PROCTER & GAMBLE COMPANY
ASTRAZENECA LP

Omeprazole Magnesium Tablets

NDA No. 21-229

Advisory Committee
Briefing Document

May 6, 2002

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ACG	American College of Gastroenterology
AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area Under the Curve
AZLP	AstraZeneca Limited Partnership
CI	Confidence Interval
EE	Erosive Esophagitis
FDA	Food and Drug Administration
GDAC	Gastroesophageal Reflux Disease
GEE	Generalized Estimating Equation
GERD	Gastroesophageal Reflux Disease
$H_2RA(s)$	Histamine H_2-receptor Antagonist(s)
ITT	Intent-to-Treat
mg	Milligram
MUPS	Multiple Unit Pellet System
NDA	New Drug Application
NDAC	New Drug Advisory Committee
Ome	Omeprazole
Ome-Mg	Omeprazole Magnesium
Ome-Mg 10	Omeprazole Magnesium 10.3 mg
Ome-Mg 20	Omeprazole Magnesium 20.6 mg
OTC	Over-the-Counter
P&G	The Procter & Gamble Company
PPI	Proton Pump Inhibitors
REALM	Rapid Estimate of Adult Literacy in Medicine
R_x	Prescription

List of Abbreviations and Definition of Terms (Continued)

Abbreviation	Definition
SAE	Serious Adverse Event
SD	Standard Deviation
SUR	Safety Update Report
TEN	Toxic Epidermal Necrolysis
$t_{½}$	Elimination Half-Life
U.S. or US	United States
vs.	Versus

List of Study Numbers and Abbreviations

Abbreviation	Study Number
007	2001007
171	AMI 171
183	AMI 183
02255	02255
12179	12179

Briefing Document Organization

1. Part 1 of this document presents an overview of the briefing document.
2. Part 2 characterizes the heartburn consumer.
3. Part 3 presents summaries of the clinical pharmacology of omeprazole.
4. Part 4 presents a summary of the safety data from the OTC and select prescription (R_x) clinical trials
5. Part 5 provides an overview of the OTC Ome-Mg clinical program.
6. Part 6 summarizes the efficacy data from the two pivotal clinical trials.
7. Part 7 summarizes the data from the four consumer understanding and behavior trials.
8. Part 8 presents an overall summary of consumer understanding and behavior studies.
9. Part 9 contains a statement of the benefit and potential risk of having Ome-Mg available in the OTC setting.
10. Part 10 provides the reference citations.

1. Overview of the Briefing Document

1.1 Introduction

As background, an extensive review of efficacy and safety data for omeprazole magnesium (Ome-Mg) was presented to Advisory Committee on October 20, 2000. At this meeting, the Advisory Committee concluded Ome-Mg may be suitable for management of frequent heartburn in the over-the-counter (OTC) setting. The Committee voted favorably on the safety of Ome-Mg and the efficacy of 20 mg data from the 14-day prevention of frequent heartburn symptoms for 24-hour efficacy studies. However, the Committee recommended the Sponsor propose new labeling congruent with the existing efficacy data and with results of actual use studies.

Working with FDA, we have developed a new label and tested it in Label Comprehension and Actual Use studies to evaluate how consumers would likely use the product in an OTC setting. In addition, the following elements have been agreed to with the Agency as appropriate starting points for OTC status for Ome-Mg: the dose is 20 mg, the OTC indication is for the prevention of the symptoms of frequent heartburn for 24 hours, defined as heartburn 2 or more days per week, and the appropriate dosing of OTC Ome-Mg is a regimen-based use direction.

This briefing document provides a summary of the data and relevant supporting information that qualifies this new label for the OTC use of Ome-Mg tablets for prevention of the symptoms of frequent heartburn. It highlights the critical data from the clinical efficacy and consumer understanding and behavior program, and safety results from the clinical program as well as from worldwide prescription (R_x) clinical trials and post-marketing surveillance databases to establish suitability of Ome-Mg for OTC status. It responds directly to Advisory Committee and FDA feedback to bring the label, efficacy data, and use data into congruence.

The data presented in this Briefing Document demonstrates the following:

- Clinically and statistically significant data supporting the efficacy of 20 mg Ome-Mg in the prevention of the symptoms of frequent heartburn for 24 hours when used over 14 consecutive days
- 14 days is the appropriate self-management regimen duration for this product's OTC symptom prevention indication; use beyond that should be with the acknowledgment of a learned intermediary
- The new label enables consumers to appropriately self-select the product and use it correctly
- The use of Ome-Mg in an OTC setting with this new label does not pose undue risk to special populations, e.g., those OTC consumers who may have undiagnosed gastroesophageal reflux disease (GERD) and/or erosive esophagitis (EE) that may require healthcare professional supervision and long-term treatment. In fact, the evidence suggests use of this OTC product as labeled will allow both consumers and physicians to better identify and motivate more of the subset of frequent heartburn sufferers to seek medical guidance.

Each of these points has been carefully addressed in the context of the proposed label, selection of dose and duration of use, and clear warning language. The consumer understanding and behavior program (Label Comprehension and Actual Use testing) presented here was conducted to demonstrate consumers understand the proposed product label, appropriately self-select this as a product appropriate for use, use the product according to the label directions, and, importantly, seek appropriate healthcare professional attention.

The label proposed for OTC status of Ome-Mg is on the following page.

PROPOSED LABEL
BACK CARTON PANEL

Drug Facts

Active ingredient (in each tablet) ***Purpose***
Omeprazole magnesium 20.6 mg…….Acid reducer
(equivalent to 20 mg omeprazole)

Uses

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

Warnings

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

Do not use

- with other acid reducers

Ask a doctor before use if you have

- any of the following symptoms and have not seen a doctor
  - frequent chest pain
  - chest pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
  - trouble swallowing food
  - frequent wheezing, particularly with heartburn
  - unexplained weight loss

These may be signs of more serious conditions. Notify your doctor.

Ask a doctor or pharmacist before use if you are taking

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

Stop use and ask a doctor if

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

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

Drug Facts (continued)

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

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

Directions

Adults 18 years of age and older:

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

Children under 18 years of age: ask a doctor

Other Information

- read the directions, warnings, and package insert before use
- keep the carton and package insert. They contain important information.
- store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
- avoid product exposure to excessive heat and humidity
- protect from moisture

Inactive ingredients glyceryl monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin, polyethylene glycol 6000, polysorbate 80, polyvinylpyrrolidone, sodium stearyl fumarate, starch, sucrose, talc, titanium dioxide, triethyl citrate

Questions or comments? Call toll free

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1.2 Executive Summary

1.2.1 Target Population: The Consumer Population with Frequent Heartburn

The target population for OTC Ome-Mg is comprised of consumers with frequent heartburn, defined as heartburn symptoms two or more days per week.

Consumers with frequent heartburn are prevalent in the heartburn population in the U.S. Heartburn occurs daily in approximately 7% to 10% of the adult population[1-2], and 2 or more days per week in up to 45% of consumers with heartburn (approximately 40 million people).[3-4] Because the symptomatic presentation of GERD or EE may not be distinguishable from frequent heartburn, a small subset of frequent heartburn consumers may have undiagnosed medical conditions and need to be considered in labeling for appropriate use in the OTC setting.

The majority of consumers with frequent heartburn symptoms have seen a healthcare provider (up to 78%)[2,4], and they primarily turn to OTC heartburn remedies to manage frequent heartburn. Most OTC consumers manage their frequent heartburn symptoms with combinations of OTC heartburn medications. However, consumer surveys show that a significant proportion of consumers with frequent heartburn are dissatisfied with current OTC products, primarily because the medication does not last long enough.[5] The OTC products intended to treat episodic occasional heartburn do not provide the degree of acid control needed in the prevention of frequent heartburn. Prevention of frequent heartburn symptoms is the goal for these consumers, rather than constant treatment of ongoing symptoms, and until now there is no OTC product available that adequately addresses this need.

1.2.2 Pharmacology of Omeprazole

The pharmacology of omeprazole makes it ideally suited for the prevention of frequent heartburn symptoms. Omeprazole irreversibly inhibits the H^+/K^+ ATPase on the secretory surface of the gastric parietal cell, providing a long-lasting effect in reducing gastric acid secretion despite its relatively short plasma half-life of one hour. Resumption of normal gastric acid secretion involves regeneration of the proton pump, a process that occurs progressively during a period of 3–5 days. While Ome is effective on the first dose, the maximum inhibition of gastric acid is seen after 3 or more days of dosing.

Therefore, regimen-based therapy will provide maximum prevention efficacy. Ome-Mg is ideally suited for OTC prevention of frequent heartburn symptoms, addressing the currently unmet needs of OTC consumers with frequent heartburn.

The efficacy data presented in this submission are consistent with the pharmacology of Ome.

1.2.3 Safety

Omeprazole and Ome-Mg have been shown to have excellent safety profiles.

Ome has been marketed worldwide since 1988 under various trade names in Europe and was the

first proton pump inhibitor (PPI) approved for R_x use in the United States in 1989. Omeprazole is one of the most frequently prescribed medications worldwide, and is currently marketed in 125 countries. To date, approximately 450 million courses of prescription therapy have been used, many at doses higher (e.g., more than 80 mg) than the proposed OTC dose of 20 mg and for long durations of therapy ranging from 4 weeks to several years.

The dosage form evaluated for OTC status is a tablet consisting of multiple enteric-coated pellets formulated with Ome-Mg. The tablet form was chosen for OTC status because the tablet is more resistant to tampering than a capsule, and therefore more suitable for OTC marketing. The Ome-Mg tablet has a similar relative bioavailability to the oral R_x capsule forms of Ome. The tablet dosage form is available in 33 countries worldwide including Australia, Germany, and the United Kingdom. Ome-Mg was also approved (1999) for OTC status in Sweden, for the relief of heartburn, in doses up to 20 mg. Because of the similar bioavailability between Ome and Ome-Mg, the extensive safety database for Ome is reflective of the safety profile of Ome-Mg.

Omeprazole has demonstrated a highly favorable safety profile over 15 years of worldwide prescription marketing. There is a substantial amount of experience with the compound in the treatment of many different acid-related conditions.

The use of Ome-Mg for the prevention of frequent heartburn is expected to be safe and well-tolerated in the OTC setting, based on results from OTC and R_x therapeutic trials and post-marketing surveillance data. The summary of these safety data indicate:

- The safety profile for Ome-Mg-treated subjects is comparable to that for R_x Ome and placebo. Since the relative bioavailability of Ome-Mg is similar to that of Ome, clinical and post-marketing safety data for Ome provide evidence of long-term safety supporting the OTC proposal.
- There is no dose-related increase in AE reporting for treated subjects during the clinical studies.
- Serious adverse events (SAEs) are rare and do not occur at a rate greater than the background rate in the population treated for acid-related disorders.
- No dose adjustment is necessary in hepatic or renal impairment or in individuals characterized as slow metabolizers.
- Reports of overdosage are rare. Symptoms of overdose are transient, and have no serious clinical consequences. Importantly, there are no serious clinical sequelae to accidental ingestion by children.
- There is no evidence that Ome has abuse potential nor is there evidence that it potentiates the effects of substances of abuse.
- There is no evidence that individuals “rebound” with excessive acid production after stopping treatment with 20 mg Ome.
- There are no clinically significant hepatic metabolic drug-drug interactions, and risk potential is minimal.

- The risk of esophageal or gastric cancer in individuals with frequent heartburn is very low.
- This product is not intended for use during pregnancy or nursing. The label informs pregnant or nursing women to see a healthcare professional prior to use. In the event of unintended use by pregnant/nursing women, epidemiology data in women who have taken Ome while pregnant shows no increased risk of abnormal fetal development.

In summary, Ome has an extensive history of safe use, including patients in the R_x setting exposed to high doses for prolonged periods of time. Its excellent safety record makes it well suited for OTC status.

1.2.4 Efficacy

Ome-Mg 20 provides 24-hour prevention of the symptoms of frequent heartburn in the OTC consumer population with frequent heartburn (heartburn symptoms 2 or more days per week).

The OTC clinical support consists of two adequate and well-controlled studies in prevention of frequent heartburn for 24 hours. A total of 3124 subjects are included in the intent-to-treat (ITT) population of the efficacy studies, described in more detail in Section 5 of this document.

The studies evaluated both the 10 and 20 mg doses Ome-Mg, and product was taken for 14 consecutive days. The 20 mg dose is proposed for OTC status due to its superior acid suppression and more consistent clinical efficacy vs. 10 mg. Ome-Mg 20 is more effective than placebo in preventing heartburn symptoms for 24 hours after the first dose. With consecutive daily dosing over a 14-day period, Ome-Mg 20 was significantly more effective than placebo in the prevention of frequent heartburn.

1.2.5 Proposed Dose and Duration for OTC Status

Ome-Mg 20 provides more effective and consistent 24-hour acid suppression than 10 mg. Ome-Mg is more effective than placebo in preventing frequent heartburn symptoms for a full 24 hours after the first dose and when dosed for 14 consecutive days. The pharmacology of the drug is best suited for regimen-based dosing.

Dose: The proposed OTC dose is 20.6 mg Ome-Mg (equivalent to 20 mg Ome). This is based on the following:

- The pharmacodynamic data demonstrate that Ome 20 provides a pronounced and consistent gastric acid inhibition over 24 hours. The magnitude and consistency of this effect is significantly better for 20 mg over 10 mg (see Section 3.0).
- Ome 20 has an excellent safety profile. Review of the databases from R_x clinical trials, post-marketing surveillance data from nearly 15 years of marketing history and over 450 million courses of therapy worldwide, and from the OTC clinical program confirm the safety of this product in an OTC setting. The safety profile of Ome-Mg is not different from Ome and the relative bioavailability profiles are similar.

- In the OTC clinical program, Ome-Mg 20 shows efficacy on the first dose, last dose, and across 14 days of consecutive dosing, for the prevention of heartburn for 24 hours in the specified population of consumers with frequent heartburn. This efficacy was always directionally better than 10 mg, and in some cases statistically greater as well, even though studies were not powered to detect a statistical difference.

Duration: Because the pharmacology of omeprazole (onset to action profile, long duration of action) matches very well with the frequency of symptoms in the target population, it is proposed that the product be labeled with instructions to use for consecutive days. The proposed duration of consecutive days dosing for the OTC label is 14 days. The basis for adopting this 14-day use instruction in the OTC labeling is well substantiated.

- Two well-controlled pivotal clinical studies show clinically and statistically significant efficacy in the prevention of frequent heartburn symptoms for the 14-day period. These clinical studies (Studies 171 and 183), conducted in the OTC target population, demonstrated statistically significant prevention of heartburn symptoms for 24 hours on the first dose, the last dose, and across all 14 days. These results are consistent with existing data on Ome amelioration of heartburn symptoms within 14 days in R_x patient populations.[53-63]
- Fourteen days duration is the label instruction that has been shown to provide consumer understanding and compliance. The Actual Use study demonstrated the most consumers can and do follow the label directions, including the directions to take Ome-Mg every day, and only for 14 days. Only 34 out of 758 people recorded that they took more than 14 doses, and 41% of those contacted a healthcare provider during the trial.
- Fourteen days of therapy is an appropriate duration, after which, if symptoms continue or return, people should see a doctor. It has been shown in a 1999 study[62] that continuation or rapid return of symptoms following 14 days of Ome 20 is a good indicator of the need for continued therapy, best provided with physician oversight. The failure to respond to 14 days of therapy serves, in effect, to help the right people recognize the need for physician attention. Directing individuals whose symptoms continue or return to contact their doctor is consistent with medical practice guidelines which call for further attention if symptoms continue or return after PPI therapy. The proposed labeling includes multiple messages for such individuals to seek physician involvement. In the Actual Use study, subjects understood the need to see their healthcare provider about their heartburn. In the 3 months of the trial, two-thirds as many subjects saw a healthcare provider as had done so in the prior year (34% versus 48%), and 20% of those who had never seen a healthcare provider about heartburn did so for the first time while using the labeled product.
- Fourteen consecutive days use of omeprazole is a conservative approach for application, to the OTC setting, guidelines of the ACG, AFFP, and ACP for the management of patients with frequent heartburn symptoms. All these guidelines indicate that a PPI is an appropriate empiric course of therapy in the management of patients with frequent heartburn symptoms.[52,66-68] Some do not specify a duration[52,66-68] or specify 14 to 28 days.[65] Labeling OTC omeprazole for a 14-day regimen adopts a conservative course of therapy a physician might prescribe, and as such, is appropriate labeling for PPI use in

the OTC setting. This 14-day regimen is also consistent with the longest duration allowed for as necessary use of current OTC heartburn medications without physician direction.

- A longer duration of regimen was considered and judged to be unwarranted in the OTC setting. The primary reason identified for considering a longer duration regimen was therapy of subjects within the target population who may have more serious conditions that the product is not indicated for, e.g., erosive esophagitis (about 10% of frequent heartburn sufferers may have EE). Castell, *et al.* 1996, shows that, of the people with diagnosed EE who were healed with 28 days of Ome 20, 74% were already endoscopically healed after 14 days. It is, therefore, inappropriate to label for a longer treatment regimen than is necessary to provide prevention of frequent heartburn symptoms for 24 hours across the entire target population in order to achieve more complete healing in a small subset. A longer duration regimen would overmedicate the substantial majority of the target population. The small subset would be better served by seeking the involvement of a physician as directed by product labeling.
- Finally, we have carefully considered a label scenario allowing for multiple 14-day courses of therapy in a year. We have concluded the label direction for one 14-day course and contact your doctor if symptoms persist or return is the appropriate direction. This avoids the confusion, which would result for consumers if options for further cycles of therapy were included in the label directions. The proposed label provides a clear and understandable message that would be repeated with each subsequent re-purchase and offers the highest probability to get those whose symptoms continue or return to contact a doctor rather than continuing on their own.

In summary, the 14-day consecutive use instructions are well supported by the OTC clinical data, OTC label compliance data, conservative application of medical guidelines to the OTC setting, relevant R_x data and literature as well as consideration for subpopulations. Clear instructions for physician contact if symptoms continue or return flowing 14 days is consistent with medical practice and is the most prudent labeling. This labeling provides for safe and efficacious unsupervised use and directs those who may be at risk of a more serious condition to contact their doctor promptly following an appropriate period of use.

1.2.6 Consumer Label Understanding and Actual Product Use

The consumer behavior and understanding of product use was evaluated via two label comprehension studies, a de-selection trial, and an Actual Use trial. This program of studies established the compliance with label directions and use of the product in an unsupervised setting. Specific objectives of the program established whether consumers understood the population for which the product was best suited (self-selection on frequency of heartburn and understanding of label warning language), whether consumers understood when and how to take the product (1 tablet per day, 14 consecutive doses), and whether consumers understood when to contact a healthcare provider (in response to specific warning language or when frequent heartburn returned before taking additional product).

Across studies, consumers demonstrated a good understanding of the label in regard to the product's intended use, when to use the product, when not to use the product, and when to seek medical attention.

The Actual Use study determined consumer adherence to the label use directions under conditions of actual use. Self-selection and consumer compliance with each of the three label use directions was examined: (1) whether subjects took no more than one tablet per dose; (2) whether they took no more than one tablet per day; and (3) whether they adhered to the 14-day regimen direction. The results of the Actual Use study are summarized as follows:

- 96% of subjects took no more than 1 tablet per dose; among 10830 dosing occasions, 99% involved only one tablet.
- 91% of subjects took no more than 1 tablet per dosing day; among 10743 dosing days, 98% involved no more than one tablet.
- 79% of subjects were compliant with study use directions to use 14 doses in a 14-day period (as defined in the protocol, 11–14 doses in an 11–17 day period) or to contact a healthcare provider if more than 14 doses were taken.
- 9% of subjects took fewer than 11 doses
- 9% of subjects took 14 doses in 18 or more days
- Only 5% (34 subjects) of subjects recorded that they exceeded 14 doses during the trial, and, of these, 41% (14 subjects) contacted a doctor during the trial per label direction. Overall, 29/34 subjects (85%) had talked to a doctor about heartburn before, during or shortly after the trial.
- Thus, only 5 of 758 subjects in the trial used more than 14 doses of Ome-Mg without seeking healthcare provider consultation.

Thorough review of the consumer understanding and behavior program demonstrates that the proposed label is understood, and results in appropriate behavior from the intended population.

1.2.7 Risk and Benefit of Ome-Mg in the OTC Setting

This submission establishes that Ome-Mg is safe, effective, and suitable for prevention of the symptoms of frequent heartburn over 24 hours in an OTC setting. The pharmacodynamic profile of Ome provides 24-hour control of gastric acid production, making it an ideal candidate for the prevention of frequent heartburn.

Ome-Mg provides a clear and unique benefit to OTC consumers with frequent heartburn over currently existing therapies. Specifically, for consumers with heartburn two or more days a week, one 20 mg dose taken daily provides 24-hour frequent heartburn prevention. Statistically and clinically relevant efficacy is observed on the first day of dosing, on the last day of dosing, and throughout 14 days of consecutive daily dosing.

Omeprazole has been widely prescribed since 1988 for a broad spectrum of acid-related disorders. Since its introduction, Ome has been approved in over 125 countries and over

450 million courses of therapy have been prescribed. The long history of Ome safety and the demonstration of effectiveness in the target OTC consumer population confirm the suitability of OTC Ome at a dose of 20 mg.

