reason for non-consistency in this subgroup was exceeded length of the therapy. Looking at the pattern of intake of study medication, the data showed that 53% of Prevention-Any-Time-Only group subjects took medication for more than 10 days, exceeding the duration listed on the label.

Based on the results of this study, there were no differences in terms of consistency with label use directions by demographics. Literacy level was not evaluated for the enrolled subjects, and therefore, the behavior of the lower literacy population is not known.

Consistency with the label use directions is proportional to the length of the therapy. Non-consistency rates increased with longer use of the product. Every subject in this study received only 12 tablets. The use for a longer period of time may have been observed if more tablets were dispensed to the subjects.

Overview of Safety
One-thousand four-hundred forty (1440) subjects were supplied with 12 Ome-Mg 20 tablets. They were instructed to use the study medication as needed for a period up to 30 days. Nine-hundred thirty-nine (939) subjects took at least one dose of study medication and returned the Product Use Journal. Eighty-four (84) subjects were given study medication but did not dose with it over the 30-day usage period. Dosing information was not available from the remaining 417 subjects. Summary of the extent of exposure for the 939 subjects who took at least one dose of study medication is presented in Table 8.

Table 8. Summary of Extent of Exposure

		ITT (N=939)
Number of Dosing Days	Mean	7.44
	Std. Deviation	3.98
	Minimum-Maximum	1-12
Number of Dosing Occasions	Mean	7.52
	Std. Deviation	4.02
	Minimum-Maximum	1-12

Overall, 329 subjects (35%) reported 532 AEs. Summary of those adverse events by usage is presented in Table 9.

Table 9. Summary of Adverse Events

		ITT (N=939)
Subjects	With Any AE	329 (35%)
	With SAEs	2 (<1%)
	Withdrawals Due to AEs	6 (1%)
	Deaths	0 (0%)
Number of AEs per Subject	Reporting 0 AEs	610 (65%)
	Reporting 1 AE	193 (21%)
	Reporting >1 AEs	136 (14%)
AE Relationship to Study Medication	Unlikely	406 (76%)
	Possibly	104 (20%)
	Probably	22 (4%)
	Total Number of AEs	532 (100%)
AE Intensity	Unknown	48 (9%)
	Mild	175 (33%)
	Moderate	221 (42%)
	Severe	88 (17%)
	Total Number of AEs	532 (100%)

Table 10 presents AEs by body system and COSTART term. The most frequently reported AEs in this study were in Body as a Whole category, followed by Digestive and Respiratory systems. Total of 229 subjects (24%) reported 270 AEs in the Body as a Whole category.

Table 10. Adverse Events by Body System

	ITT (N=939)	
Body System	Subjects N (%)	AEs
Body as a Whole	229 (24%)	270
Cardiovascular	6 (1%)	6
Digestive	113 (12%)	136
Endocrine	2 (<1%)	2
Hemic/Lymphatic	2 (<1%)	2
Musculoskeletal	13 (1%)	13
Nervous	32 (3%)	33
Respiratory	49 (5%)	59
Skin	3 (<1%)	3
Special Senses	1 (<1%)	1
Urogenital	7 (1%)	7

Most common adverse events of overall incidence > 1% by COSTART terms are presented in Table 11.

Table 11. Adverse Events by Body System and COSTART Term

	ITT (N=939)	
Body System	N	%
BODY: Headache	191	20%
DIG: Diarrhea	30	3%
DIG: Flatulence	26	3%
RES: Infection	26	3%
DIG: Nausea	24	3%
BODY: Pain Back	21	2%
BODY: Pain Abdominal	18	2%
NER: Dizziness	15	2%
BODY: Pain	15	2%
DIG: Dyspepsia	12	1%
RES: Sinusitis	11	1%
BODY: Infection	1	<1%
BODY: Flu Syndrome	7	<1%
RES: Pharyngitis	6	<1%
RES: Cough	3	<1%
BODY: Injury Accident	2	<1%
CV: Migraine	2	<1%
MS: Arthralgia	2	<1%
BODY: Fever	2	<1%

The most commonly reported AE was headache (191 events, 20%). All other AEs were reported with an incidence of 4% or less. There appears to be no increase in the percentage of AEs with increasing days of use, increasing number of doses, increasing number of tablets taken, or increasing duration of use.

Deaths
There were no deaths reported.

Other Significant/Potentially Significant Events
There were two serious AEs reported. Narratives for each are given below:

SUBJECT 042023 The subject was a 56 year old, Native American female who took Ome-Mg 20 from 7-Oct-98 to 5-Nov-98. On 17-Oct-98, the subject developed a serious cough, and was hospitalized for an asthmatic attack complicated by development of possible pneumonia. The investigator considered this event unlikely related to study medication.

SUBJECT 050036 The subject was a 53 year old, white male with a diagnosis of AIDS, who took Ome-Mg 20 on 19-Oct-98. On 22-Oct-98, the subject experienced blurred vision, weakness in legs, and fatigue, and was admitted to the hospital on 25-Oct-98 with the diagnosis of hyperglycemia. The investigator felt that the hyperglycemia is due to the Crixivan and unlikely related to the omeprazole magnesium.

Discontinuation Due To Adverse Events
Six subjects had AEs that resulted in discontinuation from the study.

Subject 006028 reported AEs including fever, abdominal pain, chest pain, diarrhea, nausea, and shortness of breath. All were considered by the investigator as probably related to the study medication.
Subject 026026 reported an AE of nausea, which was considered by the investigator as probably related to the study medication.
Subject 045026 reported diarrhea, which was considered by the investigator as probably related to the study medication.
Subject 014022 reported an AE of headache, which was considered by the investigator as possibly related to the study medication.
Subject 018019 reported AEs of diarrhea, nausea, and dizziness, which were considered by the investigator as possibly related to the study medication.
Subject 051025 reported AEs of headache and stomach ache, which were considered by the investigator as possibly related to the study medication.

Vital Signs, Physical Findings, and Other Observations Related to Safety
No vital signs or physical examination was performed during the study.

Laboratory findings, Vital signs
The only clinical laboratory work done for this study was two self-administered urine pregnancy tests for women.

Drug-Demographic Interactions/Drug-Drug Interactions
Drug-demographic interactions and drug-drug interactions for Prilosec 1 were not addressed in this actual used study. Subjects taking concomitant drugs, recommended for exclusion from the prescription labeling, were either excluded from this study or withdrawn later. Of note, the proposed label for OTC marketing has only ketoconazole and itraconazole listed.

Summary of Study #014

- *This was an uncontrolled, open-label, multi-center actual use study, and had both clinical and marketing end-points.*
- *Self-selection by risk groups, was not addressed in this study.*
- *Background heartburn history was not collected, therefore it is not known if the population enrolled represents OTC targeted population.*
- *Demographics of the enrolled population is not representative of overall U.S. OTC population, as the majority (84%) of the participants enrolled into the study were Caucasian. Information about education or literacy level of the enrolled population was not collected.*
- *Subjects were given only 12 omeprazole tablets even though the study duration was 30 days. Analysis of the usage pattern for prevention of heartburn symptoms, therefore, is limited.*
- *Thirty-five percent (35%) of the study participants did not complete the study. The most common reason for discontinuation was lost to follow-up.*
- *Overall, consistency with all three labeled directions for use was achieved by 84% of the subjects.. Consistency was much better for those who used the study medication for relief, than for those who used it for prevention.*

- *More than half (55%) of the subjects in Prevention-Any-Time-Only group were non-consistent. The most common reason for non-consistency in this subgroup was exceeded length of the therapy. Fifty-three percent (53%) of Prevention-Any-Time-Only group subjects took medication for more than 10 sequential days.*
- *Despite the warning on the label, not to use the drug with other acid reducers, 20% of the participants took antacids, 19% took H2RAs, and 3% took PPIs.*
- *Safety data for omeprazole magnesium 20.6 mg tablets was consistent with Rx Prilosec profile. Most common AE in this study was headache (20%). There were no unexpected or unlabeled adverse events reported during this study. Since the subjects were given only 12 tablets of study medication, the extent of exposure was relatively short.*

Study #022

A MULTI-CENTER, OPEN-LABEL, ACTUAL-USE STUDY TO INVESTIGATE THE CONSUMER USAGE PATTERNS OF OMEPRAZOLE MAGNESIUM 10.3 MG WHEN USED BY OTC CONSUMERS

The **primary objective** of this study was to characterize the usage patterns and dosing consistency relative to each major label dosing instruction of omeprazole magnesium 10.3 mg (Ome-Mg 10) when used *ad libitum* according to proposed label instructions under naturalistic OTC conditions.

A **secondary objective** of this study was to investigate the effectiveness of omeprazole magnesium 10.3 mg in a naturalistic setting.

Design
This study was a multi-center, at-home, open-label, multi-dose study. Recruitment took place at five malls/shopping centers within the USA. Potential subjects were recruited by non-health professionals. Subject enrollment ceased when approximately 600 subjects were given study medication. The 10.3 mg dose level was chosen because it was one of the doses being investigated for possible OTC approval.

Visit 1
Consumers were screened at malls/shopping centers and asked "Do you get stomach problems?" Those responding positively were invited to participate in a research study about a proposed new OTC medication for stomach problems, were given a proposed market-ready package of omeprazole magnesium, and were instructed to: "Examine this medication as if you were looking to buy it off the shelf in a drug store or supermarket." Subjects were given as much time as necessary to read the label to themselves. Then, the interviewer asked: "Do you think this is an appropriate medication or not an appropriate medication for you to use?"

After the self-selection decision had been made, study staff asked subjects the reason for their decision. Subjects who indicated that the study medication was inappropriate for them were discharged. Subjects who indicated the study medication was appropriate for them were screened for willingness to participate in the actual-use phase of the study.

Inclusion Criteria
To be considered eligible for enrollment into this study, subjects:

- provided written informed consent (co-signed by parent or guardian if subject was 12–17 years of age, inclusive);
- determined that the study medication was appropriate to use after reading the label;
- were male or non-pregnant, non-lactating female, of any race, and at least 12 years of age;
- were male or, if female, were willing to complete two at-home urine pregnancy tests

(one before taking the initial dose of study medication and one after taking the last dose of study medication) and not use the study medication if either test was positive;
- were male or, if female of child-bearing potential, were willing to sign a birth control agreement and use an acceptable form of contraception (including abstinence) as determined by the Investigator or study staff; and
- were willing and able to complete the diary during the study period, answer a telephone interview, and return at Visit 2 with study medication packages (used, partially used, or unused) and the diary.

Exclusion Criteria

Subjects were excluded from the study if they:
- were a pregnant or lactating female;
- had active peptic ulcer disease currently treated with prescription H2RAs or PPIs;
- were currently dosing with phenytoin, warfarin, diazepam, or clarithromycin;
- had a known hypersensitivity to omeprazole or omeprazole magnesium;
- had experienced continuous abdominal pain >10 days in duration;
- had dysphagia (difficulty swallowing); or
- had previously participated in this study or any other Prilosec 1 4-week usage study since Jan-99.

Subjects were asked to answer a questionnaire to characterize their heartburn condition (duration and frequency of symptoms) and collect prescription and non-prescription medications used to treat the condition during the past year. In addition, subjects provided a list of medical conditions over the last 12 months.

Eligible subjects were supplied with 36 tablets of study medication in market-ready packages labeled Prilosec 1. Subjects who agreed to dose with the study medication were instructed to use it, as needed, according to the label dosing instructions over a period of approximately 4 weeks.

The carton labels had the following indications for use and directions:

USES:	for **relief** of heartburn, acid indigestion, and sour stomach for **prevention** of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise
DIRECTIONS:	Adults and children 12 years of age and older: for **relief** of symptoms: Swallow 1 tablet with a glass of water. for **prevention** of symptoms for 24 hours: Swallow 1 tablet with a glass of water anytime during the day, or if you prefer, one hour before those events associated with occasional heartburn, such as consuming food and beverages, stress, hectic lifestyle, lying down, or exercise. do not take more than 1 tablet a day. **do not use for more than 10 days in a row unless directed by a doctor.** do not chew or crush tablets.

Children under 12 years of age: Ask a doctor.

A diary was dispensed to all subjects eligible for the actual-use phase of the study. Subjects were asked to provide the following information in the diary: date and time of the dose, total number of tablets taken, if taken for prevention (any time during the day or 1 hour before events) or for relief of heartburn symptoms, the severity of each heartburn episode (when study medication was taken to relieve symptoms), assessment of study medication effectiveness for each dose, and whether another heartburn medication was also taken to treat symptoms. Study medication effectiveness was collected for each dose on the diary. The study medication effectiveness assessment should have been recorded in the evening just prior to omeprazole magnesium tablets bedtime. If the study medication was taken for nighttime heartburn or subjects forgot to fill out the evaluation in the evening, they were instructed to fill it out the following morning.

In addition, information about concomitant medications (including heartburn medications), and any AEs experienced were recorded in the diary.

Interim Phone Interview
At the usage period mid-point (i.e., ~2 weeks after enrollment), subjects were contacted by phone and asked about:

- how they were completing the diary to determine if they were using it correctly,
- any problems they experienced since they began taking the study medication, and
- for female subjects, the result of their urine pregnancy test.

Findings from the phone check were documented. Subjects were also reminded of their Visit 2 appointment and to bring all study materials to the appointment.

Visit 2
Subjects had the following procedures performed during this visit:

- Subjects' diaries were reviewed with each subject during this visit to address any missing, incomplete, inconsistent, or confusing diary entries.
- Subjects were asked to provide an Overall Assessment of the study medication they had been using.
- Subjects' diaries provided a history of any AEs experienced after subjects ingested their first dose of study medication. If necessary, the Investigator examined subjects who reported AEs.
- Study staff compared the amount of study medication returned to the diary entries for study medication consumption and resolved any inconsistencies at that time with individual subjects.
- Subjects were asked additional questions to better understand their use of Prilosec 1 as well as their previous experiences with OTC and Rx heartburn medications.

Statistical Methods and Analysis Plans
To evaluate consistency with the label instructions, the frequency and percentage of subjects who used the study medication according to label instructions over the 4-week usage period were summarized. Label instruction consistency was summarized on a per-

subject basis, per dosing day basis, and per dosing occasion basis. Subjects were considered consistent with dosing instructions if they:

- took no more than one tablet per dose,
- took no more than one dose per day, and
- dosed for no more than 10 consecutive days (unless directed by a doctor).

In addition, consistency with label use directions by demographic characteristics such as gender (female vs. male), race (Caucasian vs. non-Caucasian), age (< 65 years vs. ≥ 65 years), and study center were summarized by the predominant use group and overall. Predominant use was defined as using the study medication more than 50% of the time for any one of the three reasons for use (as collected on the diary). Consistency with each separate criterion was calculated by pooling across study centers. Consistency at individual study centers was also examined.

In addition, the primary consistency rates on a per-subject basis were summarized by the following exclusive usage groups:

- Prevention-Any-Time-Only users (users who record this use type exclusively),
- Prevention-1-Hour-Before-Only users (users who record this use type exclusively),
- Dual-Prevention-Only users (users who record both of the prevention use types but not relief use type),
- Relief-Only users (users who record this type exclusively), and
- Prevention-And-Relief users (users who indicate that one or more doses were taken for the prevention usage and one or more doses were taken for the relief usage).

Study medication effectiveness and overall rating of study medication was summarized using descriptive statistics. For episodes when the study medication was taken to relieve symptoms, the percentage of effective dosing occasions was summarized by heartburn severity at the time of dosing using descriptive statistics. The number and percentage of doses that another heartburn medication was taken to relieve symptoms was summarized. Consumer reasons for self-selection/non-selection of study medication and demographic parameters were summarized.

Data were excluded from evaluation of consistency and effectiveness measures if a subject did not take at least one dose of the study medication, or dosing information was not available from the returned diary. Subject data may have been excluded from the summary of consistency due to incomplete data (i.e., missing dosing dates). All subjects who returned a diary (regardless of whether they took a dose of study medication) were included in the summary of usage behaviors.

Determination of Sample Size

It was expected a 75% return rate on the diary information, which equated to a total sample size of approximately 450 subjects. Thus, assuming the study population consisted of 70% who used the study medication predominantly for relief of symptoms and 30% who used the study medication predominantly for prevention of symptoms, a worst case scenario of a 50% consistency rate would yield a ± 5.5% error rate for relief users and a ± 8.4% error rate for the prevention users. In other words, with a sample size

of 450 subjects, we can be at least 95% confident that our estimate of consistency will not differ from the true consistency rate by more than 0.055 for relief users and 0.084 for prevention users. Analogously, a sample size of 450 subjects will yield at least 99% confidence that our estimate of consistency will be within 0.073 for relief users and within 0.111 for prevention users. If the true consistency rate was 90% or greater, a sample size of 450 subjects would yield at least 95% confidence that our estimate of consistency will be within 0.033 of the true rate for relief users and within 0.051 of the true rate for prevention users.

Changes in the Planned Analyses
Label use direction consistency on a per-subject basis was planned to be summarized two ways. First, consistency was to be summarized using the three criteria without considering physician consultation for the instruction "do not take for more than 10 days in a row." Secondly, consistency was to be summarized considering physician consultation obtained from the question on the general medication use questionnaire "While you were in the study, did you speak with a doctor about how to use the study medication - Prilosec 1 - for your heartburn?" In addition to considering physician consultation as it related to this question on the general medication use questionnaire, consistency was also summarized considering other medical guidance, such as consultation with other health care professionals or previous experience with prescription heartburn medicine in the past year. Also, consistency was calculated excluding 4 subjects who did not follow the label, because they misunderstood the study procedures. However, the primary calculation of consistency includes these four subjects.

Comments
The design of this study was very similar to that of study #067 and #003. The same study objectives were used, and the same consumer behavior aspects were tested. In addition, questions were asked about self-selection and follow-up with a doctor or other health care professional. All three amendments made to the protocol have been reviewed and were found to be minor.

Dosage of the drug used in this study, omeprazole magnesium 10.3 mg tablets, was half the strength of that proposed for the OTC marketing (20.6 mg).