Ome-Mg is safe for use in the OTC setting, even in the absence of a healthcare provider, for the prevention of the symptoms of frequent heartburn. Subjects who use Ome-Mg according to the label (i.e., for 14 consecutive days) will receive benefit even if they have undiagnosed GERD or EE.[54] Some subjects may use Ome-Mg for long periods of time without physician oversight. This, however, is not a widespread concern: the literature indicates that a high percentage of subjects with frequent heartburn consult a physician (up to 78%)[2-4], and the Actual Use study showed 65% of subjects had contacted a physician about frequent heartburn. Risk that such behavior will delay diagnosis and alter the outcome of a more serious underlying condition is small and outweighed by the benefits of OTC use.

Further, the label instructs consumers at multiple points to consult a physician if symptoms return or continue.

This submission establishes that Ome-Mg is safe, effective, and suitable for prevention of the symptoms of frequent heartburn over 24 hours in an OTC setting. The pharmacodynamic profile of Ome provides 24-hour control of gastric acid production, making it an ideal candidate for the prevention of frequent heartburn.

1.2.8 The Proposed OTC Label for Ome-Mg

The proposed label is congruent with efficacy data, the target population, the pharmacology of Ome-Mg and the Actual Use study.

The proposed OTC dose for Ome-Mg is 20 mg. This dose was shown in efficacy trials to provide clinically meaningful and statistically significant prevention of the symptoms of frequent heartburn for 24 hours in the target population. In addition, review of the safety data for Ome 20, gathered over 15 years and 450 million courses of therapy, show Ome-Mg 20 to be a very safe product for its proposed use.

The indication, for the prevention of symptoms of frequent heartburn for 24 hours, is also supported by the results of the efficacy studies. This indication is consistent with the pharmacology of Ome. The inclusion of "…for 24 hours" is intended to reinforce the one-tablet-per-day regimen and ensures the product is not seen as a "cure" for heartburn. The term "prevention" has been shown in consumer research to reinforce that the product works best in preventing frequent heartburn symptoms from recurring over a 24-hour period. While each dose provides a clinically meaningful and prevention benefit, Ome-Mg works best when taken on a regimen basis, providing a distinct benefit to the consumer with frequent heartburn.

The target population, individuals with frequent heartburn symptoms, is the population with an unmet need in the OTC setting, is the population for which omeprazole is appropriate (vs. occasional episodic heartburn), and is the population tested in both the efficacy and behavioral trials. The efficacy trials showed that 14 days of Ome-Mg 20 effectively prevents frequent

heartburn in this population. Further, the Actual Use studies showed that individuals with frequent heartburn readily self-select this is a product they can use. Ome-Mg is not a product intended for individuals who treat infrequent heartburn (like H_2RAs and antacids), and very few individuals with infrequent heartburn choose Ome-Mg.

Use directions call for one tablet per day, taken in the morning. This is consistent with the design of the efficacy studies, and subjects were highly compliant with this direction in the Actual Use study.

The directions also indicate Ome-Mg should be taken every day for 14 consecutive days. This was tested of the design of the efficacy trials, and again, subjects were highly compliant with this clear and understood direction in the Actual Use study. This is the appropriate duration in the OTC setting, and directs consumers to the healthcare provider at the earliest time if symptoms persist or return.

If frequent heartburn persists or returns after 14 days of Ome-Mg, they are directed to consult their physician. This is clearly stated in two places in the labeling. Subjects in the Actual Use trial understood and complied with these directions. Risks to those who did not comply are small, and are outweighed by the benefits of the product.

The label contains warnings regarding use in children, potential drug-drug interactions, unintended use in consumers who are pregnant or nursing, and those who might experience general warning signs of potentially serious conditions that might be mistaken for, or occur with, frequent heartburn. The pregnancy warning statement on the label is standard OTC labeling. There is no increased risk in any of these situations. Further, these statements were understood by and complied with by study subjects. The general warning symptoms should be considered for all heartburn medications in the OTC setting.

2. Characterization of the Consumer With Frequent Heartburn

It is widely acknowledged that heartburn is commonly experienced, self-recognizable, and self-treated within the general consumer population. Antacids have been available for decades as an OTC therapy for the relief of heartburn and H_2-receptor antagonists (H_2RAs) have been available to the OTC population for at least 7 years for both the relief and prevention of infrequent, episodic heartburn.

Consumers with frequent heartburn, defined as heartburn two or more days per week, are prevalent in the heartburn population in the U.S. Heartburn occurs daily in approximately 7% to 10% of all consumers[1-2], and 2 or more days per week in about up to 46% of consumers with heartburn.[2-4] Some consumers in the OTC setting may have undiagnosed GERD or EE, and these consumers need to be considered in labeling for appropriate use of Ome-Mg in the OTC setting.

The majority of consumers with frequent heartburn have seen a healthcare provider (up to 78%)[2-4], and they primarily turn to OTC heartburn remedies to manage frequent heartburn symptoms. Most OTC consumers manage their heartburn symptoms with combinations of OTC heartburn medications. However, consumer surveys show that a significant proportion of consumers with frequent heartburn are dissatisfied with current OTC products, primarily because the medication does not last long enough and it does not completely prevent heartburn.[5] Prevention of frequent heartburn symptoms is the goal for these consumers. No OTC heartburn product currently addresses this need.

OTC Ome-Mg is intended for a population of consumers who experience frequent heartburn sumptoms. To fully understand the consumer with frequent heartburn and medication and health care utilization practices in this population, the Sponsor has conducted a number of qualitative and quantitative research studies aimed at understanding the beliefs, habits, and practices of the OTC remedy consumer with frequent heartburn symptoms.

Collectively, these data characterize the population of consumers with frequent heartburn.

2.1 The Frequent Heartburn Population

Frequent heartburn is common in the US population: approximately 40 million people experience heartburn symptoms 2 or more days per week.[1-4]

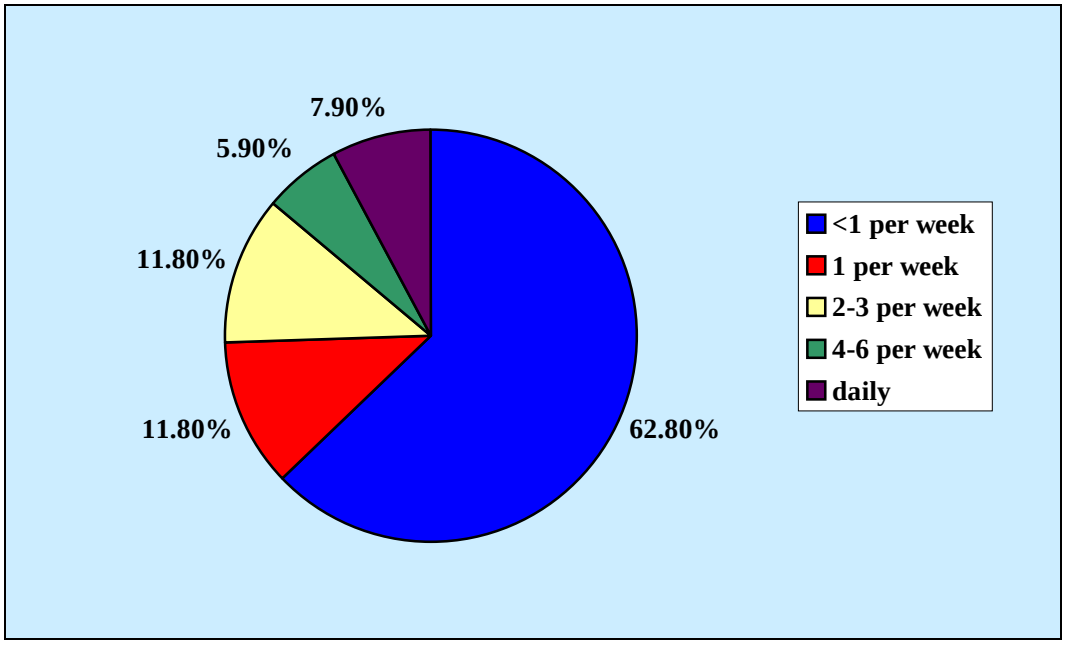
Prevalence: In the US, an estimated 50% of the total population experiences heartburn, and of those who report heartburn, up to 46% experience heartburn symptoms 2 days per week or more.[2-7,12-16,18-21,24]

Demographics: Slightly more women (58%) than men report frequent heartburn.[2,10] While heartburn can occur at any age, the mean age for a consumer with frequent heartburn is 45–50 years[1-3,6-8,10,12,16], and heartburn does have a slight tendency to increase with age. According to a United States (U.S.) survey conducted in 1995 by Nielsen[5], geographic location, marital status, family status (children), educational level, job type and level, and socioeconomic

status all play a role in the tendency to develop heartburn.

Frequency: Figure 2.1 shows the frequency of all heartburn episodes in a 1997 survey of a representative U.S. adult OTC heartburn population who were asked to recall their heartburn symptom occurrence over the past 12 months.[3]

Figure 2.1
Frequency of Heartburn in the United States Heartburn Population (1997)[3]



Duration: Overall, consumers with frequent heartburn have had a long history with heartburn.[8, 12,23-24] According to a 2000 survey by the National Heartburn Alliance, 56% of consumers report frequent heartburn for five or more years, 40% report experiencing frequent heartburn for 1–4 years, and the remaining 4% report experiencing frequent heartburn for less than a year.[8,12]

Pathophysiology: Consumers with frequent heartburn have been shown to have increased esophageal mucosal acid exposure.[14] However, frequent heartburn symptoms are not completely correlated with pathologic sequelae. A prospective study assessed consumers with frequent heartburn [of long duration (mean 11 years), moderate severity (70% of the population) and frequent occurrence (4–7 times per week)] whom had never been evaluated by a physician. In this study, erosive damage was observed in less than 50% of the population and was primarily grades I/II.[23] This finding (that long term, frequent heartburn is not necessarily associated with severe inflammatory damage) is confirmed in other published epidemiologic observations.[24-26]

2.2 Medication Habits and Practices of the Frequent Heartburn Population

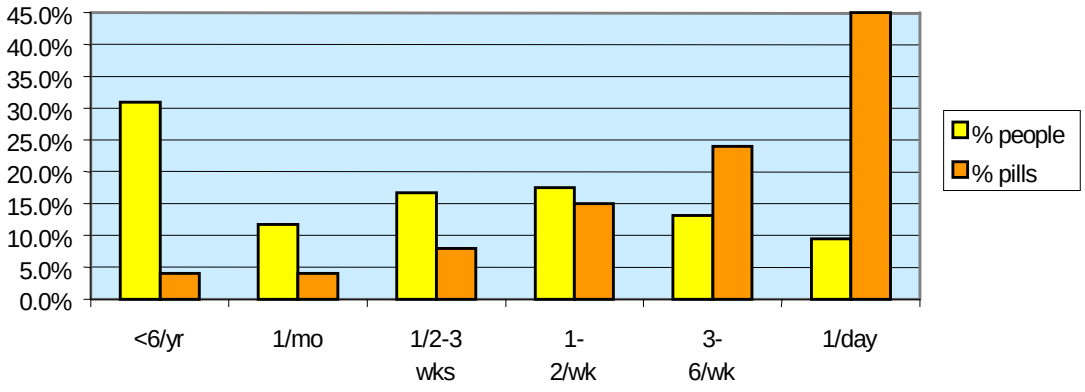
Prevalence of Medication: More than 86% of individuals with frequent heartburn report using OTC heartburn medication.[3] Nearly all OTC medication users need to take multiple courses of antacids and/or OTC H_2RAs to achieve control of frequent heartburn, especially for 24 hours.

HOW CONSUMERS MANAGE FREQUENT HEARTBURN[12]

- 80% use antacids
- 48% use OTC H_2RAs
  - 26% use OTC H_2RAs ≥ 4 days per week
- 47% medicate ≥ 2 days in a row
- 55% take medication preventatively
- 58% have spoken with a physician about heartburn
- 34% use a prescription medication

Frequency of Medication: As shown from IMS marketing information in Figure 2.2, the consumers who experience frequent heartburn account for the majority of the OTC heartburn product usage.

Figure 2.2
Volume of OTC Heartburn Product Use by Frequency of Heartburn
(All OTC Users Past 12 months)



Consumers with frequent heartburn self-medicate frequently during the day, using the full complement of available OTC heartburn medications, in an effort to prevent continuing occurrence of frequent heartburn.[12] In fact, consumers with frequent heartburn quantify the frequency of their heartburn by the number of days on which they need to dose as well as the number of days on which they experience heartburn. In one study, more than 75% of the population reported taking OTC medications to manage frequent heartburn, even though most (65%) had been to the doctor.[2]

Satisfaction with OTC Medications: Only 19% of consumers with frequent heartburn experience complete satisfaction with their current OTC therapeutic options.[7] This may account for widespread use of multiple medications during the course of the day to manage frequent heartburn.[7,12,20,22]

Antacids provide acid neutralization for only a few hours, and the 8–12 hour duration of action of OTC H_2RAs falls short of the longer duration consumers with frequent heartburn require. Several studies show that consumers develop a tolerance for H_2RAs within a short period of time, thereby rendering therapy less effective for these consumers.[9,69] Tolerance has not been shown to develop with long-term use of PPIs.[70]

2.3 Medical Utilization Patterns of the Frequent Heartburn Population

The majority of consumers with frequent heartburn symptoms see a healthcare provider about heartburn: about up to 78% of consumers with frequent heartburn are under the care of a physician for frequent heartburn.[2,7-8,10,12,16-17,27-34] In general, consumers with frequent heartburn are four times more likely to have seen a physician than the general population.[2] Most consumers with frequent heartburn see their primary care physician (62%) versus a specialist: 16% report seeing a gastroenterologist and 2% report seeing a cardiologist[16], while 30% of consumers with frequent heartburn report also consulting a pharmacist.[3]

Of those consumers with frequent heartburn who see a physician, 71% report seeing the physician more than once per year.[7,12]

However, even though consumers with frequent heartburn symptoms often see a physician, heartburn was most frequently a secondary presentation at the office visit, confirmed through both surveys of health care professionals[11] and consumers with frequent heartburn.[12,16] Further, the majority of consumers with frequent heartburn symptoms consider this to be their least important health problem, or not as important as other health issues[12], which helps explain the propensity for heartburn to be discussed as a secondary presentation.

2.4 Continuing Health Care Utilization Patterns

During the H_2RA R_x-to-OTC switch process it was hypothesized that consumers would stop seeking medical attention for heartburn, and that diagnosis of potentially more serious underlying conditions would be delayed. Andrade *et al.*[35] followed 200 patients with acid-related conditions before and after the switches, and saw no change in the overall number of doctor visits. A second study was conducted by Shaw *et al.*[36-37] in 3400 OTC consumers in 1993 (pre-switch) and again in 1997 (after the switch by several years), and again found no change in the average number of doctor visits for acid-related conditions. A third study among administrative claims for 7 million patients from 1995–1998 (MedStat Marketscan Database) noted an increased number of doctor visits for acid-related conditions.[38] These data from the H_2RA switch era may give an indication and reassurance that the already-prevalent behavior of consumers with frequent heartburn to consult the physician will not change with Ome-Mg in an OTC setting.

2.5 Professional Recommending Patterns

A Professional Habits and Practices study was conducted in 1998 among 250 primary care physicians, 150 gastroenterologists, and 181 pharmacists.[11] Primary care physicians noted that approximately 13% of their weekly patients were seen for heartburn (about 16 patients a week), while the gastroenterologists reported 25% of all patients per week were seen for heartburn (about 20 patients per week). Both professional groups noted they tended to see the same heartburn patients 3 to 4 times a year. Pharmacists report counseling about 10 patients per week about heartburn and heartburn remedies.

Various surveys report that 26% to 50% of the adult heartburn population receive a prescription for heartburn while 10% to 45% received an OTC recommendation along with a prescription and 13% received a recommendation for OTC therapy only.[3,7,11-12,28,30] About 27% received recommendation of lifestyle modification.[3,11-12] Current physician guidelines for ongoing management of symptomatic reflux have as their stated objective symptomatic management. Several call for empiric therapy with acid-reducing agents in the OTC setting, and, if symptoms can be adequately managed, no further testing or therapy is required.[52,64-68]

2.6 Heartburn Treatment Guidelines

In recent publications and reviews of guidelines for management of frequent heartburn and GERD, the stated primary goal of therapy is prompt and effective symptom relief.[52,64-67] For typical uncomplicated frequent heartburn, an initial trial of empiric therapy with a full-dose proton pump inhibitor is generally recommended, as this is considered the best chance for symptomatic relief.[52,65] If empricial therapy is unsuccessful or warning signs are present, further diagnostic testing should be considered.

The proposed OTC label for Ome-Mg is consistent with these recommendations, and provides an initial OTC course of therapy, which will serve to establish whether symptoms are associated with an acid-related condition. A 1999 study[62] in GERD subjects showed that successful symptom management after 2 weeks with 20 mg of Ome was correlated with a favorable long-term outcome ($p < 0.0001$): 33% of subjects who responded to 14 days of Ome 20 required no further treatment over the course of a year and conversely, 24% of subjects in the entire study population who required an initial course of therapy beyond 2 weeks tended to require ongoing maintenance treatment; 68% of subjects who responded to 14 days of Ome 20 required 3 or fewer 14-day courses of therapy over a year to control frequent heartburn. In addition, the proposed label clearly directs consumers to consult a physician if heartburn persists or returns after 14 doses.

2.7 Overall Summary

In summary, consumers with frequent heartburn, defined as heartburn symptoms two or more days per week, are prevalent in the heartburn population in the U.S. These consumers are quite knowledgeable about their heartburn: the majority has been to see their physician about frequent heartburn symptoms and many have had a prescription for heartburn at some point. Most OTC consumers manage their heartburn symptoms with combinations of OTC heartburn medications, although without total satisfaction in heartburn resolution. These consumers primarily seek an

OTC remedy for adequate frequent heartburn resolution, and even with frequent physician consultation often receive an OTC recommendation.

3. Clinical Pharmacology of Omeprazole

Ome-Mg has a pharmacologic profile suited for effective prevention of frequent heartburn. Ome-Mg has a long duration of action, providing long-lasting effects for more than 24 hours, and highly effective acid suppression at steady-state (within 5–7 days of consecutive dosing). These are the two most important factors in effective prevention of frequent heartburn.

Omeprazole has a very specific action at the gastric parietal cell. Ome is a proton pump inhibitor (PPI) that inhibits gastric acid secretion by irreversible specific inhibition of the H^+/K^+ ATPase enzyme at the secretory surface of the gastric parietal cell. In order to exert an effect, Ome must enter the acidic compartment of the parietal cell.[39] In this very acidic environment, Ome (a weak base) is protonated and transformed to the active sulphenamide inhibitor. This protonation and conversion can only take place at a significant rate at pH < 2. Only the acidic milieu of the parietal cell in the gastric mucosa meets this requirement; proton pumps in other locations (i.e., the colon and kidney) are not sufficiently acidic to promote protonation to the active form of the drug. Acid secretion returns when new parietal cells become active, a process that takes approximately 3–5 days.

The plasma elimination half-life ($t_{½}$) of less than 1 hour shows a rapid elimination of the drug, and the absence of Ome in the urine or feces indicates complete metabolism. Omeprazole is metabolized by two different cytochrome P450 (CYP) isoforms, CYP2C19 (responsible for about 80% of the total metabolism) and CYP3A4.[40-41] There is a small subset of the population that lacks CYP2C19 (approximately 15% of Asians and 3% of Caucasians) and are known as "slow" metabolizers who still metabolize Ome but at a slightly slower rate.[42] However, even at this slower rate, the plasma half life is still < 2 hours. Thus, Ome clears rapidly from the plasma in all subjects.

Omeprazole is completely absorbed after oral administration. Food, antacids, and H_2RAs have no clinically meaningful influence on the extent of Ome absorption.[40,43-44]

Ome-Mg is a magnesium salt version of Ome that permits tablet formulation. Ome-Mg dissociates rapidly in water to form Ome and magnesium: a 20.6 mg dose of Ome-Mg is the same as a 20 mg dose of Ome.

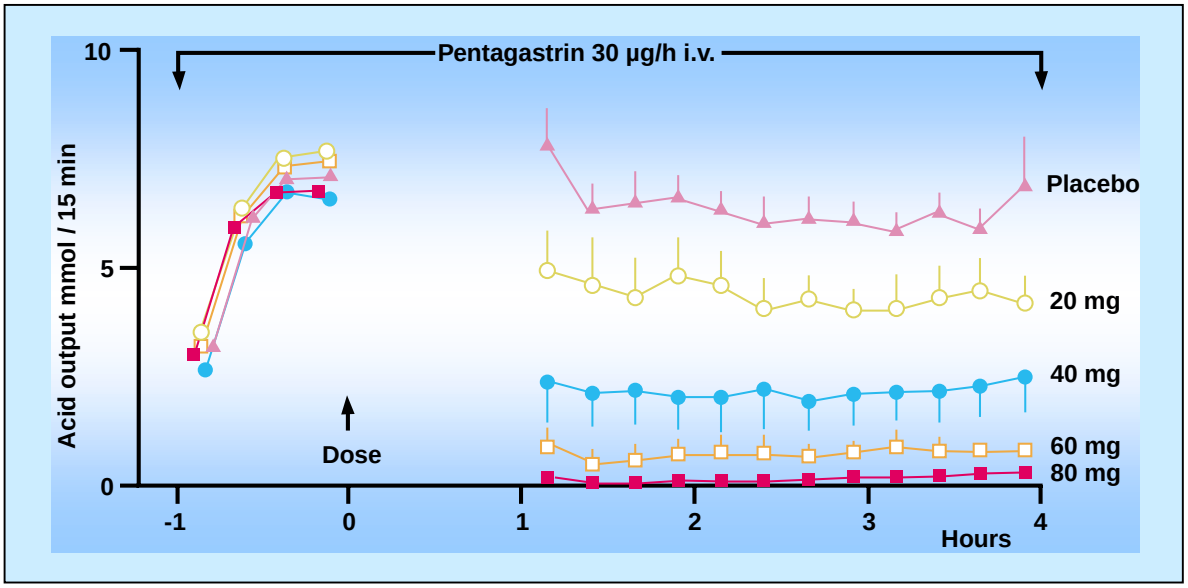
As shown in Table 3.1, Ome-Mg has a similar bioavailability profile to the commercially available Ome capsules. When Ome 20 was compared to Ome-Mg 20, relative areas under the curve were comparable within a fairly tight range.