Inclusion/Exclusion criteria were too extensive, by excluding any subjects at risk for inappropriate use of the product. Information about heartburn history and past medical history was asked, after the subject was included into the study. This information would have been useful to obtain from all comers to the study, in order to assess ability to appropriately self-select.

Data analysis was performed in two different ways: by exclusive usage patterns, and predominant usage patterns. Analysis by predominant use was considered post-hoc for the first two studies.

It was noted that three out five investigators participated in more than one study. In particular, investigators from center #1, 2 and 3 participated in studies #003 and #022,

which were the same design studies. Even though the studies were not done simultaneously, these violations make the validity of these trials questionable.

Data analyses were summarized considering physician consultation obtained from the question on the general medication use questionnaire at Visit 2. Questions about the contact with a doctor or health care practitioner were presented to the subjects at the end of last visit. Information would have been more complete and useful if subjects were asked to record in their Product Use Journal the date of the contact with a physician. Contact with a physician was not verified by the investigator.

Analyses considering medical advice were based not only on consultation with a physician or other health care provider, but were also based on subjects' experience with a prescription heartburn medicine within the year of participation in the study. If the subject dosed himself/herself for more than 10 days in a row, he/she was asked the reason for that, given the following choices: "(1) Because I'm accustomed to using heartburn medication; (2) Because I know that Prilosec 1 is used that way; (3) Because my doctor told me to use it that way; (4) Because my pharmacist or nurse told me it was okay to use it that way." Selection of one of those choices justified subjects' noncompliance with that particular label use direction. The validity of that kind of analyses is questionable.

Results

The following diagram displays a disposition of the subjects.

Recruited to participate in the study
N=923
↓
Self-selected to participate in the study after reading the label
N=627 (68%)
↓
Received study medication
N=596 (65%)
↓
Completed Study
N=529 (57%)

Over all, 68% of the targeted population decided to participated, and 65% received the drug. Following are the reasons why the others did not receive the study medication:

- 113 subjects decided not to participate after reading the label (the product was not appropriate for them to use),
- 183 subjects felt the product was appropriate to use but decided against participation,
- 19 subjects, who self-selected, did not meet Inclusion/Exclusion criteria at Visit 1,
- 4 subjects reconsidered and withdrew consent, and
- 8 subjects were withdrawn by the Investigator before receiving study medication.

Of the 596 subjects who received study medication and diaries at Visit 1, 529 subjects completed the study and the remaining 67 subjects did not complete the study. Table 1 contains the detailed reasons for study discontinuation.

Table 1. Reasons for Discontinuation

	N (%)
Did not Complete the Study (Total)	67 (100%)
• Adverse Events	5 (8%)
• Consent Withdrawn	0 (0%)
• Lost to Follow-up	60 (89%)
• Investigator/Sponsor Decision	2 (3%)

Of the 596 subjects who received study medication, 489 subjects took at least one dose of study medication as indicated in their returned diary and were included in the Intent-to-Treat (ITT) analysis set. The 596 subjects who received the study medication and diary at Visit 1 included 67 subjects who did not complete the study and 529 who did complete the study. Of these subjects who completed the study, 45 subjects did not dose with study medication. The summary of safety included 491 subjects, some of whom reported an AE regardless of returning their diary.

The ITT population (those subjects included in the summarization of usage patterns, i.e., number of dosing days, dosing occasions, tablets taken, etc.) consisted of 489 subjects who took at least one dose of study medication as indicated on their returned diary. Summary of dosing behaviors included all 529 subjects who completed the study, regardless of whether they dosed. For the purposes of summarizing label use direction consistency, subjects who had missing tablet counts and/or missing dates were excluded, with one exception: subjects who had a missing date and took only one dose were considered compliant with respect to the criteria 'take only one dose per day.' Data for 1 subject (Subject 002125) could not be summarized due to incomplete data (i.e., missing dosing date); therefore, data displays summarizing label use direction consistency are based on a total of 488 subjects.

All subjects recruited to the study were asked: "Do you think this is an appropriate medication or not an appropriate medication for you to use?" Then they were asked to provide reasons (as many that applied) for their decision. Nearly 30% of the subjects who decided not to participate in the study, after reading the product label, did so because they either did not experience heartburn or their heartburn was not felt to be that bad. Twenty-four percent (24%) of subjects did not like to try new medication without their doctor's approval, and 27% cited other reasons for not self-selecting to participate in the study. The majority of the subjects who self-selected to participate did so because they experience heartburn (80%). The category with the next highest frequency was "I want to prevent heartburn" (38%).

Comments
Validity of indications for prevention or relief, will be based on the efficacy data from the controlled clinical trials. The data about consumer's reasons for using study medication

is more important for marketing prospective, than for actual use. Eighty percent (80%) of the subjects stated that they are interested in this product because they had heartburn, and 38% stated that they want to prevent heartburn. Exact verbatim or specific reasons were not provided for subjects who decided not to participate in the study. Eleven percent (11%) of the enrolled subjects did not complete the study, and most common reason for non-completion was lost to follow-up. It is not clear what attempts were made by the investigator to contact these people.

Demographic Characteristics

Table 2 displays subject demographics for the ITT population (N=489). Of these subjects, 289 (59%) were female and 200 (41%) were male, ranging in age from 13–87 years with a mean age of 46 years. The majority, 418 of the 489 subjects (85%), were Caucasian. Of the ITT subjects, 274 (56%) indicated they had completed at least some college, 125 (26%) indicated their occupation was professional or technical, and the remaining occupations are listed by decreasing order of frequency: service worker or private household worker (13%), manager or administrator (12%), and student (10%).

Table 2. Demographic Characteristics (ITT Population)

		Overall N=489
Gender	Female	289 (59%)
	Male	200 (41%)
Age	Mean	45.60
	Std. Dev.	17.97
	Range	13-87
Race	American Indian	3 (1%)
	Asian	0 (0%)
	Black	34 (7%)
	Caucasians	418 (85%)
	Hispanic	27 (6%)
	Multi-Racial/Other	7 (1%)

Heartburn History

Most (452 out of 489) subjects experienced more than 1 year of heartburn symptoms, and half of them (N=222) suffered from heartburn for more than 5 years. Total of 291 out of 489 subjects (59%) suffered from daytime heartburn at least two times a week; nighttime heartburn frequency was similar (272/489; 56%). Food and/or beverages were found to be the most typical contributing factor (91% of subjects) of heartburn, followed by stress and/or anxiety (53%), and lying down (25%).

Prior and Concomitant Therapies

Prior to enrollment, the most common prior drug therapies were Tums, multivitamins, Tylenol, and vitamin E (>9% overall). During the study, subjects were allowed any concomitant medication, which was not specifically prohibited in the Exclusion criteria of the protocol. The most common concomitant medications were similar to the prior drug therapies and included multivitamins, Tums, aspirin, and vitamin E (>9% overall).

Comments
The majority of the subjects enrolled into this study were Caucasian (85%). Literacy level was not assessed, and therefore, behavior based on the education level could not be evaluated.

Even though the inclusion criteria did not specify a duration or frequency of heartburn symptoms, the majority of the enrolled population does not meet the sponsor's definition for the targeted OTC population having "occasional episodic heartburn." Ninety-two (92%) percent of enrolled population suffered from heartburn for more than 1 year, 59% having it at least 2 times a week during the daytime, and 56% having it at least two times a week during the nighttime.

Summary of Usage Patterns
Subjects were classified into the categories representing predominant use. The frequency and percentage of subjects eligible for summarization of label use direction consistency who used study medication in each of the predominant use categories were as follows:

- 125 Predominant Prevention-Any-Time-Only users (26%),
- 29 Predominant Prevention-1-Hour-Before-Only users (6%),
- 284 Predominant Relief-Only users (58%), and
- 50 No Predominant use (10%)

Data was summarized based on the five exclusive usage categories within two indications. The frequency and percentage of subjects within each label use direction, who used study medication in each of these usage categories, were as follows:

- 42 for the Prevention-Any-Time-Only users (9%),
- 3 for the Prevention-1-Hour-Before-Only users (1%),
- 13 for the Dual-Prevention-Only users (3%),
- 163 for the Relief-Only users (33%), and
- 267 for the Prevention-And-Relief users (55%).

Consistency with label use directions
The term 'consistency' is used in this report to describe the subjects' adherence to the label use directions: 1) took no more than one tablet per dose, 2) took no more than one dose per day, and 3) dosed for no more than 10 consecutive days.

Label use direction consistency on a per-subject basis was summarized two ways. First, consistency was summarized using the three criteria above without considering medical guidance for the instruction "do not take for more than 10 days in a row." Secondly, consistency was summarized considering medical guidance. This included subjects who exceeded 10 consecutive dosing days but who consulted their physician, another health professional, or who were experienced prescription H2RA or PPI users (in the last year). In addition, consistency was calculated excluding 4 subjects who exceeded 10 consecutive dosing days due to confusion with the study procedures.

Table 3 summarizes consistency with the three label use directions by exclusive reason for use on a per subject basis for the ITT subjects.

Table 3. Consistency with Label Use Directions (ITT Population)

	Prevention Any Time N=42 (%)	Prevention 1-Hr Before N=3 (%)	Dual Prevention N=13 (%)	Relief Only N=163 (%)	Prevention and Relief N=267 (%)	Overall N=488 (%)
Consistent with Label Use Direction	11 (26%)	2 (67%)	4 (31%)	130 (80%)	138 (52%)	285 (58%)
Not Consistent with Label Use Directions	31 (74%)	1 (33%)	9 (69%)	33 (20%)	129 (48%)	203 (42%)
• Exceeded 1 tablet per dose	10 (24%)	1 (33%)	1 (8%)	16 (10%)	66 (25%)	94 (19%)
• Exceeded 1 dose per day	2 (5%)	0 (0%)	2 (15%)	18 (11%)	67 (25%)	89 (18%)
• Exceeded 10 consecutive dosing days	29 (69%)	1 (33%)	7 (54%)	5 (3%)	63 (24%)	105 (22%)

Two hundred eighty five (285) of 488 subjects (58%) were consistent with all three label use directions. Across all subjects, 94 (19%) took more than one tablet per dose, 89 (18%) took more than one dose per day, and 105 (22%) exceeded 10 consecutive days of dosing. Consistency with the three label use directions was observed by 11 of 42 Prevention-Any-Time-Only users (26%), 2 of 3 Prevention-1-Hour-Before-Only users (67%), 4 of 13 Dual-Prevention-Only users (31%), 130 of 163 Relief-Only users (80%), and 138 of 267 Prevention-and-Relief users (52%).

Label use direction consistency was also summarized by exclusive use group considering medical guidance for the instruction "do not take for more than 10 days in a row." There were 9 subjects who exceeded 10 consecutive dosing days but consulted their physician, 2 subjects who talked to another health professional, and 46 subjects who were already under a doctor's care (had taken a prescription heartburn medication within the last year). These 57 subjects were not considered among those who were not consistent with this instruction. Four subjects (Subjects 003056, 004052, 004126, and 004076) misunderstood the study procedures. Therefore, analyses considering medical guidance excluded these 4 subjects. Overall consistency changed from a rate of 58% to 64%. The number of subjects who were not consistent with the instruction "do not take for more than 10 days in a row without consulting a doctor" decreased from 105 (22%) to 44 (9%) overall when considering medical guidance.

Consistency with Label Use Directions by Investigator
Investigators Bey and Mousaw's study centers (Study Centers 1 and 2) had the greatest overall consistency rate (64%) as compared to Investigator Senzatimore's study center (Study Center 4), which had the lowest consistency rate (48%).

Table 4 summarizes consistency with label use direction by demographic characteristics on per-subject calculation. Consistency with the three label directions was similar within a gender, race, and age categories.

Table 4. Consistency with Label Use Directions by Demographics

	Female N=289 (%)	Male N=199 (%)	Caucasian N=417 (%)	Non-Caucasian N=71 (%)	Age <65 Yrs N=398 (%)	Age >65 Yrs N=90 (%)
Consistent with Label Use Direction	175 (61%)	110 (55%)	238 (57%)	47 (66%)	240 (60%)	45 (50%)
Not Consistent with Label Use Directions	114 (39%)	89 (45%)	179 (43%)	24 (34%)	158 (40%)	45 (50%)
• Exceeded 1 tablet per dose	53 (18%)	41 (21%)	79 (19%)	15 (21%)	74 (19%)	20 (22%)
• Exceeded 1 dose per day	52 (18%)	37 (19%)	78 (19%)	11 (15%)	78 (20%)	11 (12%)
• Exceeded 10 consecutive dosing days	57 (20%)	48 (24%)	97 (23%)	8 (11%)	75 (19%)	30 (33%)

Table 5 presents overall consistency with the three label use directions by number of dosing occasions on a per subject basis for ITT subjects. In general, subjects who had fewer dosing occasions demonstrated better consistency with the three label use directions. Less than half of the subjects taking Prilosec 1 on more than 15 occasions, were consistent with all three label use directions.

Table 5. Consistency with Label Use Directions by Number of Dosing Occasions

Number of Dosing Occasions	Overall ITT Population N=488 (%)
1-5	118/132 (89%)
6-10	83/108 (77%)
11-15	50/78 (64%)
16-20	25/53 (47%)
21-25	8/40 (20%)
26-30	1/44 (2%)
31-36	0/33 (0%)
Overall	285/488 (58%)

Data about maximum number of sequential dosing days by exclusive use categories was not submitted for this study. Therefore, Table 6 displays the maximum number of sequential days of dosing by predominant use for ITT subjects. Seventy-six (76) of 126 (60%) predominant Prevention-Any-Time users had more than 10 maximum sequential dosing days. The majority (62%–84%) of the remaining predominant use groups and overall had four or less maximum sequential dosing days.

Table 6. Maximum Number of Sequential Dosing Days by Predominant Use

Maximum Number of Sequential Dosing Days	Predominant Use			No Predominant Use N=50	Overall N=489
	Prevention Any Time N=126	Prevention 1-Hr Before N=29	Relief N=284		
1-2	6 (5%)	9 (31%)	197 (69%)	18 (36%)	230 (47%)
3-4	16 (13%)	9 (31%)	42 (15%)	17 (34%)	84 (17%)
5-6	15 (12%)	0 (0%)	12 (4%)	3 (6%)	30 (6%)
7-8	3 (2%)	2 (7%)	10 (4%)	4 (8%)	19 (4%)
9-10	10 (8%)	2 (7%)	7 (2%)	1 (2%)	20 (4%)
11-12	7 (6%)	0 (0%)	0 (0%)	2 (4%)	9 (2%)
13-16	12 (10%)	1 (3%)	3 (1%)	1 (2%)	17 (3%)
17-20	14 (11%)	1 (3%)	1 (<1%)	0 (0%)	16 (3%)
21-24	6 (5%)	0 (0%)	0 (0%)	1 (2%)	7 (1%)
25-28	18 (14%)	0 (0%)	8 (3%)	2 (4%)	28 (6%)
≥ 29	19 (15%)	5 (17%)	4 (1%)	1 (2%)	29 (6%)

For maximum number of tablets per dosing occasion, 31 subjects (25%) in the predominant Prevention-Any-Time group, 7 subjects (24%) in the predominant Prevention-1-Hour-Before group, 44 subjects (15%) in the predominant Relief group, and 10 subjects (20%) in the no predominant use group took two tablets on one dosing occasion. For the predominant Relief group, 2 subjects (1%) took >3 tablets for one dosing occasion.

The sponsor, again, analyzed the minimum number of hours between doses for ITT subjects. Overall, 52% of the subjects had a minimum of at least 20 hours between doses.

Comments
For the interest of consistency, the data analysis discussion will focus on the exclusive use categories wherever it is possible. The number of subjects in some of the five usage categories was too small to make a meaningful conclusions. Most of the subjects (55%) used the study medication for relief and prevention, 33% of subjects used it for relief only, and the rest used it for prevention only.

Consistency analyses showed similar results as the previous studies. Overall, 58% were consistent with all three label use directions. Again, subjects using study drug for prevention were less consistent with the label use directions than those who used it for relief. Twenty-nine (29) out of 42 subjects in Prevention-Any-Time-Only usage category exceeded 10 consecutive dosing days. Consistency with label use directions decreased with the increase of the number of dosing occasions.

Data summary considering medical guidance, has to be evaluated with caution. The information about the change in behavior after contact with the learned intermediary would have been useful to know. The analysis done in this study does not give us this information for the following reasons. There were only 11 subjects who received any advice about the use of Prilosec 1 from a doctor or health care provider, and took the drug for more than 10 sequential days. They were reclassified as consistent with label

use directions. This reanalysis also took into account subjects' own confidence or familiarity with use of heartburn medicine. Total of 46 subjects were reclassified as consistent (even though they were not) because they stated that they are accustomed to using heartburn medication. If we exclude those 46 subjects and use only 11 who consulted a learned intermediary during the course of the study, the consistency with label use directions does not change significantly.

Analysis of maximum number of sequential dosing days, again, shows that subjects using Prilosec 1 for prevention tend to continue on treatment for longer periods of time. Data about maximum number of tablets per dosing occasion is not consistent with the previous studies. Overall, 20% of ITT population took more than one tablet at least on one occasion. There were more subjects taking more than one tablet in the Prevention than in the Relief category.

Efficacy Evaluation

This study used omeprazole magnesium 10.3 mg dosage strength, which is not currently proposed for OTC marketing. The percentage of effective dosing occasions and the percentage of dosing occasions requiring backup medication use over the study period were calculated per subject and then averaged across subjects in each group. Overall, the mean percentage of effective dosing occasions was 90%, and the mean percentage of dosing occasions requiring backup medication use was 6%. The mean percentage of effective dosing occasions was slightly higher in the predominant prevention groups and no predominant use group (91%–93%) compared to the predominant Relief group (88%). The mean percentage of dosing occasions with backup medication use was similar across predominant use groups ranging from 5%–7%.

Overall, assessment of study medication for ITT population was excellent (30%), very good (42%), good (18%), fair (6%), and poor (3%). The predominant Prevention-Any-Time and no predominant use groups had a greater percentage of subjects (38%–40%) who rated the study medication as excellent when compared to the predominant Prevention-1-Hour-Before and predominant Relief groups (25%–28%).