TABLE 3.1 RATIOS OF GEOMETRIC MEANS AND 95% CONFIDENCE INTERVALS FOR AUC_0 SUBJECTS WITH COMPLETE PHARMACOKINETIC DATA				
		95% Confidence Limits		
Treatments[a]	**Ratio**	**Lower Limit**	**Upper Limit**	**Pairwise *p*-Values**
Ome-Mg 20 (X) to Ome 20(Y)	1.042	0.980	1.108	0.188
[a] For each pair of treatments, the ratios and confidence limits represent X/Y.				

3.1 Inhibition of Gastric Acid Secretion

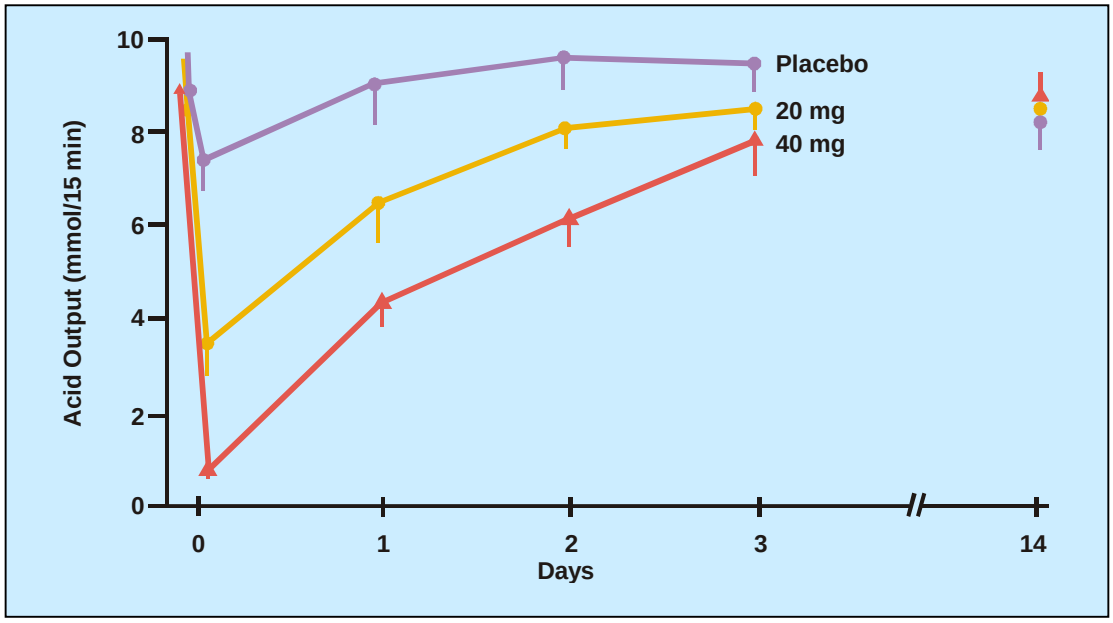
Following single oral doses of 20 to 80 mg Ome suspension in buffered sodium bicarbonate, pentagastrin-stimulated gastric acid secretion is rapidly and dose-dependently inhibited (Figure 3.1).[46] Ome begins to have an effect on gastric acid secretion in as soon as 1 hour. Other studies have shown that Ome dose-dependently inhibits basal acid secretion, as well as acid secretion induced by other stimuli, such as histamine, modified sham-feeding, and peptone, with a similar efficiency.[47-48] This finding was expected, because Ome acts at the final step in the acid secretion process and therefore inhibits gastric acid secretion equally effectively and independent of stimulus.

Figure 3.1
Effect of Single Oral Doses of Omeprazole Suspension on Pentagastrin Stimulated Gastric Acid Secretion in Healthy Subjects (n=6)



Ome has a long duration of action: more than 24 hours following a single dose, since parietal cells turn over in about 3–5 days. Both 20 mg and 40 mg single doses of Ome produced a marked inhibition of gastric acid secretion 2 hours after dosing, and the degree of acid inhibition then gradually decreased over the next 3 days (Figure 3.2).[46] With a single 20 mg dose, inhibition was not significantly different from placebo by Days 3 and 4. A 40 mg dose of Ome displayed a small but statistically significant inhibition of acid secretion at Day 3, but by Day 14 returned to baseline levels. The acid inhibitory effect of Ome lasts longer than circulating plasma levels. The return of acid output to baseline level is linear in contrast to the exponential elimination of drug from plasma.

Figure 3.2
Duration of Action of Two Different Single Oral Doses of Omeprazole Suspension Estimated by Repeated Measurements of Pentagastrin Stimulated Gastric Acid Secretion in Healthy Subjects (n=6)



The effect of repeated daily doses of Ome on gastric acid secretion has been studied in both healthy subjects and duodenal ulcer patients in order to find a clinically relevant dose.[49-50] Each dose of Ome (5 mg, 10 mg, 20 mg, 30 mg, or 40 mg) was given to the patients in a randomized order for 5–7 days, a sufficient time to reach steady-state suppression of gastric acid secretion. Pentagastrin-stimulated gastric acid secretion was measured 6 hours and 24 hours after the last dose (Figure 3.3).[49-50]

From this data, it is clear that 20 mg provides a stronger and more consistent effect than 10 mg Ome.

Figure 3.3
Individual Values for Percentage Reduction of Pentagastrin Stimulated Gastric Acid Secretion Measured Both 6 and 24 Hours After the 5th Dose of Omeprazole in Healthy Subjects (n=8)

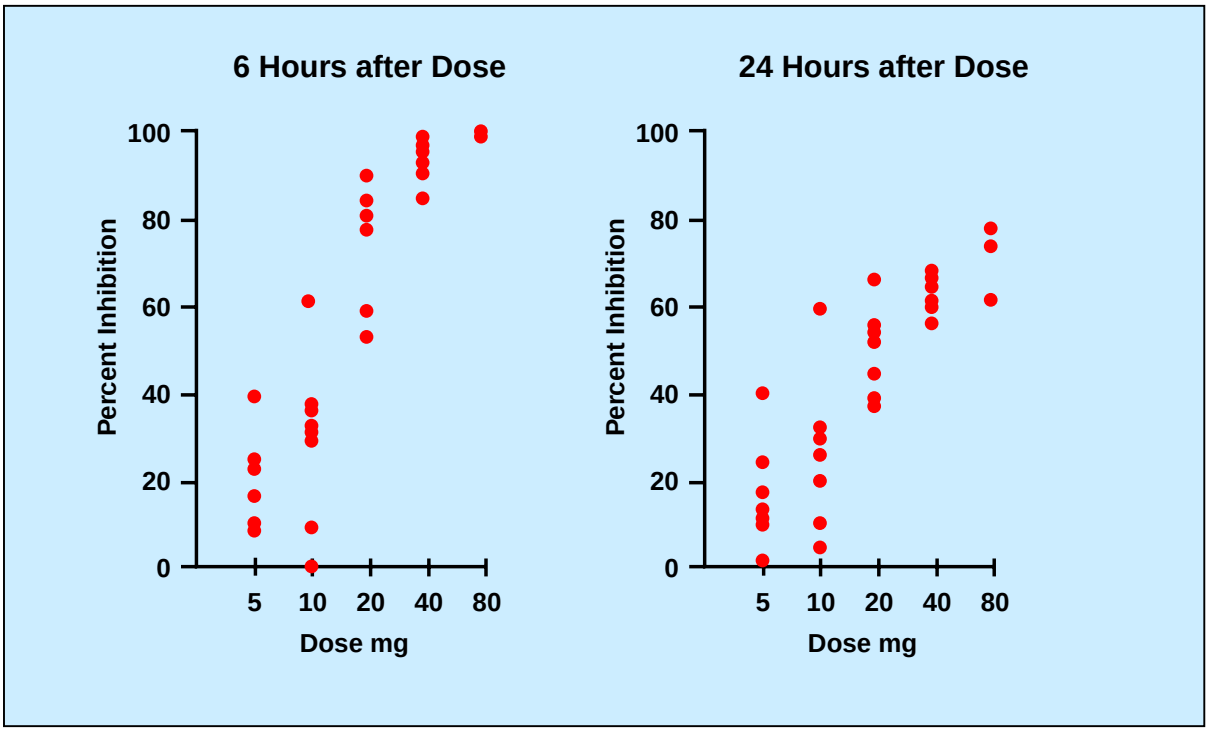


Figure 3.4
The Inhibitory Effects of 1 Week of Treatment with
Different Daily Doses of Ome on the 24-Hour Intragastric Acidity[71]

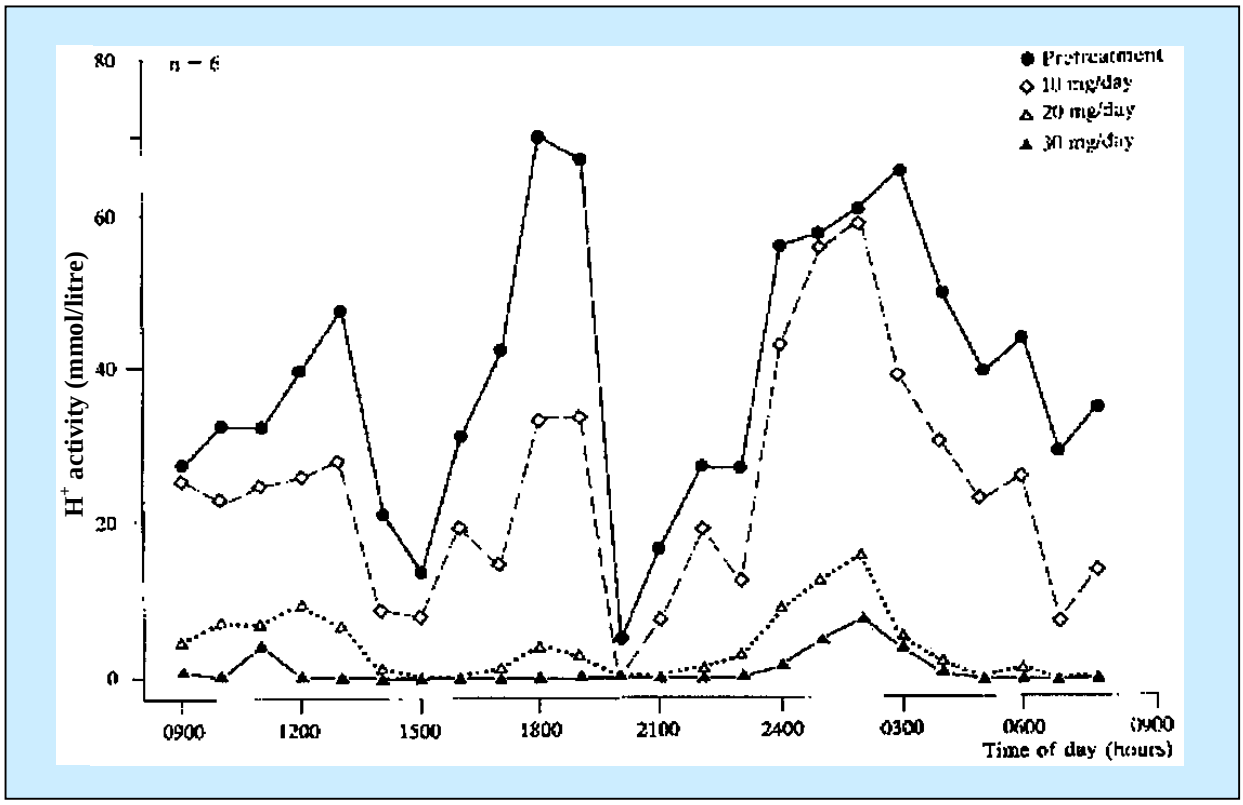
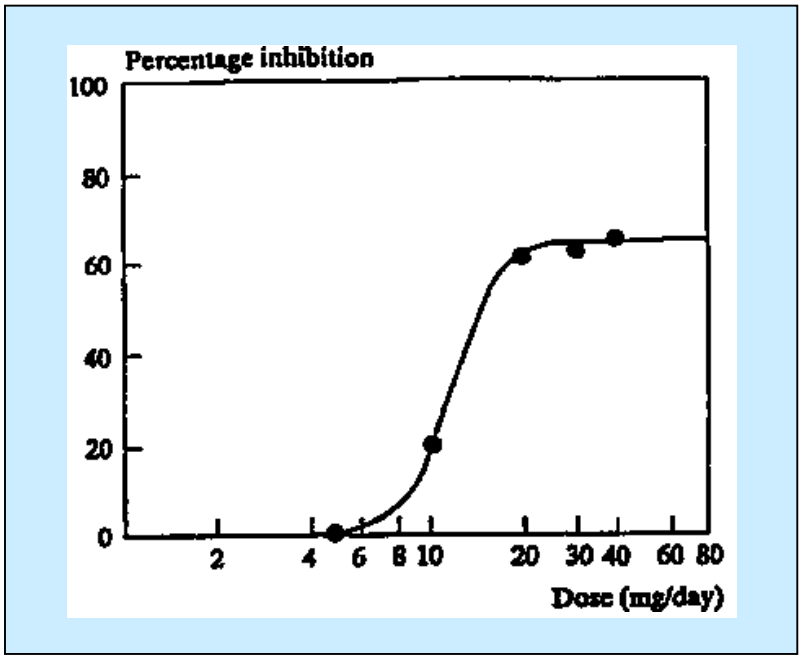


Figure 3.5
Dose Response Curve for Repeated Once Daily Doses of Omeprazole



Each Point Represents Reduction in Mean Peak Acid Output in Healthy Subjects (n=6).
The Curve Is Obtained by Using an Extended Least Squares Non Linear Regression Analysis

Figures 3.3 and 3.5 show that once daily treatment with 5 mg Ome for 5 days produced a minimal effect. Figures 3.3 and 3.4 show that a 10 mg dose of Ome did not produce a consistent inhibition of gastric acid secretion in all patients. The variation in effect for the 10 mg Ome was substantial, ranging from 0% to 60% inhibition at 24 hours after the last dose, and follows a 24-hour pattern similar to placebo. In contrast, Ome 20 showed marked 24-hour acid suppression after 1 week of therapy.

All 3 figures show a daily dose of 20 mg Ome produces a markedly stronger and more consistent inhibition than the lower doses, but not a complete blockade of gastric acid secretion over the 24-hour dosing interval (Figure 3.3).

The pharmacokinetic and pharmacodynamic profile of Ome-Mg makes it uniquely suited for prevention of frequent heartburn for 24 hours in the OTC setting. The proposed dose of 20 mg is the minimal dose with consistent long-lived acid suppression, providing maximal efficacy in this population. Further, 14 days is a suitable period of time for long-term therapy in the OTC setting, since maximum effect is attained within 5–7 days and maintained throughout therapy.

4. Summary of Safety

Omeprazole has an excellent safety profile as established by more than 15 years R_x history in the U.S. (both post-marketing surveillance and clinical trial experience). Since its introduction, Ome has been marketed through prescription in 125 countries. An estimated 450 million courses of patient therapy have been prescribed through June 2001, at daily doses ranging from 10 to 360 mg, and at therapeutic durations of 4 to 12 weeks, up to several years. The Ome-Mg AE profile from the OTC clinical trial program showed no difference between Ome-Mg and placebo. Omeprazole magnesium is approved for prescription use in 33 countries.

4.1 Brief Summary of Safety Information Submitted in the Original NDA 21-229

Initial safety reviews reviewed by the joint NDAC/GDAC (October 2000) included safety data that were available to AstraZeneca LP (AZLP) and The Procter & Gamble Company (P&G) through June 30, 1998 from:

- Clinical trials from the OTC development program with Ome-Mg multiple unit pellet system (MUPS) tablets,
- Clinical trials from prescription Ome capsules,
- Prescription Ome post-marketing surveillance data.

The most common AEs reported across clinical trials and post-marketing surveillance for Ome includes diarrhea, headache, nausea, abdominal pain, and rash. There are no differences in reporting rates for Ome relative to placebo, and no dose-related AE correlation. In the post-marketing evaluation (through June 1998), from over 300 million patient courses of therapy, SAEs were found to be associated with underlying medical conditions.

4.1.1 Clinical Trials from the OTC Development Program with Omeprazole Magnesium Multiple Unit Pellet System (MUPS) Tablets

The initial clinical program for OTC Ome-Mg consisted of 10 U.S. studies involving 11,299 subjects. Studies involved 8179 subjects who took Ome (5040 on Ome-Mg 20, 3139 on Ome-Mg 10) and 3120 subjects who took placebo. The demographics for the Ome-Mg versus the placebo groups were similar. The overall extent of exposure for Ome-Mg ranged from a single dose to taking 30 or more tablets over a 45-day period.

A comprehensive review of all AEs revealed that the most commonly involved body systems for all treatment groups were Body as a Whole, the Digestive System, and the Respiratory System. The most commonly reported AEs were headache, infection, and diarrhea. Omeprazole magnesium had a similar safety profile to placebo.

No gender-dependent increases in AE reporting were found. No age-dependent increases in AE reporting were found except for a higher AE reporting incidence in the age group 12–17 (reported from the Actual Use studies 003 and 067).

There was no dose-dependent increase in AE reporting for Ome-Mg-treated subjects in the clinical trials. In these trials, the safety profile of Ome-Mg 20-, Ome-Mg 10-, and

placebo-treated subjects was similar. The percentage of discontinuations due to AEs was similar for Ome-treated subjects (0.5%) compared to placebo-treated subjects (0.6%).

One subject who was randomized to Ome-Mg 20 died. The death was considered unlikely to be due to study medication.

A total of 28 subjects reported SAEs, with an incidence of 0.4% for Ome-Mg 10-treated subjects, 0.2% for Ome-Mg 20-treated subjects, and 0.1% for placebo-treated subjects. Only two SAEs were considered to be possibly or probably due to study medication. These occurred in the Ome-Mg 10- and placebo-treated groups. No SAE reported by subjects receiving Ome-Mg 20 was considered to be possibly or probably related to study medication. Six additional subjects reported SAEs during the placebo run-in phase of studies.

The totality of these data strongly suggests that the Ome-Mg tablets have a safety profile that is consistent with an OTC medication.

4.1.2 Clinical Trials from Prescription Omeprazole Capsules

Data from clinical trials conducted with the prescription Ome capsule, in the disease states of GERD, EE and dyspepsia, were pooled and presented in consideration of OTC Ome-Mg. A total of 5,757 unique patients were exposed to Ome in these clinical trials: 4,671 in the Non-US and 1086 in the United States. A total of 1087 unique patients were exposed to ranitidine and a total of 1,125 unique patients were exposed to placebo.

An overview of all short-term trials demonstrates that diarrhea and headache are the most frequently reported AEs for Ome and the placebo group demonstrated a similar AE profile. Thus for short-term trials (≤ 12 weeks in duration), Ome has a similar safety profile to placebo.

In long term (> 12 weeks in duration) clinical trials, the percentage of patients reporting one or more AEs and the general AE profile was similar for Ome and placebo. The safety profile for long-term usage of Ome was similar to the safety profile for short-term usage.

There was no clinically meaningful change in the AE profile for Ome when evaluations were performed according to age, race, gender, or for dose and duration of use. Patients discontinued from the clinical trials due to AEs at a rate lower on Ome than placebo.

The clinical trial data for the Rx indications of GERD, EE and dyspepsia show that Ome at doses of 10 mg, 20 mg, and 40 mg has a safety profile similar to placebo. This database includes patients who have taken up to 40 mg of Ome for up to one year. The available safety data therefore suggests that Ome is safe for OTC use.

4.1.3 Prescription Omeprazole Post-Marketing Surveillance Data

A search of the AstraZeneca safety database was conducted and summarized for reports received and verified on or before June 30, 1998, in which oral Ome was a medication associated with the report. There were approximately 300 million patient treatments worldwide up to that time. A total of 7,344 cases were retrieved which included 15,385 AEs.

The most frequently reported AEs included the following Body Systems: Body as a Whole – General Disorders, Gastro- Intestinal System Disorders, Central and Peripheral Nervous System Disorders, and Skin and Appendage Disorders. The most commonly reported AEs were diarrhea, headache, nausea, abdominal pain, and rash. These AEs are consistent with the current approved labeling for PRILOSEC®.

Within this review, a total of 287 deaths were noted, 145 of which were coded as deaths (142) or sudden death (3) and an additional 142 cases in which death was an outcome but was not coded as an AE. The most reported AE terms in this group were myocardial infarction, sepsis, cardiac arrest, hepatic failure, and cardiac failure. Each report dealing with an outcome of death was reviewed extensively. The common theme in these cases was that multiple causative factors were present which could have resulted in the death of the patient. In many other cases not enough information was received in order to determine the cause of death. A review of these cases suggests no clinically meaningful trend exists to establish a cause and effect relationship between Ome intake and an outcome of death.

A total of 1,750 patients experienced a SAE not resulting in death. The body systems that were most commonly involved include Body as a Whole – General Disorders, Gastro-Intestinal System Disorders, Liver and Biliary System Disorders and Central and Peripheral Nervous System Disorders. The most frequent SAEs reported were thrombocytopenia, hepatitis, interstitial nephritis, fever, and drug interaction. The Ome post-marketing database includes the treatment of patients who were seriously ill with concurrent underlying medical conditions. The natural medical history of these conditions was in some instances a contributing cause of subsequently reported SAEs. In addition, Ome was frequently used to prevent and/or treat occurrences such as stress ulcers, EE, and other causes of acute gastrointestinal bleeding in high-risk individuals.

4.2 Safety Update Report

4.2.1 Clinical Trial Data

The four-month Safety Update Report (SUR) provided information from four (4) Ome magnesium clinical trials in an OTC population. A total of 4 U.S. clinical studies involving 7130 subjects are included in this safety analysis as part of the consideration of OTC Ome-Mg. These studies involve 4914 subjects who have taken Ome-Mg (2211 on Ome-Mg 20, 2703 on Ome-Mg 10) and 2216 subjects who have taken placebo. Three of the studies were double-blind placebo controlled studies and the fourth was an uncontrolled actual use trial.

The four additional OTC clinical trials were conducted by The Procter and Gamble Company. A total of 4423 subjects in the safety database were exposed to Ome-Mg for a single dose, and an

additional 491 subjects were exposed to Ome-Mg 10 for up to 4 weeks of treatment duration. Of the 4914 subjects exposed to Ome-Mg, 2211 subjects were exposed to Ome-Mg 20 and 2703 subjects to Ome-Mg 10. In addition, 2216 subjects were exposed to placebo.

A comprehensive review of all AEs revealed that in general the most commonly involved body systems groups were the Body as a Whole, the Digestive System, and the Respiratory System. In general, and consistent with data previously reviewed from OTC and prescription clinical trials and reviews of the worldwide post-marketing surveillance database, the most commonly reported AEs were headache, diarrhea, and nausea. Ome-Mg has a similar safety profile to both Ome and placebo.

No gender-dependent increases in AE reporting were found. No age-dependent increases in AE reporting were found except for a higher AE reporting incidence in the 12–17 age group (1 report out of 7 subjects in this age group). There was no apparent dose-dependent increase in AE reporting for Ome-Mg-treated subjects during the single-dose, double-blind, placebo-controlled clinical trials. In these trials, the safety profiles of Ome-Mg 20-, Ome-Mg 10-, and placebo-treated subjects were similar.

The percentage of discontinuations due to AEs was similar for Ome-treated subjects compared to placebo-treated subjects. One subject who was randomized to Ome-Mg 10 died; the death was considered Unlikely to be due to study medication. A total of 3 subjects reported SAEs (including the death), all on Ome-Mg 10. All were considered to be Unlikely due to study medication.

4.2.2 Post-Marketing Data– Ome-Mg (MUPS) Tablet Formulation - SUR

The SUR also provided all worldwide serious and non-serious post-marketed prescription Ome-Mg MUPS tablet AE information reported to AZLP in Sweden through December 31, 1999, from countries where the tablet formulation was marketed. The period from first launch in February 1998, and up to December 31, 1999, encompasses 11.6 million patient treatment courses of Ome-Mg (MUPS) tablets. During the same time period 219 AE reports were notified to AstraZeneca. The most commonly reported AEs were diarrhea, headache, nausea, and abdominal pain, consistent with previous reports. There was no evidence to suggest that the AE pattern for Ome MUPS tablets is different from that of Ome capsules.

4.3 Updated Safety Information Included in the Resubmission of NDA 21-229

Updated safety data is provided from the P&G Actual Use Study 2001007, and updated worldwide post-marketing experience with Ome-Mg MUPS tablets is reported from the time period covering January 1, 2000, through June 30, 2001.

4.3.1 Clinical Trial Adverse Event Data from P&G Actual Use Study 2001007

Study 007 was a single actual use study involving 758 subjects who received Ome-Mg 20. A comprehensive review of all AEs revealed that in general the most commonly involved body systems groups were the Body as a Whole, the Digestive System, and the Respiratory System. In general, and consistent with previous reports, the most commonly reported AEs were headache, diarrhea, pain abdomen, pain and pain back. No particular AE in any body system was more prevalent in any one of the subgroups analyzed, i.e. gender, ethnicity, age, or women of childbearing potential. Subjects over the age of 65 were not susceptible to an increase in AEs. With the exception of headache, AEs were reported by less than 4% of the study population, and the majority of AEs were reported by less than 2% of the study population.

The most frequently reported AE for Ome-Mg 20 was headache, but was not severe enough to cause discontinuation of therapy. The incidence of headache is consistent with the Ome capsule safety profile and previous clinical trial data.

The three discontinuations due to an AE represented 0.4% of the study population. One SAE resulting in hospitalization occurred during the treatment period one day after two doses of Ome-Mg 20 were taken. This SAE was considered to be unrelated to treatment.

In summary, results from this actual use study demonstrated that the AEs reported with Ome-Mg 20 are consistent with reports from Ome and previous Ome-Mg studies, and are not different than reporting rates seen with placebo. All AEs were self-limiting, and with the exception of headache, were reported at a low frequency by subjects.

4.3.2 Updated Post-Marketing Data – Omeprazole magnesium (MUPS) Tablet Formulation

The reporting period of January 1, 2000, through June 30, 2001, encompasses more than 27 million patient treatment courses of Ome-Mg tablets. A review of reports shows that 109 SAEs among 63 (60 non-fatal and 3 fatal) patients and 430 non-SAEs among 257 patients were reported to AstraZeneca.

The five most common AEs reported for non-serious events were consistent with previous reports and confirm the excellent safety profile of Ome-Mg: Drug ineffective, Dyspepsia, Dermatitis, Abdominal pain, and Nausea.

The most common SAEs reported were Dyspnea, Hepatic function abnormal, Abdominal pain upper, Angioneurotic edema, Dermatitis, Liver function tests abnormal, Pancytopenia, Stevens Johnson Syndrome, Toxic epidermal necrolysis (TEN), and Vomiting.

For the reporting period of this safety summary, January 1, 2000 through June 30, 2001, there continues to be no evidence to suggest that the AE pattern of Ome-Mg tablets is different from that of Ome capsules. The collective safety experience of the Ome capsule and the Ome-Mg tablet strongly suggests Ome has an excellent safety profile and supports the use of Ome-Mg when administered to consumers in an OTC population.

4.4 Other Safety Related Issues

4.4.1 Drug/Drug Interactions

The potential for metabolic drug interactions with Ome (metabolized primarily by the CYP2C19 pathway) has been systematically studied in a manner to maximize the ability to detect such an interaction. In the OTC Ome-Mg clinical program, diazepam, phenytoin, warfarin, and clarithromycin were labeled as drug interactions until the NDA had been reviewed. Upon complete assessment of the pharmacology data, the potential metabolic drug-drug interactions with diazepam and clarithromycin and Ome are judged to not be of clinical significance.

However, while interactions between warfarin or phenytoin and Ome are unlikely, the narrow therapeutic window for these drugs leads to the conservative precaution of listing them on the labeling for Ome-Mg for OTC use.

Since treatment with Ome will result in an increased intragastric pH (decreased acidity), there is a potential for either increasing or decreasing the absorption of drugs that have pH-dependent absorption. Some of the drugs/compounds that might be expected to exhibit altered absorption have been tested in studies with Ome in daily doses of 20 mg or 40 mg. The absorption of amoxicillin, bacampicillin and ethanol was unaltered, while for digoxin and nifedipine a slight increase in absorption was observed (10% and 26%, respectively). The effect on nifedipine did not have any clinical relevance, based on simultaneous pharmacodynamic measurements. The effect on digoxin was not considered to have any clinical relevance in the majority of patients. In line with the results obtained with histamine H_2-receptor blockers, e.g., a 95% decreased relative bioavailability of ketoconazole after ranitidine, it could be predicted that the absorption of ketoconazole and possibly also itraconazole would be decreased by Ome treatment because of the elevated pH obtained. Accordingly, results of one study demonstrated that absorption was decreased by 80% if ketoconazole was administered 6 to 8 hours after a 60 mg dose of Ome. In another study, the absorption of itraconazole was decreased by 64% if administered after 2 weeks' treatment with Ome 40 mg daily.

4.4.2 Unintended Use in Special Populations

4.4.2.1 Pregnancy

PRILOSEC® (omeprazole) Delayed Release Capsules were first approved for marketing in the U.S. in 1989. The initial product labeling regarding use of Ome during pregnancy was based on five non-clinical studies. Reproductive toxicology studies conducted in rabbits and rats at doses about 5.6 to 56 times the human dose on a body surface area basis produced dose related increases in embryo-lethality, fetal resorptions and pregnancy disruptions in the rabbits and embryo-fetal lethality and slight, reversible effects on post-natal body weight gain in the rats. These findings were secondary to maternal toxicity as the doses used were toxic to the dams of both species. Teratology studies conducted in pregnant rats and pregnant rabbits did not disclose any evidence that Ome was teratogenic. At that time, the clinical experience with Ome was limited. As expected, pregnant women were excluded from clinical trials and even general exposure information from worldwide marketed surveillance was limited to a few countries. Based on these data PRILOSEC® was assigned a Pregnancy Category C.

The sponsor subsequently submitted a supplement that included 16 non-clinical reproductive toxicology studies for prescription Ome. The new reproductive toxicology studies, not available at the time the original NDA was approved and the category C assigned, provided a more complete context in which to interpret the results of the original studies.

The supplement also included additional clinical information gathered during the market history of Ome. Information was submitted from epidemiological studies conducted by three independent groups on the use of Ome during pregnancy. These three studies were conducted in Sweden, Canada, and United Kingdom/Italy. The studies jointly included women who used Ome at some time during their pregnancy, along with matched cohorts who used H_2RAs, non-teratogenic agents, or untreated reference groups. The three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used Ome during pregnancy to the frequency of abnormalities among offspring of mothers exposed to H_2RAs or other control cases.

The studies together represent over 1200 cases of women who were exposed to Ome during pregnancy (> 1000 exposed in the first trimester), and none of the studies indicated an increased risk of adverse pregnancy outcome, particularly major malformations, among the offspring of women in the Ome cohorts. These studies have not shown that Ome increases the risk of abnormalities when administered during the first trimester of pregnancy and have not shown any effect of Ome on rates of miscarriage, low birth weight, or pre-term delivery. However, the power of these studies to identify such differences is limited.

A review of post marketed surveillance reports, including those found in published literature, resulted in sporadic reports of congenital abnormalities among infants born to women who took Ome during their pregnancies. These cases are noted in the currently approved labeling for the product. There is, however, no cluster of specific anomalies among these reports that would suggest a syndrome occurring among Ome exposures at a rate above the rate for these types of malformations among general populations.

Although the proposed OTC label does not propose Ome-Mg be used in a pregnant or nursing consumer, if inadvertent use occurred data suggest there are no additional risks. Therefore, the proposed OTC label instructions regarding use of Ome-Mge during pregnancy are appropriate: "If pregnant or breast-feeding, ask a health professional before use."

4.4.2.2 Pediatric/Adolescents

Ome-Mg is not indicated for use in those who are under 18 years of age. However, in the event that a child ingests Ome there is information available on the use of Ome in children. In response to FDA's inclusion of Ome on the list of drugs for which pediatric dosing information would be medically important, five clinical studies were conducted in pediatric patients aged 1 month to 16 years. Rare SAEs occurred but none were considered attributable to Ome by the investigator. No deaths occurred during these clinical trials. The AE profile for pediatric patients was similar to the profile seen in adults. Adverse events outside the safety profile established for Ome in adults appear to reflect ongoing medical disorders in the patient subjects recruited for these trials. The drug is handled kinetically in pediatric patients the same way it is handled in adults.

Ome administered to pediatric patients as intact capsules or sprinkled in applesauce was generally well tolerated with an AE profile resembling that in adults. As in adults, AEs of the gastrointestinal body system such as diarrhea and constipation were the most frequently reported events. Data do not suggest that there is an increase in AE profile with an increase in dose. At around puberty the metabolic capacity of human livers are the same as adults. The data suggests that children 6 years of age or older have dose/weight adjusted AUC close to the values reported in adults.

Overall, the safety profile in adolescent and pediatric patients appears to be favorable and similar to results in adults.

4.5 Overall Safety Conclusion

The clinical trial data for the R_x indications of GERD, EE and dyspepsia show that Ome at doses of 10 mg, 20 mg and 40 mg has a safety profile similar to placebo. This database includes patients who have taken up to 40 mg of Ome for up to one year. These data suggest that Ome is safe for OTC use. The bioavailability of Ome-Mg is similar to Ome, and AE profile is also similar, supporting the excellent safety profile for Ome and the use of Ome-Mg in the OTC setting.

Based on an evaluation of the total data on the metabolic drug-drug interactions between Ome and drugs metabolized via the CYP2C19 microsomal system (e.g., diazepam, phenytoin, and warfarin), clinically relevant interactions are unlikely to occur for any of these drugs with daily doses of 20 mg Ome. However, the narrow therapeutic window for warfarin and phenytoin leads to the conservative precaution of listing them on the labeling for Ome for OTC use.

Administration of oral ketoconazole or itraconazole with Ome can decrease the absorption of the antifungal agents. Itraconazole now includes labeling for decreased absorption with concomitant proton pump inhibitor use in the prescription labeling. A warning for ketoconazole is proposed until such time the prescription labeling includes a warning for the concomitant use with proton pump inhibitors.

Evaluation of information from preclinical studies conducted after the approval of Ome in the US as well as three epidemiological studies conducted on the use of Ome during pregnancy and clinical information gathered during the market history of Ome suggests there is no increased risk if unintended use occurs. In addition, the data support the following language on OTC label instructions regarding use of Ome during pregnancy: "If pregnant or breast-feeding, ask a health professional before use."

The use of Ome-Mg for the prevention of frequent heartburn over a short therapeutic duration – i.e., 14 days – is expected to be safe and well tolerated in the OTC population. The information presented suggests that Ome has a favorable safety profile, which is similar for patients of all ages with the most common AEs being consistent with current labeling for the prescription product and with clinical study experience.

5. Clinical Program Overview

Two adequate and well-controlled efficacy studies (171 and 183) were conducted to determine the safety and effectiveness of Ome-Mg in the prevention of frequent heartburn for 24 hours, over a 14-day dosing period. In addition, four new consumer research trials were performed which included 2 Label Comprehension trials (02255 and 12179), 1 De-Selection trial (17859), and 1 Actual Use trial (2001007).

In the pivotal efficacy studies (171 and 183), subjects with heartburn 2 or more days per week (representative of the OTC consumer with frequent heartburn) were enrolled. Subjects were excluded if they had physician-diagnosed GERD or EE, or took medications that might interfere with evaluation of the safety or efficacy of Ome-Mg. Inclusion criteria focused on past and present heartburn experience. During screening, subjects must have reported a history of heartburn over the past 30 days with heartburn occurring at least 2 days per week and which were known to be at least partially responsive to OTC medications. Continued participation in the studies required that subjects demonstrate heartburn on at least 2 days during the 7-day run-in period.

The Actual Use trial (007) was a mall intercept trial that used supplemental advertising to simulate market conditions. The study also, with FDA permission, required subjects to purchase study medication (again, in an attempt to simulate market conditions and the consumer decision point in the market). There were no restrictions on participation, although subjects were not permitted to purchase medication if they were pregnant, less than 18 years of age, allergic to Ome, or had participated in any prior Use Study for Ome-Mg. All subjects excluded from the use portion of the trial were allowed to participate in the self-selection portion of the Actual Use trial.

6. Efficacy Program

Omeprazole magnesium's long duration of action and its ability to inhibit all stimuli of gastric acid secretion suggest that Ome-Mg might be particularly effective in preventing heartburn for a full 24 hours. Since maximum effectiveness is attained by Day 5–7 with consecutive daily dosing, a regimen of 14 days' consecutive use is appropriate in an OTC setting.

Thus the design of the efficacy trials for prevention of frequent heartburn utilized the unique pharmacologic profile of Ome-Mg in the OTC population of consumers with frequent heartburn (heartburn 2 or more days per week).

6.1 Study Design and Clinical Methods

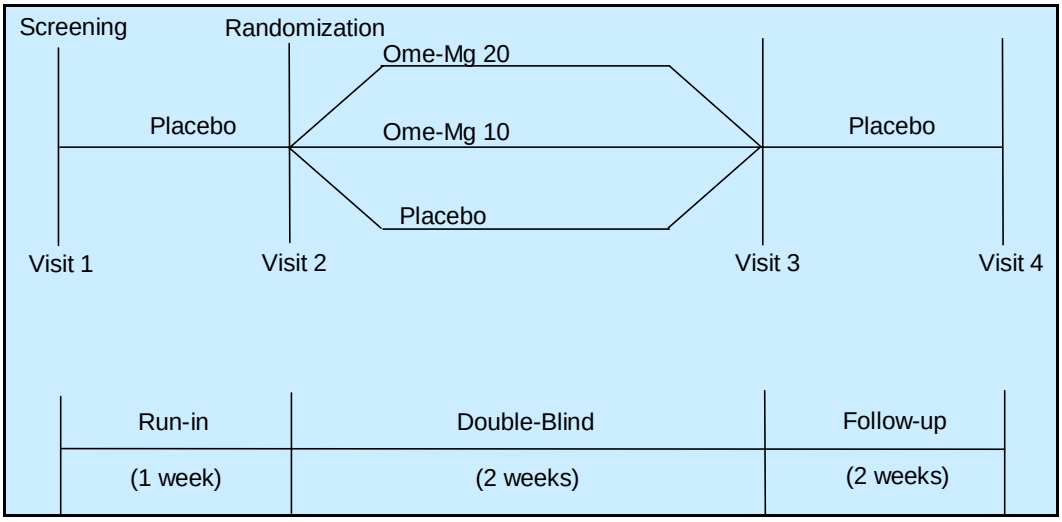
Both studies were multi-center, double-blind, randomized, double-dummy, parallel, and placebo-controlled. Each study tested placebo, and 10 mg and 20 mg of Ome-Mg for 14 consecutive days of use, determined to be the appropriate time to establish efficacy for OTC use. The studies were similar with respect to design, conduct, and data analysis. Collectively, 3162 subjects were randomized to treatment: 2109 to active medication and 1053 to placebo.

The studies lasted 5 weeks and had three phases: (1) a 1-week, single-blind, placebo run-in phase; (2) a 2-week, double-blind, treatment phase in which patients were randomized to receive a single daily dose of either Ome-Mg 20, Ome-Mg 10, or placebo per day; and (3) a 2-week, single-blind, placebo, follow-up phase. Subjects took their daily dose of study medication each morning.

The proposed OTC dose of Ome-Mg is 20 mg, and results of Ome-Mg 20 are provided in detail. A summary of the results of Ome-Mg 10 is provided in Section 6.2.3.

A schematic of the design follows in Figure 6.1.

Figure 6.1
Study Schematic for 14-Day Heartburn Prevention Trials



The primary efficacy variable was: No Heartburn over the previous 24 hours (i.e., Complete Prevention of Heartburn or Heartburn-Free for a full day). Efficacy was evaluated following the first dose of medication, on the last dose, and over 14 days of dosing during the double-blind phase.

Secondary efficacy variables included:

1. Complete Prevention of Nocturnal Heartburn and Occurrence of No More than Mild Heartburn following the first dose of medication and across all 14 days of dosing during the double-blind phase, and

2. Occurrence of No More than Mild Heartburn following the first dose of medication and across all 14 days of dosing during the double-blind phase.

Occurrence of the first episode of heartburn, of any severity, was also investigated during a 2-week, single-blind placebo, follow-up phase.

Each morning subjects (a) rated the most severe episode of heartburn for the previous 24-hour period using a 5-point scale, (b) indicated whether or not nocturnal heartburn was experienced, and (c) recorded information on use of an antacid (Gelusil®), which was provided as a backup medication to be used at the subject's discretion.

6.1.1 Statistical Methods

For both studies, a Cochran-Mantel-Haenszel test statistic was used to compare treatment effects on Day 1 for complete prevention of heartburn over 24 hours, complete prevention of nocturnal heartburn, and the occurrence of no more than mild heartburn over 24 hours. A logistic regression analysis was used to compute odds ratios for each treatment comparison and to assess treatment-by-center interaction for the primary efficacy variable. For each endpoint, an Analysis of Variance (ANOVA) was conducted with each of the three variables to compare treatments with regard to mean percent of days over the 2-week, double-blind phase when an event took place. Generalized Estimating Equations (GEE) were used to assess the same three variables over repeated doses.

6.1.2 Demographics and Other Baseline Characteristics

Collectively, 3162 subjects were randomized to treatment across 49 centers in Trials 171 and 183. A total of 3124 subjects were included in the ITT dataset for statistical analysis: 2085 to active medication (1047 to Ome-Mg 20) and 1039 to placebo. The 38 randomized subjects excluded from the ITT dataset either did not dose with study medication, recorded no efficacy data, or were enrolled previously in the same study.

Table 6.1 provides a summary of demographic and heartburn baseline characteristics by dose group and trial. Baseline characteristics were similar across treatment groups and trials. The mean reported baseline heartburn frequency was 5 days per week, of mild severity.