As part of effectiveness evaluation, the sponsor analyzed the effective dosing occasions by baseline heartburn severity for relief of symptoms dosing occasions for ITT subjects. The percentages of effective dosing occasions overall were 93% for mild heartburn, 89% for moderate heartburn, and 72% for severe heartburn.

Concurrent Use of Heartburn Medication

Concurrent use of other heartburn medication for the ITT subjects was analyzed by predominant usage categories. These medications were obtained from the medication log if the subject reported they took a backup heartburn medication after dosing with the study medication on the same day. Overall, 88 of 489 subjects (18%) used antacids on the same day as the study medication. Eleven (11) of 489 subjects (2%) overall used H2RAs on the same day as study medication. The rate of concurrent PPI use consisted of 13 of 489 subjects (3%). Overall, 19 of 489 subjects (4%) took other medications or did not specify the medication.

Comments
This study used omeprazole magnesium 10.3 mg strength, which is only half the strength that of proposed for OTC marketing (20.6 mg). The appropriate dose of omeprazole for OTC marketing will be based on the safety and efficacy data gathered from the controlled clinical trials. Most of the participants in this study rated effectiveness of omeprazole magnesium 10.3 mg as very good or excellent. The rating was higher in the Prevention than in the Relief usage category, and for mild or moderate heartburn than for severe.

Concurrent use of other heartburn medication, which was evaluated by predominant usage categories, is not accurate. Usage pattern for prevention or relief in the same subject overlap. Such an analyses does not give the answer to the question, who really needed a back-up medication.

Overview of Safety
Of the 596 subjects who received study medication, 489 took at least one dose as indicated in their returned diary and were included in the ITT analysis set. The summary of safety includes 491 subjects, which included subjects who reported an AE regardless of whether they returned for Visit 2 with their diaries. Tables 7 summarizes the extent of exposure overall for the 489 subjects who took at least one dose of study medication. Prevention-Only users dosed for a mean of 20.3 days as compared to a mean of 6.3 days for Relief-Only users and a mean of 15.0 days for Prevention-And-Relief users. Overall, summary of adverse events is presented in Table 8.

Table 7. Summary of Extent of Exposure

		ITT (N=489)
Number of Dosing Days	Mean	12.7
	Std. Deviation	9.2
	Minimum-Maximum	1-36
Number of Dosing Occasions	Mean	13.3
	Std. Deviation	9.8
	Minimum-Maximum	1-36

Table 8. Summary of Adverse Events

		Safety Subjects (N=491)
Subjects	With Any AE	139 (28%)
	With SAEs	3 (1%)
	Withdrawals Due to AEs	5 (1%)
	Deaths	1 (<1%)
Number of AEs per Subject	Reporting 0 AEs	352 (72%)
	Reporting 1 AE	87 (18%)
	Reporting >1 AEs	52 (11%)
AE Relationship to Study Medication	Unlikely	125 (60%)
	Possibly	75 (36%)
	Probably	10 (5%)
	Total Number of AEs	210 (100%)
AE Intensity	Unknown	1 (<1%)
	Mild	82 (39%)
	Moderate	77 (37%)
	Severe	50 (24%)
	Total Number of AEs	210 (100%)

Total of 139 subjects reported 210 adverse events. Most of them were mild or moderate. There appears to be no increase in the percentage of AEs with increasing days of use, increasing number of doses, increasing number of tablets taken, or increasing duration of use. Table 9 presents AEs by body system and COSTART term.

Table 9. Adverse Events by Body System

	N=491	
Body System	Subjects N (%)	AEs
Body as a Whole	79 (16%)	89
Cardiovascular	5 (1%)	5
Digestive	38 (8%)	44
Endocrine	3 (1%)	3
Hemic/Lymphatic	0 (0%)	0
Musculoskeletal	11 (2%)	12
Nervous	5 (1%)	7
Respiratory	33 (7%)	36
Skin	3 (1%)	3
Special Senses	4 (1%)	4
Urogenital	7 (1%)	7

The most frequently reported AEs were in the Body as a Whole category where 79 subjects (16%) reported 89 AEs. Most common adverse events of overall incidence > 1% by COSTART terms are presented in Table 10. Overall, the most commonly reported AE was headache (56 subjects, 11%), followed by respiratory infection (4%), and diarrhea (3%). All other AEs had an incidence of 2% or less overall.

Table 10. Adverse Events by Body System and COSTART Term

	N=491	
Body System	N	%
BODY: Headache	56	11%
RES:Infection	19	4%
DIG: Diarrhea	16	3%
BODY: Pain Back	11	2%
MS:Myalgia	5	1%
BODY: Pain	5	1%
DIG: Pain Abdominal	5	1%
RES:Rhinitis	5	1%
DIG:Constipation	4	1%
UG:Dysmenorrhea	4	1%
DIG: Flatulence	4	1%
DIG: Nausea	4	1%
DIG:Pain	4	1%
BODY: Pain Abdominal	4	1%
RES: Pharyngitis	4	1%
MS: Arthralgia	3	1%
NER:Depression	3	1%
BODY:Pain Chest	3	1%
RES:Sinusitis	3	1%

Deaths

Subject **001141,** a 47 year old, black male with no significant prior medical history, was found dead in his home on 8-Oct-99. An autopsy conducted on 8-Oct-99 revealed cardiomegaly, hypoplastic right coronary artery, and no acute trauma. The final cause of death was attributed on 9-Nov-99 to combined heroin and ethanol toxicity. The subject was given Ome-Mg 10, but the duration of study medication therapy, start dates, and stop dates are unknown. The investigator considered this event unlikely related to study medication.

Other Serious Adverse Events

The following are narratives of subjects who experienced SAEs while dosing with omeprazole magnesium 10.3 mg.

Subject Number **002104**

Subject 002104 was a 35 year old female, with a previous medical history significant for bipolar disorder and asthma, on lithium and bronchial inhalers, was hospitalized for exacerbation of bipolar disorder attributed to disruption in medication. The duration of study medication therapy, start dates, and stop dates are unknown. The investigator considered the event unlikely related to study medication.

Subject Number **002147**

Subject 002147 was a 52 year old white female, with a previous medical history significant for myasthenia gravis, narcolepsy, hypothyroidism, migraines, and arthritis, on Ritalin, Mestinon, Synthroid, Celebrex, Lasix, Fioricet, Rolaids, and Prilosec, was hospitalized for E. Coli UTI. The investigator considered the event unlikely related to study medication.

Discontinuation Due To Adverse Events

There were 5 subjects who discontinued study participation due to an AE. One of the discontinuations (Subject 001141) has already been discussed. The other 4 cases are listed bellow:

Subject **004127** discontinued study participation because of flatulence. This subject took a total of eleven tablets of study medication from 11-Sep-99 to 24-Sep-99.

Subject **005010** discontinued study participation because of a headache. This subject took one tablet of study medication on 11-Sep-99.

Subject **005016** discontinued study participation because of diarrhea and slight nausea. This subject took one tablet of study medication on 10-Sep-99.

Subject **005107** discontinued study participation because of swelling at the end of his nose. This subject took a total of three tablets of study medication from 16-Sep-99 to 23-Sep-99.

Comments

The incidence of adverse events in this study was lower than in the previous two studies. This can be explained by the lower dose of omeprazole used. No new safety signals were observed during this study.

Summary of Study #022

- *This was uncontrolled, open-label, actual use study to test consumer usage patterns of omeprazole magnesium 10.3 mg tablets.*
- *Formulation of the drug used in this study, omeprazole magnesium 10.3 mg tablets, was only half the strength of that proposed for the OTC marketing (20.6 mg).*
- *Inclusion/Exclusion criteria were too broad, and excluded all subjects at risk for inappropriate use of the product.*
- *Majority of the subjects enrolled into this study were Caucasian (85%).*
- *Ninety-two (92%) percent of enrolled population suffered from heartburn for more than 1 year, 59% were having it at least 2 times a week during the daytime, and 56% were having it at least two times a week during the night time. This data raise a concern, because population enrolled into the study does not meet the sponsor's definition of OTC targeted population - with occasional episodic heartburn.*
- *Most of the subjects (55%) used the study medication for relief and prevention, 33% of the subjects used it for relief only, and the rest used it for prevention only.*
- *Overall, 58% were consistent with all three label use directions.*
- *Twenty-nine (29) out of 42 subjects (69%) in Prevention-Any-Time-Only usage category exceeded 10 consecutive dosing days. Consistency with label use directions was decreasing with increase in a number of dosing occasions.*
- *Because of the methodology used to test subjects' behavior to consult a physician, the validity of the consistency data reanalyzed considering medical guidance is questionable. There were only 11 subjects who received advice for use of Prilosec 1 from a doctor or health care provider during the study and took the drug for more than 10 sequential days.*

- *Overall, 20% of ITT population took more than one tablet at least on one occasion. There were more subjects taking more than one tablet in the Prevention than in the Relief category.*
- *Most of the participants in this study were satisfied with the effectiveness of omeprazole magnesium 10.3 mg.*
- *Safety data for omeprazole 10.3 mg gathered from this study showed no unexpected or unlabeled adverse events.*

Study 091

A SINGLE-PRODUCT, UNBLINDED STUDY OF OMEPRAZOLE, 20 MG, TO INVESTIGATE CONSUMER PERCEPTIONS OF PRODUCT PERFORMANCE WHEN USED ACCORDING TO PROPOSED LABEL INSTRUCTIONS

The **primary objective** of this study was to characterize the usage patterns and satisfaction response when omeprazole was used *ad libitum* according to proposed label instructions.

Overall Study Design and Plan
This study was a single-product, multiple-center, multiple-dose, uncontrolled study. Subjects were screened by study nurses at the 12 study centers. The purpose and procedures of the study was explained to potential subjects prior to enrollment. All subjects agreeing to participate were required to provide written informed consent and undergo eligibility screening which included a medical/medication history and a urine pregnancy test if the subject was female (all females were required to take a urine pregnancy test). The subjects completed a medical history form, which included information on tobacco and caffeine use history. Enough subjects were screened to provide approximately 300 subjects dosing with study medication. The total number of subjects recruited was divided as evenly as possible among the centers. Eligible subjects were supplied with 20 omeprazole (20 mg) capsules. All subjects who agreed to take the study medication were to use it for the labeled indications as needed for a period of 14 to 21 days.

The subject was scheduled to return at the end of the 14 to 21 day study period with the study medication package, the Product Use Journal, and any unused study medication to the study center.

Visit 1
The following procedures were performed during Visit 1:

- The sub-investigator obtained written informed consent from each subject who elected to participate in this study.
- Demographic information was collected at Visit 1 to define the subject population. In addition, subjects were questioned regarding the etiology of their heartburn over the last month.
- The sub-investigator obtained a complete medical history, including tobacco and caffeine use.
- Subjects provided a history of past (within 30 days) and current medications.
- All female subjects had a urine pregnancy test. All female subjects of child-bearing potential were to sign a birth control agreement.
- The Product Use Journal was dispensed during Visit 1. Subjects were trained on how to properly complete the Product Use Journal. For each dose of the study medication, the subject was asked to provide the following information in the Product Use Journal: day and time of the dose, number of capsules in the dose, and whether the dose was taken for prevention or relief.

Inclusion Criteria

To be considered eligible for enrollment into this study, subjects must:

- have provided written informed consent;
- have had a history of relieving and/or preventing heartburn occurring at least 2 days per week over the past 30 days;
- have had a history of antacid or acid reducer use at least 2 days per week over the past 30 days;
- have been male or non-pregnant, non-lactating female, in good general health, any race, and at least 18 years of age (women of child-bearing potential must have been using an acceptable form of contraception [including abstinence] as determined by the Investigator and had a negative urine pregnancy test at Visit 1);
- have been willing to substitute the study medication for his/her regular oral OTC heartburn medications during the study period; and
- have been willing and able to complete the Product Use Journal during the study period, and willing to return to the study center for Visit 2 with any unused study medication, the study medication package, and the Product Use Journal at the end of the study period.

Exclusion Criteria

Subjects were excluded from the study if they:

- had difficulty swallowing or persistent abdominal pain (any other medical condition or situation which the investigator felt constituted a safety concern [e.g., gastrointestinal bleeding, malignancy, etc.]);
- had the need for any treatment with phenytoin (Dilantin), diazepam (Valium), or warfarin (Coumadin) at any time between Visit 1 and Visit 2;
- had participated in another investigational medication or device study within 6 months of Visit 1; and
- were pregnant or lactating.

Eligible subjects were supplied with the study medication after all Inclusion/Exclusion criteria were satisfied. Each subject who agreed to take the study medication used it as needed instead of their regularly used OTC heartburn medication for a period of 14 to 21 days according to the labeled dosing instructions. Subjects had up to 21 days to return to the study center for Visit 2.

Visit 2

Subjects had the following procedures performed during Visit 2.

- The Product Use Journals were reviewed during this Visit 2 to address any missing, incomplete, inconsistent, or confusing Product Use Journal entries with each subject. Changes made to the Product Use Journal at this time were initialed by the subject.
- Subjects completed product evaluations.
- Each subject was interviewed to determine what concomitant medications were used during the study period.

- At the time subjects returned for Visit 2, subjects were queried as to their general well-being since they ingested their first dose of study medication. If necessary, the Investigator examined the subject. All adverse event (AE) data were documented on the CRFs.
- Study staff compared the amount of study medication returned to the Product Use Journal entries for study medication consumption and resolved any inconsistencies at that time with the subject.

The carton label used in this study had the following directions:

USES:	**Prevents** you from getting heartburn, acid indigestion, and sour stomach. **Relieves** your symptoms of heartburn, acid indigestion, and sour stomach.
DIRECTIONS:	To **Prevent** symptoms for 24 hours on days you expect to get symptoms, swallow 1 capsule with water. Or, if you prefer to wait until you think food or beverage may cause symptoms, swallow 1 capsule with water one hour in advance. To **Relieve** symptoms: swallow 1 capsule with water. **Do not take more than one capsule every 24 hours.**

Each bottle was placed in a test kit. The top flap of the kit was labeled with a non-removable one-panel label containing study number and distribution information. The inner flap of each kit was labeled with a non-removable one-panel label containing the same use directions as on the bottle along with instructions not to use more than 14 consecutive days.

Prior and Concomitant Therapy

Subjects were instructed to replace their normal therapy for heartburn or other acid-related symptoms. Subjects were allowed any concomitant medication, which was not specifically excluded in the Exclusion criteria.

Usage Patterns and Acceptance and Liking Attributes

Usage patterns were collected and summarized to determine:

- for which label use indication the product was used (Prevention, Relief, or Dual/Prevention and Relief), and
- consistency with the label use directions (1) take only one capsule per dose, (2) take no more than one dose per day (based on calendar day and 24-hour period), and (3) take for no more than 14 consecutive days.

Subjects were asked to rate various acceptance and liking parameters following a 14 to 21 day product usage period. Information for these attributes was collected on 9-point acceptance and liking scales.

Statistical Methods Planned and Determination of Sample Size
All data were checked for accuracy, completeness, and compliance with the study protocol. Statistical analysis was the responsibility of the Sponsor's Biometrics and Statistical Sciences Department.

Descriptive statistics were used to summarize baseline demographic variables for each usage group (Prevention-Only users, Relief-Only users, and Dual users). Consistency with label dosing directions and satisfaction scores were summarized using descriptive statistics by usage group and in total by pooling across centers. Consistency rates at individual centers were also examined, and any consistency rate at an individual center which deviated from the pooled consistency rate by more than two pooled standard errors was noted. Dosing patterns including the subjects' behaviors over the study period were also summarized.

Safety was investigated by evaluating all reported AEs. Verbatim terms on the CRFs were linked 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, relationship to study medication, and body system for each usage group. All subjects taking study medication were included in the safety analysis.

Comments
This study was not considered an actual use study by the sponsor, and was submitted as a marketing study. Even though the primary objective of the study was the same as in the other actual use studies, the methodology was different. This review will focus on the actual use issues consistent with the other actual use studies.

The formulation of omeprazole, 20 mg capsules, used in this study, is not the same as proposed for OTC marketing.

One of the inclusion criteria was subjects' agreement to substitute currently used heartburn medication with omeprazole. Therefore, self-selection was not addressed in this study.

The sponsor is proposing that omeprazole be marketed OTC for "acute episodic heartburn." However, subjects targeted for enrollment in this study had to have a history of heartburn occurring at least 2 days per week for which they used heartburn medication, raising a question if this is the targeted OTC population. Furthermore, people with active ulcer disease were not excluded from the study.

The label used in this study had the same indications for use as the other actual use studies except for the warning (on the flap of the carton containing the bottle) not to use more than 14 consecutive days.

There were 9 investigators for 12 enrollment centers. Some of the investigators had more than one enrollment site under their supervision. Seven investigators including principal investigator were also involved in conduction of study #014.

Results
Following chart displays a summary of the subject disposition for the study.

Screened at Visit 1
N=373 (100%)
↓
Met Inclusion/Exclusion Criteria
N=368 (99%)
↓
Completed Study / Did not Complete study
N=352 (96%) N=16 (4%)

Six (6) subjects did not meet Inclusion and Exclusion criteria. Of the 368 who received study medication and the Product Use Journal, 16 did not return the Product Use Journal, and thus, there were no data for those subjects. Of the 368 subjects who received study medication, 352 completed the study. Table 1 contains the reasons for discontinuation of the study for the 16 subjects who did not complete.

Table 1. Reasons for Discontinuation of the study

Reason for Discontinuation	Enrolled Population (N=368)
Adverse Event	1 (<1%)
Consent Withdrawn	2 (2%)
Lost to Follow-up	11 (3%)
Investigator/Sponsor Decision	2 (1%)
Total	16 (4%)

Among the 368 subjects who received study medication, 5 did not take any: one subject withdrew due to an unintended pregnancy, consent was withdrawn by two subjects, and two other subjects were discontinued due to investigator's decision. Eleven (11) more subjects were lost to follow-up, and it was therefore not known whether they used study medication.