TABLE 6.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS (STUDIES 171 AND 183)				
Study	**171**		**183**	
Characteristic	**Ome-Mg 20 N=523**	**Placebo N=519**	**Ome-Mg 20 N=524**	**Placebo N=520**
Gender				
Female	297 (56.8%)	287 (55.3%)	283 (54.0%)	293 (56.3%)
Male	226 (43.2%)	232 (44.7%)	241 (46.0%)	227 (43.7%)
Race				
Asian	4 (0.8%)	7 (1.3%)	1 (0.2%)	4 (0.8%)
Black	63 (12.0%)	57 (11.0%)	32 (6.1%)	33 (6.3%)
Caucasian	401 (76.7%)	399 (76.9%)	443 (84.5%)	445 (85.6%)
Hispanic	48 (9.2%)	51 (9.8%)	36 (6.9%)	33 (6.3%)
Other	7 (1.3%)	5 (1.0%)	12 (2.3%)	5 (1.0%)
Age (Years)				
Mean (SD)	44.5 (12.77)	43.7 (13.22)	46.7 (14.22)	46.0 (14.14)
Min/Max	18–86	18–79	20–84	18–79
Heartburn Frequency % of Days during Run-In				
Mean (SD)	74.3 (24.39)	75.2 (24.18)	74.2 (23.57)	74.2 (24.19)
≥ 50%	419 (80.1%)	422 (81.3%)	426 (81.3%)	417 (80.2%)

6.2 Efficacy Results

6.2.1 Primary Efficacy Parameter (Heartburn-Free for 24 Hours)

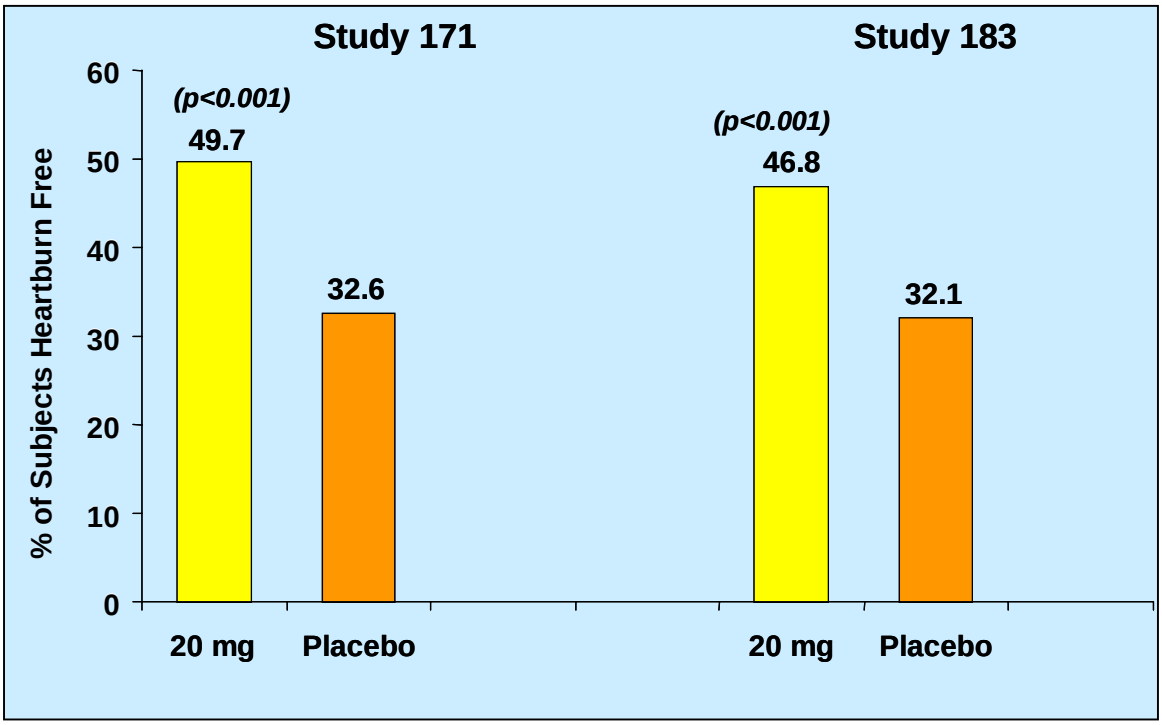
The primary variable, Heartburn-Free for 24 Hours, was generated on report of no heartburn (i.e., complete prevention), for the 24 hours preceding the evaluation.

In each study, a significantly greater percentage of subjects in the Ome-Mg 20 treatment group were Heartburn-Free than in the placebo group after the first dose ($p < 0.001$), after the last dose ($p < 0.001$), and over all 14 doses ($p < 0.001$).

Day 1

Figure 6.2 displays results of the analyses for the primary efficacy parameter, Heartburn-Free for a Full Day (No Heartburn over 24 Hours) on Day 1.

Figure 6.2
Percent of Subjects with 24 Hour Prevention of Heartburn — Day 1



Study 171, the percentage of subjects who were Heartburn-Free for the full day after the first dose was 49.7% for Ome-Mg 20; 17.2% greater than placebo. In Study 183, 46.8% of subjects on Ome-Mg 20 were Heartburn-Free for the full day after the first dose; 14.6% greater than placebo.

Table 6.3 displays results of the analyses for the primary efficacy parameter, Heartburn-Free for a Full Day (No Heartburn over 24 Hours) on Day 1.

TABLE 6.3
ANALYSIS OF PRIMARY EFFICACY VARIABLE
NO HEARTBURN OVER 24 HOURS ON DAY 1

INTENT-TO-TREAT SUBJECTS

STUDY 171	**Ome-Mg 20**	**PLACEBO**
Heartburn-Free (%)	49.7% (260/523)	32.6% (169/519)
COMPARISON	***P*-VALUE**[a]	**DIFF IN PROP. (95% CI)**[b]
Ome-Mg 20 vs. Placebo	**<0.001**	17.2% (11.3, 23.0)
STUDY 183	**Ome-Mg 20**	**PLACEBO**
Heartburn-Free (%)	46.8% (245/524)	32.1% (167/520)
COMPARISON	***P*-VALUE**[a]	**DIFF IN PROP. (95% CI)**[b]
Ome-Mg 20 vs. Placebo	**<0.001**	14.6% (8.8, 20.5)

[a] *p*-Values for treatment comparisons obtained from Cochran-Mantel-Haenszel chi-square test with Investigator as a stratification variable.

[b] Estimated difference in proportions (expressed as a percent) and 95% confidence interval using a normal approximation.

Over 14 Days Dosing Period

The primary therapeutic gain (difference between Ome-Mg 20 and placebo) in studies 171 and 183 was seen by Day 6, and remained consistently high after that time. Figure 6.3 and Tables 6.4 and 6.5 highlight this pattern for Ome-Mg 20 and placebo. In study 171, most of the rate increase was realized by Day 4–5 for Ome-Mg 20, and in study 183 most of the rate increase is realized by Day 6 for Ome-Mg 20.

Figure 6.3
Percent of Subjects with 24 Hour Prevention of Heartburn — Time Course Over 14 Days
Studies 171 and 183

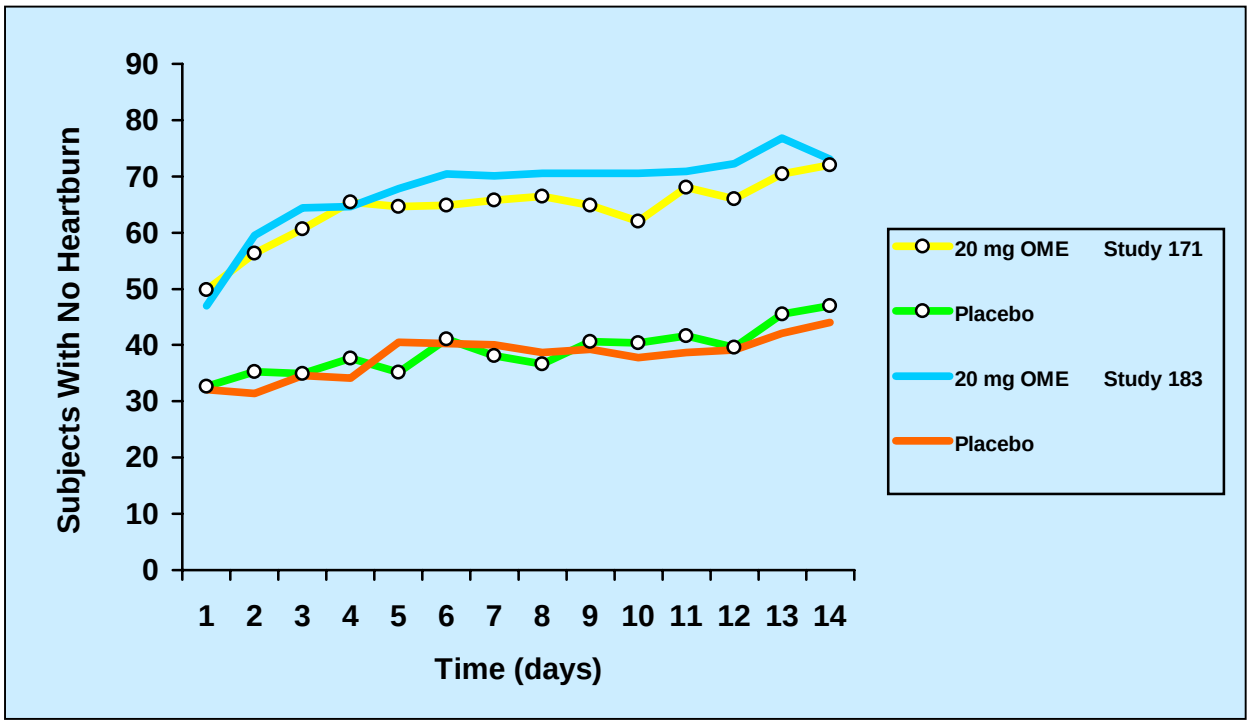


TABLE 6.4
NUMBER AND PERCENT OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS, BY DAY

STUDY 171: INTENT-TO-TREAT SUBJECTS

Day	Ome-Mg 20 N=523		Placebo N=518		Difference
	N[a]	%[b]	N[a]	%[b]	%
1	522	49.8	517	32.7	17.1
2	520	56.3	515	35.3	21.5
3	518	60.6	516	34.9	25.7
4	520	65.4	515	37.7	27.7
5	520	64.6	514	35.2	29.4
6	521	64.9	513	41.1	23.8
7	517	65.8	514	38.1	27.7
8	520	66.5	511	36.6	29.9
9	518	64.9	508	40.6	24.3
10	516	62.0	510	40.4	21.6
11	512	68.0	511	41.7	26.3
12	512	66.0	507	39.6	26.4
13	507	70.4	497	45.5	24.9
14	482	72.0	464	47.0	25.0

[a] Number of ITT subjects in treatment group with non-missing values
[b] Percent of subjects with No Heartburn over 24 hours

TABLE 6.5
NUMBER AND PERCENT OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS, BY DAY

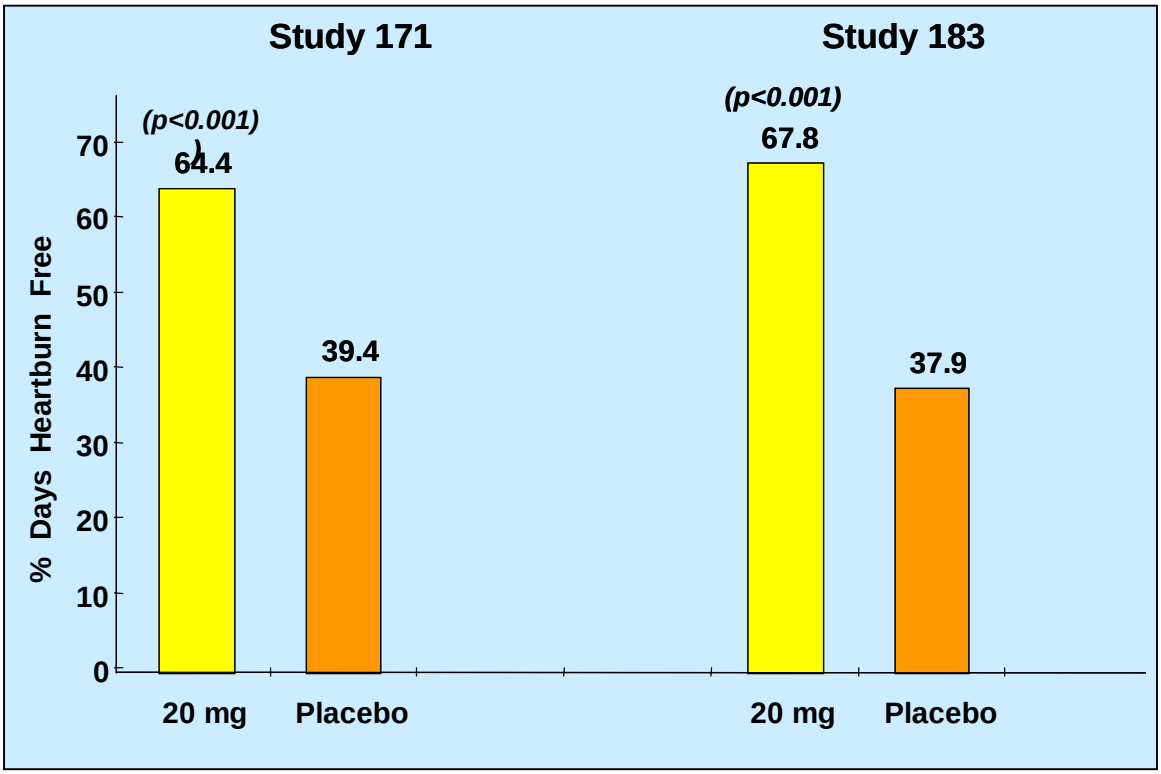
STUDY 183: INTENT-TO-TREAT SUBJECTS

Day	Ome-Mg 20 N=524		Placebo N=520		Difference
	N[a]	%[b]	N[a]	%[b]	%
1	521	47.0	520	32.1	14.9
2	524	59.5	519	31.4	28.1
3	523	64.4	518	34.6	29.8
4	522	64.6	516	34.1	30.5
5	519	67.8	516	40.5	27.3
6	520	70.4	514	40.3	30.1
7	518	70.1	514	40.1	30.0
8	519	70.5	512	38.7	31.8
9	518	70.5	514	39.3	31.2
10	517	70.6	511	37.8	32.8
11	516	70.9	512	38.7	32.2
12	514	72.0	509	39.1	33.1
13	508	76.8	499	42.1	34.7
14	478	73.0	480	44.0	29.0

[a] Number of ITT subjects in treatment group with non-missing values
[b] Percent of subjects with No Heartburn over 24 hours

Another way of looking at efficacy across 14 days of dosing is to examine the percent of days subjects were heartburn-free. With consecutive daily dosing, Ome-Mg treated subjects had a significantly greater percentage of heartburn-free days than did placebo-treated subjects, as seen in Figure 6.4

Figure 6.4
Percent of Days with No Heartburn — Across 14 Day Dosing Period



6.2.2 Secondary Parameters

Day 1

The secondary variable, No Nocturnal Heartburn, represents the ability of Ome-Mg to prevent heartburn at the end of the full day after morning dosing under conditions favorable to development of heartburn, i.e., a supine position. The secondary variable, No More than Mild Heartburn, allows development of heartburn that is easily tolerated (Mild), but still considers the treatment successful.

Table 6.6 displays the results of the analyses for both secondary efficacy parameters on Day 1. In general, the results of these secondary variables corroborated the findings for the primary variable. Ome-Mg 20 was significantly superior to placebo in all analyses with one exception (No Nocturnal Heartburn following first dose in Study 183).

In Study 171, the percentage of subjects with No Nocturnal Heartburn following the first dose was 78.4% for Ome-Mg 20, 8.0% higher than placebo (70.4% with No Nocturnal Heartburn). The difference was statistically significant. In Study 183, the percentage of subjects with No Nocturnal Heartburn following the first dose was 77.7% for Ome-Mg 20, not significantly different from placebo (73.9%).

In Study 171, the percentage of subjects with No More than Mild Heartburn following the first dose was 81% for Ome-Mg 20, 9.4% higher than placebo (71.6% with No More than Mild Heartburn) and was statistically significant. Results of Study 183 were similar. The percentage of subjects with No More than Mild Heartburn following the first dose was 81.8% for Ome-Mg 20, 11% higher than placebo (70.8% with No More than Mild Heartburn), and was statistically significant compared to placebo.

TABLE 6.6
ANALYSIS OF SECONDARY EFFICACY VARIABLES
PERCENTAGE OF SUBJECTS WITH NO NOCTURNAL AND NO MORE THAN MILD HEARTBURN ON DAY 1

HEARTBURN OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Placebo
No Nocturnal Heartburn[a]		
Study 171	**78.4%[b]**	70.4%
Study 183	77.7%	73.9%
No More Than Mild Heartburn Over 24 Hours[a]		
Study 171	**81.0%[b]**	71.6%
Study 183	**81.8%[b]**	70.8%

[a] Percentage of subjects with indicated outcome. Treatment difference tested using Cochran-Mantel-Haenszel chi-square test with Investigator as a stratification variable.

[b] Comparisons with placebo that resulted in a *p*-values ≤ 0.05 are shaded and bolded in table.

Over 14 Dosing Days

Table 6.7 shows the results for the secondary parameters No Nocturnal Symptoms and Symptoms No More than Mild over 24 hours, across 14 consecutive days of dosing. Ome-Mg-treated subjects had a greater percentage of nights with No Nocturnal Heartburn symptoms. Consecutive daily dosing with Ome-Mg also resulted in a greater percentage of days with No More than Mild heartburn versus placebo. For all outcomes, Ome-Mg 20 provided significantly greater protection against heartburn than placebo in both studies.

TABLE 6.7
MEAN PERCENTAGE OF DAYS (ADJUSTED) WITH INDICATED OUTCOME OVER 14 DAYS OF DOUBLE-BLIND PHASE[a]

HEARTBURN OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Placebo
No Nocturnal Heartburn[b]		
Study 171	**84.7%[c]**	74.5%
Study 183	**86.1%[c]**	75.4%
No More Than Mild Heartburn Over 24 Hours[b]		
Study 171	**88.6%[c]**	75.9%
Study 183	**88.6%[c]**	73.7%

[a] Percentage based on number of days with valid data. Subjects with less than 5 days of valid data were excluded from this analysis.

[b] Estimated mean percent of days with indicated outcome (least squares mean from ANOVA model with Treatment and Investigator as factors). Treatment difference tested using t-test.

[c] Comparisons with placebo that resulted in *p*-values ≤ 0.05 are shaded and bolded in table.

As seen in Table 6.8, the results for primary and secondary variables across 14 days are generally corroborated by a GEE analysis of the data across 14 days of dosing.

TABLE 6.8
ANALYSIS OF EFFICACY VARIABLES USING GEE
TREATMENT COMPARISONS BASED ON ALL 14 DAYS OF DOUBLE-BLIND PHASE

HEARTBURN OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20 vs. Placebo		
	Odds Ratio[a]	**95% CI[a]**	***P*-Value[b]**
No Heartburn Over 24 Hours			
Study 171	2.90	(2.46, 3.42)	**<0.001**
Study 183	3.61	(3.06, 4.26)	**<0.001**
No Nocturnal Heartburn			
Study 171	1.90	(1.57, 2.30)	**<0.001**
Study 183	1.98	(1.64, 2.38)	**<0.001**
No More Than Mild Heartburn Over 24 Hours			
Study 171	2.40	(1.97, 2.93)	**<0.001**
Study 183	2.67	(2.20, 3.24)	**<0.001**

a Estimated odds ratio and 95% confidence interval (CI) obtained from GEE model with Treatment, Center, and Day as categorical explanatory variables (exchangeable correlation assumed). Robust variance estimate used. The odds ratio is the ratio of the estimated odds of having the indicated outcome in the first group relative to the second group shown.

b *p*-Values for treatment comparisons from Wald chi-square test.

6.2.3 Results with Ome-Mg 10: Primary Efficacy Parameter (Heartburn-Free for 24 Hours): Day 1 and Across All 14 Days, and Dose-Response

Subject demographics were comparable across all treatment groups in both studies.

In each study, a significantly greater percentage of subjects in the Ome-Mg 10 treatment groups were Heartburn-Free than in the placebo group ($p \leq 0.003$ for the first dose, $p \leq 0.05$ across 14 doses).

For Day 1 results, in Study 171, Ome-Mg 20 had a significantly higher percentage of Heartburn-Free subjects than Ome-Mg 10 ($p = 0.008$), while in study 183, the two doses produced similar levels of effectiveness for first dose evaluations.

For results across all 14 days of dosing, in Study 183, Ome-Mg 20 had a significantly higher percentage of Heartburn-Free subjects than Ome-Mg 10 ($p \leq 0.05$), while in study 171, the two doses produced similar levels of effectiveness.

Table 6.9 details the results for Ome-Mg 20, Ome-Mg 10, and placebo for the primary efficacy parameter, percent of subjects with no heartburn for 24 hours, on Day 1 and across all 14 days.

TABLE 6.9
MEAN PERCENTAGE OF DAYS (ADJUSTED) WITH INDICATED OUTCOME OVER 14 DAYS OF DOUBLE-BLIND PHASE[a]

HEARTBURN OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	Placebo
No Heartburn over 24 Hours			
Day 1			
Study 171	**49.7%[a,b]**	**41.5%[a]**	32.6%
Study 183	**46.8%[a]**	**45.2%[a]**	32.1%
Day 14			
Study 171	**69.7%[a]**	**71.7%[a]**	42.7%
Study 183	**73.0%[a]**	**66.4%[a]**	43.0%
Across 14 Days			
Study 171	**64.4%[a]**	**60.8%[a]**	39.4%
Study 183	**67.8%[a,b]**	**61.4%[a]**	37.9%

[a] p-values for comparisons obtained from Cochran-Mantel-Haenszel chi-square test with investigator as a stratification variable; significantly different from placebo (significant values bolded)

[b] p-values for comparisons obtained from Cochran-Mantel-Haenszel chi-square test with investigator as a stratification variable, Ome-Mg 20 significantly difference from Ome-Mg 10

Table 6.10 shows the GEE analysis over 14 days of the treatment comparisons (Ome-Mg 20 vs. placebo and Ome-Mg 10) for the primary and secondary prevention variables.