Demographic and Other Baseline Characteristics, and Concomitant Medication
Table 2 displays subject demographics for the ITT subjects. Two hundred fourteen (214) subjects (61%) were female, while 138 subjects (39%) were male. Three hundred three (303) subjects (86%) were Caucasian. The subjects' ages ranged from 18–77 (mean: 45.3) years.

Table 2. Demographic Characteristics (ITT Population)

		Overall (N=352)
Gender	Female	214 (61%)
	Male	138 (39%)
Age	Mean	45.31
	Std. Dev.	13.26
	Range	18-77
Race	American Indian	3 (1%)
	Asian	2 (1%)
	Black	27 (8%)
	Caucasians	303 (86%)
	Hispanic	11 (3%)
	Multi-Racial/Other	6 (2%)

The most common factor contributing to heartburn was food and/or beverage, mentioned by 329 subjects (93%). Anxiety/stress was a contributor to heartburn for 204 subjects (58%). Ninety-eight (98) subjects (28%) were smokers and 11 subjects (3%) using other nicotine products.

Subjects were allowed any concomitant medication, which was not specifically excluded in the Exclusion criteria of the protocol. The most commonly taken pre-study and concomitant heartburn medications were Tums (38%), Pepcid (27%), Rolaids (18%), Zantac (19%), and Tagamet (14%), Prilosec (2%).

Comments
Demographics of the enrolled population, again, is not representative of the overall U.S. OTC population. Information about the literacy or education level would be useful, but was not collected.

Data submission analyses did not allow to separate pre-study and concomitant medications. Since one of the inclusion criteria required to have heartburn, it is not surprising that significant number of subjects in this study were taking other heartburn medicine. Overall, more subjects used other heartburn medications than in the other actual use studies.

Summary of Usage Patterns
The Intent-to-Treat (ITT) population consisted of 352 subjects and was the basis for summarizing the label use direction consistency and acceptance evaluations. These subjects were classified into the following 3 categories representing use patterns within the two indications:

- 55 (16%) for the Prevention-Only group,
- 78 (22%) for the Relief-Only group, and
- 219 (62%) Prevention and Relief (Dual user).

The term "consistency" was used to describe the subjects' adherence to the label use directions:

1) consumed no more than one capsule per-dose,
2) took no more than one dose per-day, and

3) dosed for no more than 14 consecutive days.

The last instruction, regarding use exceeding 14 consecutive days, appeared only on the inner flap of the box containing the medication bottle and not on the bottle itself.

The frequency and percentage of subjects who used the study medication consistent with the label directions over the study period are summarized on a per-subject basis and a per-dosing occasion basis. Table 3 summarizes label use direction consistency on a per subject basis.

Table 3. Label Use Direction Consistency by Usage (ITT Population)

	Prevention-Only Users N=55	Relief-Only Users N=78	Dual Users N=219	Overall N=352
Consistent with Label Use Direction	26 (47%)	71 (91%)	181 (83%)	278 (79%)
Not Consistent with Label Use Directions	29 (53%)	7 (9%)	38 (17%)	74 (21%)
Exceeded 1 tablet per dose	2 (4%)	5 (6%)	15 (7%)	22 (6%)
Exceeded 1 dose per day	0 (0%)	4 (5%)	7 (3%)	11 (3%)
Exceeded 14 consecutive dosing days	27 (49%)	0 (0%)	18 (8%)	45 (13%)

Overall 278 of 352 (79%) subjects were consistent with the three label-use directions, 22 subjects (6%) took more than one tablet per dose, 11 subjects (3%) took more than one dose per day, and 45 subjects (13%) exceeded 14 consecutive days of dosing. Prevention only users were less consistent and tended to continue on treatment for more than 14 days. The best consistency rates by usage group were in the Relief-Only and Dual users categories.

Across the study centers, the consistency rates on a per-subject basis ranged from 52% to 95%.

Product Use Summary

Table 4 represents the maximum number of sequential days of dosing per subject. Twenty-seven (27) of 55 Prevention-Only users (49%) had a maximum number 15 or more sequential days of dosing, while the Relief-Only users did not have any subjects take the study medication for more than 8 consecutive days. Sixty-two of 78 Relief-Only users (79%) used the study medication a maximum of 1–2 days in a row. Moreover, only 18 of 219 of the Dual users (8%) used the study medication for 15 or more consecutive days, while the most common duration of usage for the Dual users (49%) was 1–2 days.

Table 4. Maximum Number of Sequential Dosing Days (ITT Population)

Maximum Number of Sequential Days of Dosing	Prevention-Only Users N=55	Relief-Only Users N=78	Dual Users N=219	Overall N=352
1-2	5 (9%)	62 (79%)	107 (49%)	174 (49%)
3-4	3 (5%)	11 (14%)	51 (23%)	65 (18%)
5-6	4 (7%)	4 (5%)	14 (6%)	22 (6%)
7-8	1 (2%)	1 (1%)	9 (4%)	11 (3%)
9-10	3 (5%)	0 (0%)	4 (2%)	7 (2%)
11-12	1 (2%)	0 (0%)	1 (<1%)	2 (<1%)
13-14	11 (20%)	0 (0%)	15 (7%)	26 (7%)
15-16	26 (47%)	0 (0%)	16 (7%)	42 (12%)
More than 16	1 (2%)	0 (0%)	2 (1%)	3 (1%)

Comments
As it was mentioned earlier, this study used different methodology. Subjects were classified by the usage pattern into three groups. There were no Prevention-1-Hour-Before or Dual-Prevention usage categories. The label used in this study was different in terms of duration of treatment. It was stated not to use the product for more than 14 consecutive days, as opposed to other studies and the proposed label – not to use for more than 10 consecutive days. This warning was only on the inner flap of the box, not on the immediate bottle itself. Because of these discrepancies, data from this study have to be applied with caution.

Consistency with label use directions was analyzed in two ways: by calendar day and by 24-hour period. In the opinion of this reviewer, the number of tablets taken within the same day is more important, than the interval in hours between two dosing occasions.

Overall, consistency with three label directions was achieved by 79% of study participants. Prevention-Only users were less compliant with label use directions. Almost half of them (49%) continued on treatment for more than 14 consecutive days.

Overview of Safety
Formulation of omeprazole used in this study is different than that of proposed for OTC marketing. Therefore, safety review will focus on serious AEs and new safety signals.

Three hundred sixty eight (368) subject were each supplied with 20 capsules of omeprazole 20 mg to use needed according to the label for a period of 14 to 21 days. Of 368 subjects 352 completed the study and took at least one dose of the study medication. Overall, most subjects: took 10 or fewer capsules (68%), took 10 or fewer doses (70%), dosed for 10 or fewer days (69%).

Overall, 60 (17%) of the subjects on omeprazole 20 mg reported 81 AEs. There appeared to be no increase in the percentage of AEs with increasing days of use, increasing number of doses, or increasing number of capsules taken.

Table 6. Summary of Adverse Events

		ITT (N=352)
Subjects	With Any AE	60 (17%)
	With SAEs	1 (<1%)
	Withdrawals Due to AEs	0 (0%)
	Deaths	0 (0%)
Number of AEs per Subject	Reporting 0 AEs	292 (83%)
	Reporting 1 AE	42 (12%)
	Reporting >1 AEs	18 (5%)
AE Relationship to Study Medication	Unlikely	12 (15%)
	Possibly	56 (69%)
	Probably	13 (16%)
	Total Number of AEs	81 (100%)
AE Intensity	Unknown	0 (0%)
	Mild	37 (46%)
	Moderate	33 (41%)
	Severe	11 (14%)
	Total Number of AEs	81 (100%)

The most frequently reported AEs were in the digestive system and body as a whole categories. The most commonly reported AEs were headache (17 subjects), nausea (12 subjects), and diarrhea (10 subjects).

Deaths
There were no deaths.

Other Serious Adverse Events (SAE)
There was one SAE reported. **Subject 003008** was hospitalized due to toxic fume poisoning/asthma. The investigator characterized the event as severe and felt that the event was unlikely to be due to the study medication. There was no action taken with respect to the study medication. At the time of the reporting, the subject had fully recovered and had completed study participation.

Discontinuation Due To Adverse Events
Subject 004013 became pregnant and withdrew from the study before dosing with the study medication.