TABLE 6.10
ANALYSIS OF EFFICACY VARIABLES USING GEE
TREATMENT COMPARISONS BASED ON ALL 14 DAYS OF DOUBLE-BLIND PHASE

HEARTBURN OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20 vs. Placebo			Ome-Mg 20 vs. Ome-Mg 10		
	Odds Ratio[a]	95% CI[a]	*P*-Value[b]	Odds Ratio[a]	95% CI[a]	*P*-Value[b]
No Heartburn Over 24 Hours						
Study 171	2.90	(2.46, 3.42)	**<0.001**	1.18	(1.00, 1.40)	**0.050**
Study 183	3.61	(3.06, 4.26)	**<0.001**	1.32	(1.12, 1.56)	**<0.001**
No Nocturnal Heartburn						
Study 171	1.90	(1.57, 2.30)	**<0.001**	1.12	(0.92, 1.38)	0.259
Study 183	1.98	(1.64, 2.38)	**<0.001**	1.30	(1.06, 1.60)	**0.011**
No More Than Mild Heartburn Over 24 Hours						
Study 171	2.40	(1.97, 2.93)	**<0.001**	1.23	(0.99, 1.51)	0.059
Study 183	2.67	(2.20, 3.24)	**<0.001**	1.25	(1.01, 1.55)	**0.042**

a Estimated odds ratio and 95% confidence interval (CI) obtained from GEE model with Treatment, Center, and Day as categorical explanatory variables (exchangeable correlation assumed). Robust variance estimate used. The odds ratio is the ratio of the estimated odds of having the indicated outcome in the first group relative to the second group shown.

b *p*-Values for treatment comparisons from Wald chi-square test.

Tables 6.11 and 6.12 show the day-by-day results for Ome-Mg 10 vs. placebo. For study 171, most of the therapeutic gain is realized by Day 7 for Ome-Mg 10, and by Day 6 for Ome-Mg 10 in study 183.

Comparing Tables 6.4/6.5 with Tables 6.11/6.12, it can be seen that Ome-Mg 20 produced a stronger result earlier than Ome-Mg10, confirming the known pharmacology of Ome-Mg (see Section 3.0).

TABLE 6.11
NUMBER AND PERCENT OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS, BY DAY

STUDY 171: INTENT-TO-TREAT SUBJECTS

DAY	OME-MG 10 N=518		PLACEBO N=518		DIFFERENCE
	N[a]	%[b]	N[a]	%[b]	%
1	518	41.5	517	32.7	8.8
2	518	50.0	515	35.3	14.7
3	516	55.8	516	34.9	20.9
4	516	55.8	515	37.7	18.1
5	515	58.8	514	35.2	23.6
6	516	60.3	513	41.1	19.2
7	515	62.7	514	38.1	24.6
8	513	62.6	511	36.6	26.0
9	512	64.1	508	40.6	23.5
10	513	63.2	510	40.4	22.8
11	513	63.9	511	41.7	22.2
12	513	64.5	507	39.6	24.9
13	504	70.8	497	45.5	25.3
14	472	70.6	464	47.0	23.6

[a] Number of ITT subjects in treatment group with non-missing values
[b] Percent of subjects with No Heartburn over 24 hours

TABLE 6.12
NUMBER AND PERCENT OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS, BY DAY

STUDY 183: INTENT-TO-TREAT SUBJECTS

DAY	OME-MG 10 N=520		PLACEBO N=520		DIFFERENCE
	N[a]	%[b]	N[a]	%[b]	%
1	519	45.3	520	32.1	13.2
2	518	51.2	519	31.4	19.8
3	519	56.3	518	34.6	21.7
4	517	58.4	516	34.1	24.3
5	518	62.7	516	40.5	22.2
6	515	66.0	514	40.3	25.7
7	515	66.0	514	40.1	25.9
8	517	64.6	512	38.7	25.9
9	516	66.1	514	39.3	26.8
10	516	61.4	511	37.8	23.6
11	515	63.5	512	38.7	24.8
12	513	64.1	509	39.1	25.0
13	504	68.3	499	42.1	26.2
14	486	67.3	480	44.0	23.3

[a] Number of ITT subjects in treatment group with non-missing values
[b] Percent of subjects with No Heartburn over 24 hours

6.2.4 Outcomes During the Follow-up Phase

Based on estimates shown in Table 6.13, the first episode of heartburn, any severity and independent of the need to treat the episode, occurred for more than 50% of the placebo-treated subjects within 1 day. The first episode of heartburn occurred within 3 days for 75% of placebo-treated subjects, and within 4–5 days for 75% of Ome-Mg-treated subjects. In both studies, Occurrence of Heartburn for the Ome-Mg 20 and placebo groups was comparable beyond Day 5 or 6. Data was collected by daily diary for 2 weeks following cessation of dosing.

TABLE 6.13
NUMBER OF DAYS TO FIRST OCCURRENCE OF HEARTBURN
DURING FOLLOW-UP PHASE (AFTER TWO WEEKS DAILY DOSING)
PER-PROTOCOL SUBJECTS

	50th Percentile[a]		75th Percentile[a]	
	171	183	171	183
Ome-Mg 20	3	3	5	5
Placebo	1	1	3	3

[a] Estimated using Kaplan-Meier method.

6.3 Efficacy Conclusions

These study results provide substantial evidence of statistically significant and clinically meaningful effectiveness of Ome-Mg 20, compared to placebo, in the prevention of frequent heartburn for 24 hours when administered in the morning for 14 consecutive days. The maximum benefit in complete heartburn prevention was manifest in 5–7 days of dosing, well within the 14-day period.

These studies support the following proposed OTC label use indication for Ome-Mg 20:

- for **prevention** of the symptoms of frequent heartburn for 24 hours.

7. Consumer Understanding and Behavior Program

This section contains a discussion and evaluation of the data that examine label understanding and consumer usage patterns of Ome-Mg among adults. Results of these studies were used to aid in the development of the proposed OTC label.

The following studies were conducted: two Label Comprehension Studies 02255 and 12179 (in which no medication was dispensed), one De-Selection Study 17859 in consumers with infrequent heartburn (in which no medication was dispensed) and one Actual Use Study 007 in which consumers could purchase and use product.

Collectively, these studies demonstrate the ability of the consumer population to understand the product label, and use Ome-Mg safely and effectively according to the product label.

7.1 Label Comprehension Study Number 02255

The objective of the label comprehension study was to determine whether a population of general consumers, including those targeted to various aspects of the label, understood the self-selection, use direction, and warning language on the proposed OTC label for Ome-Mg.

The study was conducted among 684 consumers recruited by mall-intercept, by telephone, or through advertising. The study population consisted of the following groups: general population (included subjects with no or infrequent heartburn), literate subjects with frequent heartburn, low-literate subjects with frequent heartburn, subjects with heartburn who were taking one or more medications listed in the drug-drug interaction statement, and subjects with heartburn who were pregnant or nursing.

7.1.1 Methods

The following key communication objectives were evaluated.

- Product is intended for use by adults 18 years of age or older for the prevention of frequent heartburn.
- Not to use or to ask a health professional before using if subject:
  - Is allergic to Ome
  - Has any of the general warning symptoms under the “Do not use” section of the label
  - Is taking one of the medications listed in the drug-drug interaction statement
  - Is currently pregnant or nursing a baby
- Stop use and ask a doctor if:
  - stomach pain continues or worsens
  - heartburn continues or returns after using every day for 14 days
- Product should be used only once a day (1 tablet in 24 hours) for 14 days
- What to do in the case of overdose

The label tested in this comprehension trial is shown on the following page.

PRILOSEC1 LABEL COMPREHENSION LABEL – STUDY 02255

Drug Facts

Active ingredient (in each tablet) ***Purpose***

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

Uses

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

Warnings

Allergy alert Do not use if you are allergic to omeprazole

Heartburn Warning. Heartburn can be a sign of a more serious condition. Notify your doctor if you have had heartburn for 3 months or longer without talking to your doctor.

Do not use

- if you have trouble swallowing food, wheezing, a chronic cough or hoarseness, have vomited blood, black/tarry stools, chest pain or unexplained weight loss. This may be a sign of a more serious condition. See your doctor.
- if you have a sudden increase of your heartburn symptoms with nausea and vomiting; chest pain; pain spreading to your arms, neck or shoulders; sweating; shortness of breath or lightheadedness. See your doctor.
- with other acid reducers

Ask a doctor or pharmacist before use if you are taking

- warfarin (blood thinning medicine)
- phenytoin (seizure medicine)
- diazepam (anxiety medicine)
- clarithromycin (antibiotic medicine)
- itraconazole (prescription antifungal medicine)
- ketoconazole (prescription antifungal medicine)

Stop use and ask a doctor if

- stomach pain continues or worsens ▶

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

Drug Facts (continued)

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

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

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

Directions

Adults 18 years of age and older:

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

Children under 18 years of age: ask a doctor

Other Information

- read the directions, warnings and package insert before use
- keep the carton and package insert. They contain important information.
- store between 20-25°C (68-77°F)
- protect from moisture

Inactive ingredients glyceryl monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin, polyethylene glycol 6000, polysorbate 80, polyvinylpyrrolidone, sodium stearyl fumarate, starch, sucrose, talc, titanium dioxide, triethyl citrate

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

Questions or comments? Call toll free

Distributed By Procter & Gamble, Cincinnati, OH 45202

Design

This study was conducted in 12 geographically diverse sites across the U.S. (primarily shopping malls). A total of 684 subjects, 18 years of age or older, participated in the study. No study medication was administered.

Potential subjects were screened (including completion of a REALM test[51] for literacy) and placed into one or more of the following groups: subjects with no or infrequent heartburn, literate subjects with frequent heartburn, low-literate subjects with frequent heartburn, subjects with heartburn who were taking one or more medications listed in the drug-drug interaction statement, and subjects with heartburn who were pregnant or nursing. Subjects within each group were given a proposed market label for the OTC product. After allowing them to read the label, subjects were asked questions to determine their comprehension of the suitability of the medication for their use. In addition, condition-specific scenarios were also presented.

TABLE 7.1
LABEL COMPREHENSION STUDY COHORT INFORMATION
STUDY 02255

Cohort	Number of Subjects	Subject Type	Recruitment Method
1	229	Subjects with no or infrequent heartburn	Spontaneous intercept in malls/shopping centers or prerecruited
2	155	Literate subjects with frequent heartburn	
3	162	Subjects with frequent heartburn at a 7^{th}–8^{th} grade or lower reading level	
4	96	Subjects with heartburn who were taking a medication listed in the drug-drug interaction statement	Advertising or existing databases
5	42	Subjects with heartburn who were pregnant/breastfeeding	Advertising or existing databases

Each subject was asked a series of direct questions on self-selection of the product relative to their own personal experience of heartburn and conditions of appropriate use (e.g., how many tablets should be taken per day, how many consecutive days should product be taken, what product is intended for).

In addition, subjects were asked questions on a series of more than 50 scenarios relative to appropriate selection and use of the product: questions dealt with appropriate use in scenarios of use for prevention of frequent heartburn to treatment of episodic heartburn, scenarios of self-selection, scenarios related to specific warnings (including use with concomitant medication, use while pregnant/nursing, use with general warning symptoms present, and general use directions). Study participants were presented a scenario and then asked a question to determine if they understood how to use the product.

7.1.2 Results

All consumers identified Ome-Mg as a product for heartburn. Overall, 76% to 96% of respondents correctly answered questions about prevention of frequent heartburn scenarios.

Self-selection results indicated that 99% of the consumers with frequent heartburn understood that this was a product they could use. Seventy-eight percent (78%) of the no heartburn/ infrequent heartburn subjects correctly indicated the product was not intended for them.

Scenarios on all label warnings had a high level of correct/acceptable responses (88% to 100%). The majority of respondents understood they were to take 1 tablet a day (95%) for 14 days (91%) and that they should not take the product for more than 14 days (92%).

Half (50%) the subjects taking labeled medications with a potential for drug-drug interaction indicated they would not use the product or would consult a doctor prior to use, when such medication was identified on the label with only the generic drug name. The percent correctly responding for such medications increased to 82% when brand names of these medications were also shown. Responses to scenarios on medications labeled for drug-drug interactions were correct/acceptable 94% to 99% of the time.

Pregnant/nursing women (91%) knew not to take the product or to ask their doctor before use. Responses to scenarios relative to pregnancy or nursing were correct/acceptable 99% of the time.

For consumers with a general condition warning symptom as identified in the "Do Not Use" section of the label (in other words, a symptom often confused with heartburn or one which might indicate presence of a more serious underlying condition, such as chest pain, wheezing, or trouble swallowing), scores for understanding on direct scenarios were considerably higher than the direct self-selection question (41%), indicating consumers understood the warning but may not have felt it applied to them. Scenarios on general condition warning symptoms showed a high level of understanding (89% to 100%).

When comparing literate vs. low-literate frequent heartburn subjects, there were no differences in responses between the groups except for the following areas: prevention of heartburn use (94% vs. 79%, respectively); episodic relief of heartburn use (61% vs. 49%, respectively); label directions (95% to 99% vs. 82% to 89%, respectively); and label warning direct scenarios "do not use with acid reducers" and "children under 18 years of age ask a doctor" (89% vs. 97% and 99% vs. 96% respectively).

7.1.3 Summary

Overall, consumers with frequent heartburn understood the uses of the product, the label warnings, and directions in Label Comprehension study 02255. Direct scenarios related to correct product use (prevention of frequent heartburn) were better understood than direct scenarios related to incorrect product use (episodic relief). Consumers taking medications listed in the drug-drug interaction statement understood the warning better when the brand names were provided. For consumers with a general condition-warning symptom, scores for understanding

on direct scenarios were considerably higher than the direct self-selection questions, indicating these subjects understood the warning but may not have felt it applied to them.

7.2 Label Comprehension Study Number 12179

The inclusion of several elements of information and consumer education specific to frequent heartburn on the proposed OTC label for Ome-Mg include general heartburn warning statements, which are indicated as "general condition warning symptoms". General condition warning symptoms are included on the label in an attempt to provide the consumer with additional perspective regarding other conditions which may be confused with heartburn or may indicate the presence of a more serious underlying condition, consistent with American College of Gastroenterology (ACG) guidelines. This language was re-tested in this second Label Comprehension study to clarify wording, making the warning more understandable and useful to the consumer.

In the initial Label Comprehension Study 02255, 41% of consumers with frequent heartburn who had one or more of the general condition warning symptoms indicated they would not use the product or would ask a doctor prior to use, even though comprehension scores for the direct scenarios were much higher (89% to 100%). This indicates that consumers with general condition warning symptoms understood the label, but, on the basis of their experience with the condition and/or prior physician advice, may have felt they did not need to consult a doctor prior to use of the product if they had already consulted with a physician for the warning symptom. It is also possible this group did not realize they needed to be currently experiencing the symptom to report it.

The label warning language for general condition warning symptoms was modified with consultation from gastroenterologists who participated in the creation of the original ACG guidelines from which the language tested in Label Comprehension Study 02255 was derived.[52,64] The modified label was retested in Label Comprehension Study 12179 and results indicate that those consumers who meet label criteria and have seen a physician for the general condition warning symptom understand the clarified label language. The label was tested among 145 consumers who were pre-recruited using market research data collection databases. The subjects had frequent heartburn and reported one or more of the general condition warning symptoms relating to the modified label.

The differences in wording for the general condition warning symptoms warning between the original label tested in Label Comprehension study 02255 and this study is detailed below:

General Condition Warning Symptom: Label Language	
Label Comprehension Study 02255	**Label Comprehension Study 12179 and Proposed Label**
Do Not Use • If you have trouble swallowing food, wheezing, a chronic cough or hoarseness, have vomited blood, black/tarry stools, chest pain or unexplained weight loss. This may be a sign of a more serious condition. See your doctor. • If you have sudden increase of your heartburn symptoms with nausea and vomiting; chest pain' chest pain spreading to your arms, neck, shoulders; sweating; shortness of breath or lightheadedness. See your doctor.	**Ask a doctor before use if you have** • Any of the following symptoms and have not seen a doctor: – Frequent chest pain – Chest pain; shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness – Trouble swallowing food – Frequent wheezing, particularly with heartburn – Unexplained weight loss These may be signs of a more serious condition. Notify your doctor.

Results of this research, presented below, indicate consumers with general condition warning symptoms understand the clarified label.

7.2.1 Methods

The objective of this study was to evaluate how well the consumer with frequent heartburn and a general condition warning symptom understood the conditions (i.e., uses and warnings) under which Ome-Mg could be used based on reading the label.

Measures of Comprehension
Comprehension was assessed from responses to questionnaires. The following key communication objectives were evaluated.

- Product use
- Consumer self-selection
- Direct scenarios on the label general condition warning contraindicated symptoms

Participants were told to read the label, then asked a series of direct questions and specific scenarios related to appropriate product use. Study participants fell into 3 categories: Okay to use (infrequent general condition warning symptoms); Okay to use (general condition warning symptoms reported to healthcare provider), and Ask a doctor first (general condition warning symptoms not yet reported to healthcare provider).

7.2.2 Results

Overall, consumers noticed the general condition warning symptoms warning on the label (97%), and the majority of consumers understood the general condition warning symptoms on the label. When presented the direct scenarios relative to the general condition warning symptoms, 92% to 94% of responses were correct/acceptable. Self-selection among consumers with frequent heartburn accompanied by a symptom was 81%: respondents had a correct self-selection response by indicating they would ask a doctor first, had already talked with their doctor or had infrequent general condition warning symptoms.

All consumers correctly identified Ome-Mg as a product for heartburn, and specifically for frequent heartburn by 78% of participants.

7.2.3 Summary

The understanding and intent of consumers with frequent heartburn and a general condition warning symptom to comply with this specific aspect of the label was improved by the modified label language. The wording included in the final proposed label is a result of this testing program.

7.3 De-Selection Study Number US0117859 in Consumers With Infrequent Heartburn

In order to understand whether consumers with infrequent heartburn (symptoms one day per week or less) would understand the intent of the product label, a study was conducted to assess the de-selection rate for this population of consumers: the rate at which consumers with infrequent heartburn did not choose Ome-Mg as a product suitable for their heartburn, in the context of the full array of available OTC heartburn remedies. Although there is no standard method by which to evaluate de-selection, this research was designed as an attempt to address the question.

7.3.1 Methods

The primary objective of this study was to ascertain whether consumers with infrequent heartburn understood Ome-Mg was not appropriate for their heartburn when faced with a representative sample of currently available OTC heartburn medications. The objective was addressed based on the consumer choosing from a representative variety of OTC heartburn medications. No subject used the product.

Design

Ninety-seven (97) consumers with infrequent heartburn (heartburn once a week or less) were brought to a simulated retail aisle for OTC heartburn remedies, complete with products and infrastructure one would expect to find in a retail grocery, drug, or mass merchandise venue. A comprehensive array of currently marketed heartburn products was displayed on the shelf, along with prices. Branded and generic OTC heartburn products, including Ome-Mg, were on the shelf for consideration. Ome-Mg was marked with a shelf tag noting it was a new product, so that consumers would notice it on the shelf, also mimicking retail presence.

Each consumer first completed a self-administered heartburn habits and practice questionnaire. The consumer was then taken to the store aisle where they were instructed to consider their own heartburn needs and select the heartburn product(s) they would purchase for their own personal use. They were invited to pick up the products, read labels, and compare prices just as if they were shopping, and recorded their selection with the interviewer.

7.3.2 Results

Ninety-two out of 97 (95%) of consumers with infrequent heartburn chose another product (not Ome-Mg) as the product most appropriate for their heartburn. Of the 5 consumers (5%) who did choose Ome-Mg, one cited experiences of situational frequent heartburn (i.e., daily heartburn while traveling) as an appropriate use of the product. The majority (82%) of consumers who decided against using Ome-Mg understood that it was for frequent heartburn situations.

7.3.3 Summary

Results from this study indicate it is unlikely that consumers with infrequent heartburn would select Ome-Mg. When faced with the full array of currently available OTC products on the shelf plus OTC market-ready packages of the product, 95% of consumers with infrequent heartburn selected other OTC heartburn medications more appropriate for their occasional heartburn.

7.4 Usage Study Number 2001007

Actual Use Study 2001007, (hereinafter referred to as Study 007), was a three-month study conducted to evaluate the usage patterns and effectiveness of Ome-Mg in preventing frequent heartburn in a naturalistic setting. The label tested in the Actual Use trial was the same as that tested in Label Comprehension study 02255 (section 7.1).

The results of the Actual Use study support the safe use of Ome-Mg 20 by the OTC consumer with frequent heartburn, and support the ability of the consumer with frequent heartburn to safely use the product within the proposed OTC label directions.

7.4.1 Methods

The primary objective of this study was to investigate how consumers use Ome-Mg under proposed label conditions in a naturalistic OTC setting. A secondary objective was to investigate the effectiveness of Ome-Mg in a naturalistic setting.

The following indicators of consumer behaviors were examined:

- Percentage of subjects who correctly self-selected to use the study medication,
- Percentage of doses where no more than one tablet of study medication was taken per dose,
- Percentage of dosing days where no more than one dose and no more than one tablet of study medication was taken per day, and
- Percentage of subjects compliant with the 14-day dosing regimen and those who took between 11–14 doses of study medication (80% to 100% of regimen) in an 11–17 day period (80% to 120% of dosing directions).

If a subject took more than 14 doses of the product, they must have consulted a healthcare provider to be considered compliant with dosing directions. The study also evaluated physician contact prior to, during, and immediately after the trial.

Efficacy was assessed from diary entries made by the subjects at Visit 2. Return of heartburn and consumer behavior for treatment of frequent heartburn after the trial was assessed via follow-up telephone contact three months after study initiation for that subject.

Design: General Considerations

The three-month study was an open-label, multi-center study and evaluated use, as needed, of one dose level of Ome-Mg (Ome-Mg 20) over an approximate 8-week home-use period. Subjects were recruited via mall-intercept. Advertising was also used to recruit for this study. Subjects with a high-school education or less were REALM tested[51] to determine reading ability. Subjects determined for themselves whether the study medication was appropriate for them to use by reading the proposed package labeling (i.e., subjects self- selected whether the product was appropriate for them to use). Subjects also needed to agree to purchase product at intended

market price to participate, to mimic consumer decision-making about product use in the market. Information was collected from subjects on heartburn history, medication and physician history.

In total, 5060 consumers were approached at the mall and asked, "Do you get heartburn?" A total of 3061 consumers said no, and 698 consumers declined to participate in an interview. A total of 1301 consumers were interviewed as to self-selection, willingness to purchase medication/participate in a study, and to gather information on heartburn history (including medication and physician history). A total of 435 subjects declined to participate further in the trial. Primary reasons for not participating further included no interest in participating and the need to check with a healthcare provider before taking a new medication. In all, 866 subjects indicated they could use the product and were willing to purchase and use the product. Of those, 758 (89%) subjects used study medication and returned a diary.

Study medication was packaged in 14-count blisters. Subjects were told at multiple points during the process that they could buy more than one carton or could return to buy additional product. Subjects were permitted to buy up to 4 cartons of product during the trial.

The study site was open to each subject for 8 weeks after study initiation. Subjects could return to the site at any time during that period to purchase additional product. All kiosks were open during regular mall hours for the duration of the study.

Return of frequent heartburn, and consumer behavior regarding return of frequent heartburn after the trial, was assessed via follow-up telephone contact 4 weeks after the 8-week use period (12 weeks after the initial interview). Consumers were asked if their frequent heartburn returned and, if so, what they did.

Usage Patterns
Self-selection profiles, usage patterns, and physician utilization patterns were summarized for the entire study population as well as specifically for the subgroup with low reading ability and essential demographics.

Efficacy Evaluations
Efficacy of Ome-Mg was assessed at Visit 2 (8 weeks after study initiation) using a 5-point scale (poor, fair, good, very good, excellent).

Statistical Methods
Descriptive statistics were used to summarize the data. No tests of hypothesis were undertaken.

Study Population
Collectively, 5060 subjects were approached in the mall setting and 1301 agreed to participate in an interview. Of these, 866 identified the product as one they could use and were willing to purchase the product. This group constitutes the self-selection population, since they not only identified that they could use the product but also were willing to purchase. Twelve subjects were not permitted to purchase product: 4 had participated in a previous use trial with Ome-Mg, 4 withdrew informed consent, 3 were < 18 years of age, and 1 was pregnant. A total of 854 subjects purchased study medication and received a diary, and of these 758 subjects (89%)

used the product and returned a diary from which usage patterns were determined. The 758 subjects who returned a diary constitutes the use population.

7.4.2 Results

7.4.2.1 Demographics of the Self-Selection Population

Demographic data from the population of subjects who returned a diary (the most complete data set), including the 12 subjects not permitted to dose (n=770) were discussed in the study report. The population demographics are shown in Table 7.2.

A more conservative estimate of self-selection, however, is drawn from the population of subjects who purchased Ome-Mg and received a diary regardless of whether they returned a diary (n=866), since the willingness to purchase and use product is an important factor in self-selection. This ITT population is comprised of the subjects noted above as well as the 92 subjects who returned no diary, and 4 subjects who returned a blank diary.

Of the 866 subjects, 58% were female, 68% were Caucasian, 16% were Black, and 11% were Hispanic. Subjects averaged 48 years of age (range 18–91) and 8% of subjects had a low reading ability (8^{th} grade or less) as measured by the REALM test. More than 90% of subjects reported having heartburn for a year or more, with 90% of these reporting a history of frequent heartburn (heartburn 2 days per week or more) and 43% reporting heartburn 6–7 days per week. Forty percent (40%) had a prescription for a heartburn medication within the last year. More than 90% also reported taking an OTC heartburn medication.

Of the 92 subjects who purchased product but did not return a diary, 82 subjects (89%) were lost to follow up, 8 subjects (9%) reconsidered or withdrew consent, one subject experienced and AE (stomach pains) and discontinued study medication after 3 doses, and one subject was withdrawn by the investigator for an AE (burning in the chest, nausea/vomiting, dizziness, fever, and chills). These 92 subjects overall tended to have the same duration and history of frequent heartburn management as those who purchased product and did return a diary. These subjects also tended to have less frequent heartburn, be younger, more diverse, and have a slightly higher level of low literacy than those subjects who returned a diary. Most importantly, of those who purchased product but did not return a diary, 90 subjects (98%) purchased only 1 carton of product. Detailed demographic comparisons are found in Table 7.2.

TABLE 7.2
DEMOGRAPHIC COMPARISON OF SUBJECTS WHO PURCHASED PRODUCT AND RETURNED DIARY OR DID NOT RETURN DIARY
ACTUAL USE STUDY 007

	Subjects Who Purchased Product and Returned Diary (N=770)[a]	Subjects Who Purchased Product and Did Not Return Diary (N=92)
Gender (Female)	59%	52%
Race		
Caucasian	70%	50%
Black	14%	33%
Hispanic	10%	17%
Age Mean	49	39.6
Frequent HB	90%	81%
Low-Literacy by REALM	8%	11%
Duration of HB	91% ≥1 year	89% ≥1 year
Consulted Healthcare Provider Prior to Study	48%	54%
History of OTC Medication Use for HB	91%	88%
History of Rx Medication Use for HB	40%	34%
Purchased 1 carton	93%	98%

a Includes 12 subjects who self-selected to use Ome-Mg but were not permitted to purchase.

7.4.2.2 Self-Selection Patterns

In order to be counted as having correctly self-selected the product for use, subjects had to respond correctly to all six self-selection criteria. Overall, using all six criteria above, 81% correctly self-selected that Ome-Mg was appropriate for them to use for the ITT population (n=866). Using only those subjects who returned a diary (n=758), the correct self-selection rate for all six criteria was 83%.

In the subjects who returned a diary, more than 90% of the subjects had frequent heartburn on recall (heartburn or heartburn medication use 2 days per week or more). Detailed information on use patterns for self-selection variables are discussed more fully in section 7.5.3. For the remaining self-selection criteria:

- 99.9% of those who purchased Ome-Mg were not pregnant or nursing (1 pregnant)
- 99.6% were age 18 years or older (3 <18 years of age)

- 100% of the subjects did not have an allergy to Ome.
- 91.7% did not have a general condition warning symptom for which they had not already seen a physician (82 with a symptom)
- 98.1% did not take a medication listed in the drug-drug interaction section of the label (8 with one of these medications)

7.4.2.3 Consistency with Label Use Directions

Overall, 95% of subjects used only 1 carton (14 tablets or less) of Ome-Mg during the trial, 2% used 2 cartons, 1% used three cartons, and 1% used 4 cartons.

One Tablet Per Dose: Within the study, 96% of subjects took no more than 1 tablet per dose and 99% of all dosing occasions involved only 1 tablet.

No More than One Tablet per Day: Within the study, 91% of all subjects took no more than 1 dose per day and 98% of all dosing days involved only 1 tablet.

11–14 Tablets within 11–17 Days: Overall, 79% of the subjects dosed as directed on the label within protocol specifications (11–14 doses within 11–17 days) and/or had consulted with a physician about heartburn during the trial if they took more than 14 doses. Those who did not dose exactly according to the label did not dose in a manner that presents a risk.

Low-Literacy: The results noted did not differ appreciably in the low-reading ability group: 98% took no more than 1 tablet per dosing occasion, 99% took no more than 1 tablet per dosing day, and 73% dosed as directed by the label within protocol specifications.

Other Dosing Patterns: Dosing patterns different than above included:

- those who dosed fewer than 11 tablets (9%)
- those who dosed 11–14 tablets over fewer than 11 days (< 1%)
- those who dosed 11–14 tablets in > 17 days (9%; of these, 71% dosed in more than 30 days)
- those who dosed more than 14 doses (34 subjects, 5%; 41% of the subjects had contacted a healthcare provider during the trial; 85% of the subjects had contacted a healthcare provider for frequent heartburn before, during, or soon after the trial).

Overall, 53 subjects bought more than one carton of Ome-Mg, and 34 subjects returned a diary for more than 1 carton use. Of the subjects who purchased more than one carton but didn't return all diaries, a total of 96 cartons were purchased and 43 diaries were returned. Assuming worst case usage patterns for this group of subjects, use patterns would be reported as: 53 subjects may have used more than 1 carton of Ome-Mg (7%) and of these, 15 out of 53 subjects contacted a doctor during the trial (28%), since no actual use or doctor contact information is available for those subjects who did not return a diary.

Efficacy
An overall assessment of Good, Very Good, or Excellent was reported by 93% of subjects in the study.

Return of Heartburn
A total of 758 subjects returned a diary with product use information, and 649 subjects (85%) returned information at the 3-month follow-up telephone call. Of these, 43% did not have frequent heartburn return.

In those in whom frequent heartburn did return, one-third of the 370 subjects whose heartburn returned contacted a doctor and/or took a prescription medication, and 57% took only an OTC heartburn medication (65% took an antacid only, 26% took an H_2RA only, and 9% took both). An additional 8% of this population did nothing about their returning heartburn, and the remaining 10% made lifestyle changes.

In the total study population, at the 3 month telephone interview, all subjects continued to display behavior consistent with label use directions:

- 43% continued to be free of frequent heartburn symptoms
- 19% contacted a physician and/or took a prescription heartburn medication
- 32% took an OTC heartburn medication:
  - 21% took antacids
  - 8% took OTC H_2RAs
  - 3% took a combination of antacids and OTC
- 6% did nothing or made a lifestyle modification

Further, of the 373 subjects in whom frequent heartburn did return, only 16 (4%) had taken more than 14 tablets during the trial. Of these 16 subjects, 7 subjects (44%) contacted a doctor during the trial and 15/16 (94%) had consulted a physician about their frequent heartburn either prior to during or soon after the trial.

Thus, the return of frequent hearburn for 43% of subjects in the Actual Use study can be measured in months.

Comparison of Symptom Return Data
The efficacy trials 171 and 183 utilized a 14-day Ome-Mg 20 course of therapy in consumers with frequent heartburn. Return of the first heartburn symptom, of any severity, was evaluated using a daily diary card for 2 weeks immediately following cessation of therapy, regardless of whether or not they would have treated that episode. By Day 5 or 6, the rates of heartburn occurrence per day were similar in those who had received Ome-Mg 20 and those who had received placebo.

The Actual Use trial was an open label Ome-Mg 20 study in which 90% of subjects had frequent heartburn and 93% used only a single 14-day course of therapy. The assessment of return of

frequent heartburn during the Actual Use trial relied on the subject's self-definition of return of frequent heartburn, documented by response to a telephone interview 12 weeks after study initiation. The results of the Actual Use trial demonstrated that, when subjects self-defined "return of frequent heartburn", 57% had a return of frequent heartburn at the 3-month telephone interview following a 14-day course of Ome-Mg 20.

In assessing the literature in GERD patients for relapse after 14 days of Ome 20, results also suggest the time course to return of symptoms is measured in months. Three studies in the literature evaluated return of symptoms following a 14- or 28-day course of therapy with Ome 20.

In Carlsson *et al.*[72], the rate of heartburn recurrence in GERD patients following cessation of Ome 20 treatment for 4 to 8 weeks was 30% at 1 month following treatment and 75% at 6 months. Relapse was defined as self-reported by the patient to the investigators and was defined as recurrent symptoms of any severity on at least 2 days during the preceding week.

Lind *et al.*[73-74], reported that the rate of relapse following 4 to 8 weeks of Ome 20 in medically diagnosed GERD patients was less than 5% at 2 months following cessation of dosing. However, these subjects also used Ome "on demand" for their symptoms, although those who used placebo in the "on demand" portion of the trial had a relapse rate that exceeded 20% at 2 months. Relapse in these studies was defined as "discontinuation of treatment due to unwillingness to continue".

In a study by Bardhan *et al.*[62], GERD patients received 2 weeks of Ome 20 or an additional 2 weeks of therapy if symptoms had not abated at the initial treatment. Patients were followed for 1 year for relapse, defined as moderate to severe symptoms for at least 2 days in each of the preceding 2 weeks, or the need for 3 doses of antacids per day. Using this definition, relapse was 72% at 12 months. This study also noted that successful amelioration of symptoms after 2 weeks of Ome 20 was a powerful prognostic prediction of continued successful control ($p < 0.0001$): 68% of subjects with successful control of symptoms after 2 weeks required no more than three 14-day courses of therapy to control symptoms over the course of a year. Importantly, 33% of these subjects required only one 14-day course of Ome 20 for the entire year. Conversely, those subjects (24% of study) who required an initial course of therapy beyond 2 weeks tended to require ongoing maintenance treatment.

The following table details study information for "relapse" from several published studies, the efficacy studies 171/183, and the Actual Use study.

TABLE 7.3
COMPARISON OF RELAPSE ENDPOINTS IN STUDIES WITH GERD PATIENTS IN THE RX SETTING

VS. STUDIES WITH FREQUENT HEARTBURN SUBJECTS IN THE OTC EFFICACY AND USE STUDIES

Study	Treatments	Measurements	Relapse Endpoints
Carlsson[72]	4 or 8 weeks	Self-reported to investigator	Symptoms of any severity on 2 or more days in preceding week
Bardhan[62]	2 or 4 weeks	Self-reported to investigator	Symptoms, moderate to severe for at least 2 days in each of previous 2 weeks or 3 doses of AA per day
Lind[73-74]	4 or 8 weeks	Self-reported to investigator	Discontinuation due to unwillingness to continue
007	2 weeks	Self-reported by telephone interview	Symptoms defined as frequent heartburn (per label) by consumer
171/183	2 weeks	Daily diary cards	First symptom of any severity recorded day-by-day

The results in the Actual Use study are closer to that of the published literature, as are the means of data collection (recall), although definition of "relapse" differs somewhat from study to study. In contrast, the results of the efficacy studies, which asked subjects to record return of any symptom, of any severity, on a prospective day-by-day basis using a diary, makes not judgment about whether these subjects would then consider their "frequent heartburn" to have returned. This is a very different method of data capture and different definition of return of syptoms. Thus, resuts from the efficacy trials cannot be compared to the results from the Actual Use trial or published literature in GERD patients.

Summary of Self-Selection and General Use Behavior in the Actual Use Trial 007

The Actual Use study was designed to look at several endpoints of consumer behavior relative to the proposed OTC label for Ome-Mg.

The study showed that the label led to highly accurate self-selection. For each of the 6 self-selection criteria individually, appropriate choice was greater than 90% across the population. Over all 6 criteria, appropriate self-selection was 81% (n=866).

Subjects who elected to use the product were highly compliant with label dosing instructions. Of the 3 primary compliance parameters for dosing directions, more than 91% of subjects were consistent with taking no more than 1 tablet per dose and no more than 1 tablet per day. Overall, 79% of subjects were consistent with the label use directions and/or contacted a physician during the trial. Only 34 subjects (5%) took more than 14 doses in the trial. Of these, 14 subjects (41%) contacted a physician during the trial and 85% had contact with a physician about frequent heartburn either prior to, during, or soon after the trial. Only 5 subjects out of 758 took more than 14 doses and did not contact a doctor.

Overall, 95% of the subjects in the study only used 1 carton (≤ 14 tablets) of study medication.

Further, 93% of subjects rated the product good, very good, or excellent after the study.

The product label caused consumers to seek increased interaction with healthcare professionals regarding their heartburn. Overall, 75% of subjects in the trial had healthcare provider contact about heartburn prior to, during or soon after the trial. Nearly as many subjects consulted a physician in association with this 3-month trial (34%) as had contacted a physician during the entire year prior to the trial (48%), and 20% of subjects who had never previously contacted a physician about frequent heartburn did so during or soon after the trial for the very first time.

A 14-day regimen of Ome-Mg prevented frequent heartburn from returning in 43% of subjects at the 3-month follow-up interview. For those in who frequent heartburn did return, about one-third saw a physician and/or took a prescription medication, whereas 57% went to an available OTC medication (primarily antacids only, indicating that perhaps the heartburn that returned was less bothersome than had previously been experienced).

Importantly, this study does not provide evidence for significant ongoing chronic use, either daily or as needed for symptoms. Even among those whose frequent heartburn returned, only 16 (4%) used more than 14 tablets, and of those, all but 1 subject had physician contact regarding heartburn prior to, during or soon after the trial. Therefore, among 649 subjects, only 1 subject took more than 14 tablets, was not in any way under the care of a healthcare provider for frequent heartburn, and had frequent heartburn return.

Consumers demonstrated a high level of appropriate self-selection in meeting all criteria. Consumers also demonstrated a high level of compliance to the labeled dosing directions in both adherence to the dosing regimen, and appropriate consultation of the physician.

One SAE was reported in this trial, but was not attributed to Ome-Mg. Reported AEs were mild and transient, and showed the same general reporting frequency as in the worldwide post-marketing surveillance program for Ome-Mg. The study provides additional assurance that, in an OTC setting, Ome-Mg is safe for the prevention of frequent heartburn, and that consumers will be compliant with the proposed OTC labeling.

8. Overall Summary of Consumer Behavior (Label Comprehension and Actual Use Studies)

8.1 Ability of the Consumer to Correctly Self-Select the Product for Use

Results of Label Comprehension, De-Selection and Actual Use studies demonstrate consumers appropriately self-select on the basis of their frequency of heartburn.

Results of Label Comprehension Study 02255 demonstrate that 99% of consumers with frequent heartburn knew the product was appropriate for their heartburn, while 78% of the consumers with no heartburn/infrequent heartburn indicated correctly the product was not appropriate for their heartburn based on the product label.

Based on the results of Label Comprehension Study 02255, De-Selection Study 17859 was specifically designed to better understand behavior of the consumer with infrequent heartburn. This study was conducted in consumers with episodic (infrequent) heartburn to assess whether, when faced with the full array of available OTC heartburn remedies, this consumer group understood that Ome-Mg was intended to be used by those with frequent heartburn. Results from this study showed that 95% of consumers with infrequent heartburn correctly chose a product intended for occasional heartburn rather than Ome-Mg.

This was further substantiated by results from the Actual Use study, which showed that more than 90% of participants who purchased and used the product were consumers with frequent heartburn. These data from the label comprehension, de-selection, and actual use studies overall confirm the ability of consumers to appropriately self-select the product for use.

8.2 Ability of the Consumer Population to Use the Product as Directed

Label Comprehension and Actual Use studies indicate that consumers understood and complied with the label directions on how to take the product: to take one tablet a day, to take the product on 14 consecutive days, and to seek the advice of a doctor if they needed to take the product beyond 14 days.

Consumers with frequent heartburn and a low reading ability scored lower in some aspects in the Label Comprehension study. However, usage patterns in the Actual Use study were not appreciably different between the general population and those with a low reading ability for compliance with label directions, indicating that the label is well understood.

Results of Label Comprehension Study 02255 demonstrated that consumers understand the conditions in which they can use the product based on reading of the carton label. For the use directions, 95% of the subjects knew to take only 1 tablet per day and 91% knew not to take for more than 14 consecutive days without consulting a doctor.

In the Actual Use study, 96% of subjects took no more than 1 tablet per dose (99% of all dosing occasions were one tablet per dose) and 91% of all subjects took no more than one dose per day (98% of all dosing days contained only one dose). Overall, 79% of subjects dosed as directed on

the label within protocol specifications and/or had consulted with a physician about heartburn during the trial.

These results did not differ appreciably in the low-reading ability group. Ninety-eight percent (98%) took no more than 1 tablet per dosing occasion, 99% took no more than 1 dose per dosing day and 73% dosed as directed within protocol specifications.

In the Actual Use study, 93% of the subjects purchased only one carton of study medication. A total of 53 subjects (7%) bought more than 1 carton of study medication.

Of the subjects who purchased and used study medication, 95% only took 1 carton (≤ 14 tablets) of study medication. Importantly, most subjects took the product as a regimen; among the few subjects that took the product intermittently, no subject did so for more than 14 tablets. Only 34 subjects of 758 subjects recorded taking more than 14 doses. Of these, 41% had contacted a physician during the trial, per label directions. Thus, the great majority of subjects in this trial did not exhibit a behavior of long-term dosing without seeking medical advice.

8.3 Ability of the Consumer to Understand the Warnings on the Label

Warning statements for age, allergy, and pregnancy are well understood by the consumer. Consumer comprehension of drug-drug interactions is improved by providing brand names, and warning statements for contraindicated symptoms are improved by clarifying the label warning.

Age and Allergy: Label Comprehension Study 02255 indicated that consumers understood the product is intended for people age 18 years and older (97%) and that they should not use the product if they are allergic to Ome (94%). In the Actual Use study, no subjects who were allergic to Ome self-selected this as a product they could use. Three subjects (0.4%) less than 18 years of age indicated the product was appropriate for them to use.