Summary of Study #091

- *This was uncontrolled, open-label study to test consumer perception of omeprazole 20 mg capsules performance.*
- *Formulation of the drug used in this study, omeprazole 20 mg capsules, is different from the proposed formulation for OTC marketing – omeprazole magnesium 20.6 mg tablets.*
- *Because of the methodology used, self-selection for treatment was not addressed in this study.*
- *Marketing objectives were the primary focus of the study.*

- *Inclusion criteria allowed enrolling subjects with symptoms more consistent with diagnosis of gastroesophageal reflux disease than with the proposed targeted population by the sponsor "with acute episodic heartburn." In order to be enrolled into this study, all subjects had to have heartburn at least 2 times a week.*
- *Demographically enrolled population was similar to that of the other three actual use studies, majority being Caucasians (86%).*
- *Consistency with three label use directions was achieved by 79% of ITT subjects.*
- *Consistency rate with label use directions was much lower in Prevention group. Almost half of the Prevention-Only Users (49%) exceeded 14 sequential days of treatment duration.*
- *Safety data gathered in this study showed no unexpected or unlabeled AEs for omeprazole 20 mg capsules.*

Statistical Consult for NDA 21-229

NDA 21-229
Name of Drug: Prilosec (omeprazole)
Applicant: Proctor and Gamble Co.
Indication: Treatment of Heartburn
Documents Reviewed: Electronic documents for use studies (003, 014, 022, 067, 091) submitted by sponsor on 1/27/00 and 4/25/00.
Medical Reviewer: Dr. Ling Chin and Dr. Daiva Shetty
Statistical Consultant: Laura Lu, Ph.D.
Date of Review: 9/11/00

I. Introduction

The sponsor conducted a total of 5 OTC use studies (Studies 003, 014, 022, 067, 091) to assess consumer compliance. These are uncontrolled studies with one-arm (omeprazol). Study 003 was the primary actual use study with 1514 patients recruited and 1093 patients participated. The primary objective of these studies was to characterize the usage patterns/dosing compliance of omeprazole magnesium when used according to proposed label instructions under naturalistic OTC conditions. Per Dr. Ling Chin's request, this statistical consult provides comments for Study 003. Comment #3 also applies to Studies 022 and 067.

II. Statistical Comments

1. Confidence Intervals

The primary information for compliance provided by the sponsor was the consistency (with label in terms of dosing compliance) rates among the patients who took at least one dose of medication and had complete data. Confidence intervals are more informative than the a single rate estimation by providing a range for the estimation rate based on estimation error. Therefore, this reviewer presents the 95% confidence intervals for the consistency rate in overall and prevention/relief patient populations for the actual use study 003 in Table 1 below. According to the company, a total of 815 patients had compliance status (consistent or inconsistent) with 812 of these from the completer's group and 3 of these from the incompleter's group. But it is not sure how these 815 patients were associated with the detailed patient disposition groups presented in Table 1a in Appendix A.

Table 1. Point Estimation and Confidence Intervals for Consistency Rate (Study 003)

	Prevention Any Time (N = 36)	Prevention 1 hr Before (N = 28)	Dual Prevention (N = 13)	Relief (N = 316)	Prevention And Relief (N = 422)	Overall (N = 815)
Consistency (n (%))	9 (25%)	9 (32%)	7 (54%)	254(80%)	228 (54%)	507 (62%)
95% Confidence Interval	(11%, 39%)	(15%, 49%)	(27%, 81%)	(76%, 84%)	(49%, 59%)	(59%, 65%)

2. Lost-to-Follow-up Patients

In Study 003, a total of 210 patients were lost to follow-up (see Table 1a in Appendix A) without returning the product use journal, so no information was available in actual use pattern. Among the baseline characteristics, frequency of heartburn during day time in the past, frequency of heartburn during night time in the past, Rx medication use (whether Rx medication was used for heartburn before), and medication factor (whether medication was a factor contributing to heartburn in the past) were strongly associated with consistency rate (p=0.001). Detailed results presented in Tables a2-a5 in Appendix A show that consistency rate decreases as the frequency of heartburn increases, and the consistency rate is lower among patients who used Rx heartburn medication before and among patients whose heartburn was contributed by use of medication. To assess the potential difference in consistency rates among the lost-to-follow-up patients and the completers, the distribution of heartburn frequency, Rx medication use and medication factor among the completers and lost-to-follow-up patients were compared in Tables 2-5 below. Tables 2 and 3 below show that the lost-to-follow-up patients tend to have heartburn less frequently compared with the completer group. Tables 4-5 show that the proportion of patients who used Rx medication before and the proportion of patients whose heartburn was contributed by use of medication were less among lost-to-follow-up patients than that of the completer group. So based on association between baseline characteristic and consistency rate, there is no evidence showing that the consistency rate in the lost-to-follow-up patients were lower than that in the completer group. However, since the consistency rate could be influenced by unobserved factors such as reason for taking the medication, there is still chance that the consistency rate in the lost-to-follow-up group is lower than that in the completer's group.

Table 2. Distribution of Frequency of Heartburn During Daytime (Study 003)

Patient Population	Frequency of Heartburn During Daytime				
	Rarely	1	2-3	4-5	>=6
Completer (N=874)	170 (19.5%)	174 (19.9%)	319 (36.5%)	101 (11.6%)	110 (12.6%)
L-T-F-U* (N=210)	83 (39.5%)	52 (24.8%)	57 (27.1%)	11 (5.2%)	7 (3.3%)

*: Lost-to-follow-up patients

Table 3. Distribution of Frequency of Heartburn During Nighttime (Study 003)

Patient Population	Frequency of Heartburn During Nighttime				
	Rarely	1	2-3	4-5	>=6
Completer (N=874)	298 (34.1%)	160 (18.3%)	267 (30.6%)	77 (8.8%)	72 (8.2%)
L-T-F-U* (N=210)	103 (49.1%)	47 (22.4%)	40 (19.1%)	15 (7.1%)	5 (2.4%)

*: Lost-to-follow-up patients

Table 4. Distribution of Rx Medication Use (Study 003)

Patient Population	Rx Medication Use	
	Yes	No
Completer (N=874)	95 (10.9%)	779 (89.1%)
L-T-F-U* (N=210)	8 (3.8%)	202 (96.2%)

*: Lost-to-follow-up patients

Table 5. Distribution of Medication Factor (Study 003)

Patient Population	Medication Factor	
	Yes	No
Completer (N=874)	26 (3.0%)	848 (97.0%)
L-T-F-U* (N=210)	0 (0.0%)	210 (100.0%)

*: Lost-to-follow-up patients

3. Analyses Based on Predominant Use Groups

Consistency rates were also provided by predominant use groups (where predominant use is defined as using the study medication more than 50% of the time for anyone of the three reasons for use: 1) predominant Prevention-Any-Time users, 2) predominant Prevention-1-Hour-Before users, 3) predominant Relief users, and 4) no predominant use (includes those subjects who did not use the study medication more than 50% of the time for any one of the three reasons for use)). Since the analyses based on predominant use groups were not prespecified and there is no clear rationale for this reclassification, judgement should be based on the results from the prespecified analyses based on strict prevention/relief groups.

Laura Lu

Mathematical Statistician

Concur:

9/13/00

Stan Lin, Ph.D.
Team Leader

CC:
HFD-180/Walsh
HFD-560/Keravich
HFD-560/Chin/Shetty/Katz/Ganley
HFD-560/Div. File
HFD-725/Lu/Lin ST./Huque
HFD-725/Div. File

Appendix A

Table 1a. Patient Disposition in Study 003

Reason for Discontinuation	**N**
Received Study Medication and Product Use Journal	1093
Completed Study	874
Took at Least 1-Dose Medication	822
Did Not Take Medication	52
Did Not Complete Study	219
Adverse Event	4
Subject Reconsidered/Withdrew Consent	4
Lost to Follow-Up	210

Table 2a. Frequency (Daytime) BY Consistency Status

Heartburn History: Frequency During Daytime
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
2-3	109	202	311
	13.37	24.79	38.16
	35.05	64.95	
	35.39	39.84	
4-5	50	50	100
	6.13	6.13	12.27
	50.00	50.00	
	16.23	9.86	
>=6	75	32	107
	9.20	3.93	13.13
	70.09	29.91	
	24.35	6.31	
ONCE	37	118	155
	4.54	14.48	19.02
	23.87	76.13	
	12.01	23.27	
RARELY	37	105	142
	4.54	12.88	17.42
	26.06	73.94	
	12.01	20.71	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

Table 3a. Frequency (Night) BY Consistency Status

Heartburn History: Frequency During Night
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
2-3	110	145	255
	13.50	17.79	31.29
	43.14	56.86	
	35.71	28.60	
4-5	32	44	76
	3.93	5.40	9.33
	42.11	57.89	
	10.39	8.68	
>=6	47	25	72
	5.77	3.07	8.83
	65.28	34.72	
	15.26	4.93	
ONCE	38	109	147
	4.66	13.37	18.04
	25.85	74.15	
	12.34	21.50	
RARELY	81	184	265
	9.94	22.58	32.52
	30.57	69.43	
	26.30	36.29	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

Table 4a. Rx Medication Use By Consistency Status

Heartburn History: Rx Medication Use (Y=Yes, N=No)
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
N	253	471	724
	31.04	57.79	88.83
	34.94	65.06	
	82.14	92.90	
Y	55	36	91
	6.75	4.42	11.17
	60.44	39.56	
	17.86	7.10	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

Table 5a. Medication Factor By Consistency Status

MEDICAT(Heartburn Factor: Medication, 1=Yes, 2=No)
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
1	18	7	25
	2.21	0.86	3.07
	72.00	28.00	
	5.84	1.38	
2	290	500	790
	35.58	61.35	96.93
	36.71	63.29	
	94.16	98.62	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

NDA 21-229
HFD-560 Division Files
HFD-180 Division Files
HFD-560 Ganley/Katz/ Shetty/Chin/Cothran
HFD-180 Walsh