Pregnancy: In Label Comprehension Study 02255, 91% of the pregnant/nursing women (n = 42) knew not to take Ome-Mg or to ask their doctor before use. In the Actual Use study, one pregnant woman out of 449 women indicated Ome-Mg was a product she could take.

Drug-Drug Interactions: In Label Comprehension Study 02255, 50% of the subjects who were taking a medication listed in the drug-drug interaction statement indicated they would ask a doctor prior to use. Correct self-selection increased to 82% when brand names of these medications were shown to the subjects. This confirms findings from previous Label Comprehension studies with Ome-Mg.

The label used in the Actual Use trial listed 6 medications in the drug-drug interaction statement: warfarin, phenytoin, diazepam, clarithromycin, itraconazole and ketoconazole. For reasons described in the safety section, only 3 of these are included in the proposed OTC label (warfarin, phenytoin, and ketoconazole).

Overall, 8 subjects (2%) entered the trial taking one of three medications listed in the proposed OTC label, and of these, 5 subjects (63%) consulted a physician during the trial about

concomitant use. There were no SAEs reported in this group. Given the high level of compliance with label directions, the consumer clearly understands the label warning.

General Condition Warning Symptoms: In Label Comprehension Study 02255, 41% of consumers with frequent heartburn and one or more general condition warning symptoms indicated they would not use the product or would ask a physician prior to use. Comprehension scores for the direct scenarios relative to general condition warning symptoms were high (93% to 99%). These data suggest the consumers understood the warning but perhaps did not feel the warning language applied to them.

Label Comprehension Study 12179 was conducted to evaluate consumer understanding of a clarified label for general condition warning symptoms warnings. The warning language was modified with consultation from gastroenterologists who proposed the original American College of Gastroenterology (ACG) guidelines from which the original language was derived[51]. The new language was intended to be simpler and to clarify that the warning is intended for those who have not had the symptom assessed by a physician. Comprehension testing among a specific cohort of consumers with both frequent heartburn and at least one of the label-related general condition warning symptoms showed a high level of understanding of the revised label. Overall, 81% of consumers had a correct self-selection response. In addition, comprehension of warning scenarios was 92% to 94%. Results of this research indicate consumers with general condition warning label symptoms understand the modified label.

In Actual Use Study 007, 82 subjects of 866 (9%) had a history of experiencing one or more general warning symptoms without having previously consulted a doctor about that symptom (70% had already spoken to a doctor). Seven of the 82 (9%) were previously or currently using prescription Ome and all took 14 or fewer tablets during the study. None of these subjects experienced a SAE associated with the condition defined by these general condition warning symptoms.

Based on the results of Label Comprehension Study 12179, the current proposed OTC label contains the modified language relative to the contraindicated symptoms in order to improve consumer comprehension.

8.4 Ability of Consumers to Understand When to Consult a Physician

Label Comprehension and Actual Use studies indicate that consumers understand when to contact a physician.

Results of Label Comprehension Study 02255 showed that 92% of subjects knew they should not take the product for more than 14 days unless directed by their physician.

In the Actual Use study, 48% of the subjects reported having seen a physician about their frequent heartburn in the prior year. During the study, 34% (255 subjects) consulted with a physician or had an appointment to discuss their heartburn. Therefore, in association with this study, nearly two-thirds as many subjects (34% versus 48%) consulted with a physician about their frequent heartburn as had done so in the entire year prior to the study. Importantly 20% of

the subjects who had never consulted a physician for frequent heartburn prior to the Actual Use study did so during the Actual Use study for the first time.

Of the 34 subjects who took more than 14 doses and returned a diary, 41% contacted a physician during the study and 85% contacted their doctor prior to, during, or soon after the study.

For subjects who reported a general warning sign when participating in the study, 91% had already seen a physician about the condition. For the 82 subjects who entered the Actual Use study and had not previously seen a physician about their general warning sign, of them (9%) were previously or currently using prescription Ome. All 82 subjects took 14 or fewer tablets during the study. None of these subjects experienced a SAE associated with the condition defined by these general condition warning symptoms, and reported AEs in this group were not different from those in the general study population.

8.5 Conclusion

In evaluating the complete program of consumer behavior trials, the label clearly communicates essential elements describing safe and appropriate use to the consumer seeking an OTC heartburn remedy. Consumers with infrequent heartburn will not tend to choose Ome-Mg, and when they do, tend to use the product episodically.

Consumers with frequent heartburn do tend to appropriately choose Ome-Mg, and comprehension and Actual Use testing demonstrates that they understand conditions of use, use directions, warning statements on the label, and when to seek healthcare provider supervision.

9. Risk/Benefit of Omeprazole Magnesium in the OTC Setting

This submission establishes that Ome-Mg is safe, effective, and suitable for prevention of the symptoms of frequent heartburn over 24 hours in an OTC setting. The pharmacodynamic profile of Ome provides 24-hour control of gastric acid production, making it an ideal candidate for the management of frequent heartburn.

Ome-Mg provides a clear and unique benefit to OTC consumers with frequent heartburn over currently existing therapies. Specifically, for consumers with heartburn two or more days a week, one 20 mg dose taken daily provides 24-hour symptom prevention. Statistical and clinically relevant efficacy is observed on the first day of dosing, on the last day of dosing, and across 14 days of consecutive daily dosing.

Omeprazole has been widely prescribed, globally, since 1988 for a broad spectrum of acid-related disorders. Since its introduction, Ome has been approved in over 125 countries and over 450 million courses of therapy have been prescribed. The long history of Ome safety and the demonstration of effectiveness in the target OTC consumer population confirm the suitability of OTC Ome at a dose of 20 mg.

Benefits to the OTC Consumer with Frequent Heartburn

The benefit of Ome-Mg 20 in the OTC setting is that the product provides highly effective prevention of heartburn frequent, as defined by no heartburn in a 24-hour period. This high level of preventive efficacy and long duration of action offers a new benefit to the OTC consumer with frequent heartburn, with the convenience of a single daily dose.

For nocturnal heartburn, first-dose effects were significantly better than placebo in one of two studies (8.0% for Ome-Mg 20). With consecutive daily dosing, both studies showed nocturnal heartburn prevention significantly greater than placebo by 10.2% and 10.7% of the days for Ome-Mg 20. This result combined with the known pharmacodynamic profile of Ome, supports the 24-hour duration of effect, since Ome-Mg 20 was dosed in the morning in these two multiple-dose trials.

Thus, the proposed label of 14 days consecutive use of Ome-Mg 20 for prevention of the symptoms of frequent heartburn for 24 hours fills the critical gap in OTC heartburn remedies for consumers with frequent heartburn.

A review of the recent literature confirms that 14 days provides significant for the amelioration of heartburn. Several 4-week studies in GERD patients treated with Ome 20 included symptom evaluations at both 2 and 4 weeks. In these studies, 14 days of therapy with Ome 20 was essentially as effective as 28 days in symptom management. More than 90% of patients who were heartburn-free at 4 weeks were already heartburn-free at 2 weeks.[53-63] These studies, coupled with recent publications of treatment guidelines for symptomatic reflux have as their stated objective symptomatic management. Several call for empiric therapy with acid-reducing agents in the OTC setting, and, if symptoms can be adequately managed, no further testing or maintenance therapy is required.[52,64-68]

Potential Risks of Ome-Mg in the OTC Setting

The potential for risks due to Ome-Mg in the OTC setting are very small. Ome-Mg has been shown to have a bioavailability profile similar to that of Ome. Safety was evaluated by considering AEs from clinical trials of both R_x Ome and OTC Ome-Mg indications, as well as worldwide post-marketing surveillance data for Ome and Ome-Mg. The sum total of the safety experience demonstrates Ome-Mg has a wide margin of safety and an excellent safety profile, especially during long-term use. Therefore, Ome-Mg is suitable for use and provides a very low risk in the OTC setting.

Since its introduction in 1988, Ome has been marketed through prescription in 125 countries. An estimated 450 million courses of patient therapy have been prescribed worldwide through June 2001, at daily doses ranging from 10 mg to 360 mg, and at therapeutic durations of 4–12 weeks, up to 15 years. Omeprazole's excellent safety profile, as presented in reviews of worldwide post-marketing surveillance and clinical trial experience, is established at doses comparable to and higher than those presented in this submission, and for periods of time which exceed the proposed OTC duration of use.

A review of R_x and OTC clinical trial AE data has not shown any significant issues or patterns that would prevent Ome-Mg from being used safely in an OTC setting. Evaluations of the OTC clinical trial AEs show Ome-Mg has a very similar safety profile as compared to placebo. These AEs in general are transient and not serious. The most frequently reported non-SAEs are diarrhea, headache, nausea, abdominal pain, and rash.

Gastric acid rebound is not a clinically significant concern with the short-term use (14 days) of Ome-Mg in the OTC setting.

In addition, there is no evidence there is a causal relationship between the use of Ome and the development of gastrointestinal cancer in humans.

Ome has an excellent safety profile. There are no additional safety concerns with unintended use in any population (e.g., children, pregnant or nursing women). There is minimal potential for drug-drug interaction, and limited concern about accidental overdose. Finally, there is no evidence of long-term toxicity, even at much greater exposures.

Safe Use in the OTC Setting (Absence of Physician)

An assessment of the introduction of Ome to the OTC market must include a careful evaluation of whether it can be safely used by consumers in the absence of physician involvement.

Omeprazole has a solid safety profile that provides assurance that use in the OTC setting will not give rise to adverse effects if any unintended use occurs. Although the drug is intended for use in adults, the data support safety even if used off-label by children or pregnant women. There is minimal potential for drug-drug interaction, and the proposed labeling takes the conservative step to label in cases where there is any conceivable risk. The data indicate that there is little risk for harm from accidental or intentional overdose due to the lack of serious adverse effects even at significant overdoses.

Although the Actual Use study shows high compliance with label directions, some individuals may continue to have symptoms, ignore the label directions, and continue to use Ome without physician involvement. It is the Sponsor's position that such behavior is clearly non-compliant with the label, and every reasonable step has been taken in product labeling to discourage it. However, it is necessary to assess the risk that such behavior might pose to individuals.

The inclusion of the general condition warning symptoms on the label and observations for the Actual Use trial showed that consumers understand the wording, and choose, on the basis of their experience with the symptom and physician consultation, whether or not such wording applies to them. Of the 82 subjects (out of 866) who entered the use trial with a general condition warning symptom, none had a SAE associated with the symptoms defined in the warning language. Reported AEs were mild, transient, and not different from those reported in the general population.

The types of non-compliant behavior, which need to be considered, range from continuous daily use to intermittent use of 14 days therapy. Literature[62] indicates that most people who may require more than an initial 14-day course of therapy will need only 1–3 courses of therapy to manage symptoms for a year. The study, in GERD patients, showed that successful amelioration of symptoms after 2 weeks of Ome 20 was a powerful prognostic prediction of continued successful control ($p < 0.0001$): 68% of subjects with successful control of symptoms after 2 weeks required no more than three 14-day courses of therapy to control symptoms over the course of a year. Importantly, 33% of these subjects required only one 14-day course of Ome 20 for the entire year. Conversely, subjects (24% of the study) who required an initial course of therapy beyond 2 weeks tended to require ongoing maintenance treatment. These results are very similar to those found in the Actual Use trial when return of frequent heartburn was evaluated after a single 14-day Ome-Mg 20 regimen in the OTC setting. Use of Ome-Mg in this manner, without physician oversight, is unlikely to present significant risk.

Any concern is not with those individuals who may have acid-related disorders, such as erosive esophagitis. If their symptoms are well controlled, this would be the same therapeutic endpoint that a treating physician would monitor. Ome-Mg will be a better OTC treatment than currently available OTC heartburn remedies (without physician prescription). Relief of frequent heartburn symptoms and healing of erosive esophagitis, if present, is significantly faster with Ome than with H_2RAs. If symptoms are not well controlled with Ome-Mg, each and every product re-purchase will provide another reminder in the product labeling that a physician should be consulted.

Concerns about long-term use without physician involvement would be for individuals who continue to experience symptoms over a long period of time (> 12 years).[68,75]

Available data show that the potential for use without physician involvement is actually limited. Surveys show that up to 75% of individuals with frequent heartburn have seen their physician regarding frequent heartburn and that as severity of symptoms change or increases, so do physician visits.[2,7-8,10,12,16-17,27-34] In the Actual Use study, 65% of subjects reported talking to their physician about their heartburn in the last 5 years. The Actual Use study suggests that the proposed product labeling results in increased physician contact: in the 3 months of the trial,

two-thirds as many subjects saw a healthcare provider about frequent heartburn as had done so in the prior year (34% vs. 48%), and 20% of those subjects who had never seen a physician about frequent heartburn did so for the first time while using the labeled product. Furthermore, analysis of healthcare provider contact following the OTC introduction of H_2RAs shows that such interactions remained unchanged or increased.[35-38]

Conclusion

The benefits of OTC access to Ome-Mg for the prevention of the symptoms of frequent heartburn for 24 hours clearly outweigh potential risks. The pharmacodynamics of the drug, safety and efficacy results of the clinical program, ability of the consumers to use the product safely without medical supervision, and low risk of potential negative consequences coupled with the excellent safety profile of Ome makes this an excellent product to be used for the prevention of the symptoms of frequent heartburn in the OTC setting.

The proposed label for Ome-Mg 20 in an OTC setting is congruent with the supportive data and safety profile.

- Target Population: Efficacy and behavioral studies were conducted in consumers with frequent heartburn, the target population specified on the OTC label. Satisfactory management of frequent heartburn is clearly an unmet consumer need, as currently available OTC heartburn medications simply do not have the necessary pharmacology to meet the demands of frequent heartburn.
- Indication: The indication on the proposed label is for the prevention of the symptoms of frequent heartburn for 24 hours. Pharmacokinetic and pharmacodynamic data support the 24-hour duration of action. Efficacy data confirm substantial benefit for 24-hour prevention of frequent heartburn after Day 1 and across 14 days of dosing.
- Use Directions: Use directions call for 1 tablet, taken every morning for 14 consecutive days. Fourteen days consecutive use was the duration tested in the efficacy trials, and the proposed label tested in the Actual Use trial showed a high level of compliance. Fourteen days Ome 20 therapy has been shown to have a clear benefit to the consumer with frequent heartburn, and is long enough in the OTC setting.
- Healthcare Provider Consultation: If a 14-day course of Ome-Mg 20 does not adequately manage frequent heartburn, consumers should consult a healthcare professional, as stated in several places on the label.
- Warnings: The label contains several warning statements relative to pregnancy, concomitant medications, and general warning signs. Safety data indicates there is no risk should unintended use occur in these populations. Label comprehension and Actual Use studies show the label language is well comprehended.

In conclusion, Ome-Mg is an excellent and unique OTC candidate to meet the demands of consumers with frequent heartburn.

10. References

1. P&G MRD#US983190, data in Sponsor's file Yankelovich.

2. Oliveria SM, Christos PJ, Talley NJ, Dannenberg AJ. Heartburn risk factors, knowledge, and prevention strategies: a population-based survey of individuals with heartburn. Arch Int Med 1999;159:1592–1598.

3. P&G MRD#US972782, data in Sponsor's file.

4. Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. Dig Dis 1976;21(11):953–956.

5. ACNielsen/SmithKlineBeecham Survey. Profile of consumers in need: people with sour stomachs, by demographics. Prog Groc 1995;74(9):98–99.

6. P&G MRD Number US 996633. Data in Sponsor's file.

7. P&G MRD Number US 004463. Data in Sponsor's file.

8. NHBA Mail Survey Feb–Mar 2000. Data in Sponsor's file.

9. Hurlimann S, Abbhül B, Inauen W, Halter F. Comparison of acid inhibition by either oral high-dose ranitidine or omeprazole. Aliment Pharmacol Ther 1994;8:193–201.

10. Yankelovich Partners n=507 FHB. Data in Sponsor's file.

11. P&G MRD Number US 980425. Data in Sponsor's file.

12. P&G MRD Number US 011624. Data in Sponsor's file.

13. Bennett JR, Castell DO. Overview and symptom assessment. The Esophagus, 3rd Edition, chapter 2. Philadelphia, Pennsylvania: Lippincott, Williams, & Wilkins, 1999.

14. Joelsson B, Johnsson F. Heartburn – the acid test. Gut 1989;30:1523–5.

15. Locke GR, Talley NJ, Fett SL, *et al.* Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997;112(5):1448–56.

16. American Gastroenterological Association and the Gallup Organization, Inc. A Gallup survey on heartburn across America, Princeton, NJ:1988, 2000.

17. Acuity and Harris Interactive Online Survey. Dissatisfaction with heartburn drugs common. Reuters 12/11/00 (4200 PPI users).

18. Environmental Nutrition. Heartburn: why it occurs, and ways to gain relief. Environmental Nutrition 1988;6:8.

19. Kurata JH, Nogawa AW, Chen YK, Parker CE. Dyspepsia in primary care: perceived causes, reasons for improvement, and satisfaction with care. Journal of Family Practice 1997;44(3):281–8.

20. P&G MRD Number US 972781. Data in Sponsor's file.

21. P&G MRD Number US 974088. Data in Sponsor's file.

22. P&G MRD Number US 980801. Data in Sponsor's file.

23. Robinson M, Earnest D, Rodriguez-Stanley S, *et al.* Heartburn requiring frequent antacid use may indicate significant illness. Arch Intern Med 1998;158:2373–6.

24. Jones RH, Hungin APS, Phillips J, Mills JG. Gastro-oesophageal reflux disease in primary care in Europe: clinical presentation and endoscopic findings. European Journal of General Practice 1995;1:149–54.

25. Murdock RH, Pappa KA, Geifer EE, *et al.* Endoscopic findings in a target population for over-the-counter treatment of heartburn. [abstract]. Gastroenterology 1994;106(4):A146.

26. Nyrén O, Adami HO, Gustavsson S, Lööf L. Excess sick-listing in nonulcer dyspepsia. J Clin Gastroenterol 1986;8(3):339–45.

27. Drossman DA, Li Z, Andruzzi E, *et al.* U.S. Householder survey of functional gastrointestinal disorders: prevalence, sociodemography, and health impact. Digestive Diseases and Sciences 1993;38(9):1569–80.

28. Jones R, Bytzer P. Review article: acid suppression in the management of gastro-oesophageal reflux disease—an appraisal of treatment options in primary care. Aliment Pharmacol Ther 2001;15:765–72.

29. Dent J, Brun J, Fendrick AM, *et al.* An evidence-based appraisal of reflux disease management — the Geneva workshop report. Gut 1999;44(Suppl 2):S1–16.

30. Howden CW, Henning JM, Huang B, *et al.* Management of heartburn in a large, randomized, community-based study: comparison of four therapeutic strategies. The American Journal of Gastroenterology 2001;96(6):1704–10.

31. Farup C, Kleinman L, Sloan S, *et al.* The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. Arch Intern Med 2001;161:45–52.

32. Revicki DA, Crawley JA, Zodet MW, *et al.* Complete resolution of heartburn symptoms and health-related quality of life in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1999;13:1621–30.

33. Smout AJ,. Endoscopy-negative acid reflux disease. Alimen Pharm Therapeutics 1997;11(Suppl 2):81–5.

34. Lydeard S and Jones R. Factors affecting the decision to consult with dyspepsia: comparison of consulters and non-consulters. J Royal College of General Practitioners 1989;39:495–8.

35. Andrade, SE, Gurwitz JH, Fish LS. The effect of an R_x-to-OTC switch on medication prescribing patterns and utilization of physician services. Medical Care 1999;37(4):424–30.

36. Shaw M, Talley NJ, Adlis S, *et al*. Development of a digestive health status instrument: tests of scaling assumptions, structure and reliability in a primary care population. Aliment Pharmacol Ther 1998;12:1067–78.

37. Shaw MJ, Fendrick AM, Kane RL, *et al*. Self-reported effectiveness and physician consultation rate in users of over-the-counter histamine-2 receptor antagonists. The American Journal of Gastroenterology 2001;96(3):673–6.

38. MedStat Marketscan Database 2000. Data in Sponsor's file.

39. Lindberg P, Brandstrom A, Wallmark B, Mattsson H, Rikner L, Hoffmann K-J. Omeprazole: the first proton pump inhibitor. Med Res Rev 1990;10:1–54.

40. Andersson T. Pharmacokinetics, metabolism, and interactions of acid pump inhibitors; focus on omeprazole, lansoprazole, and pantoprazole. Clin Pharmacokinet 1996;31:9–28.

41. Andersson T. Expert Report. Omeprazole; with special reference to drug interaction studies in combinations with metronidazole and clarithromycin, amoxicillin and metronidazole, or amoxicillin and clarithromycin. Clinical pharmacological documentation. May 1998.

42. Andersson T, Cederberg C, Edvardsson G, Heggelund A, Lundborg P. Effect of omeprazole treatment on diazepam plasma levels in slow vs. normal rapid metabolizers of omeprazole. Clin Pharmacol Ther 1990; 47:79–85.

43. Astra Hässle Clinical Study Report: Influence of cimetidine on the pharmacokinetics of omeprazole. (Study No. I-212) December 1982.

44. Andersson T, Bergstrand R, Cederberg C. Influence of acid secretory status on absorption of omeprazole from enteric coated granules. Br J Clin Pharmacol 1991;31:275–8.

45. Andersson T, Andren K, Cederberg C, *et al.* Bioavailability of omeprazole as enteric-coated (EC) granules in conjunction with food on the first and seventh days of treatment. Drug Invest 1990;2:184–188.

46. Lind T, Cederberg C, Ekenved G, *et al.* Effect of omeprazole – a gastric proton pump inhibitor – on pentagastrin-stimulated acid secretion in man. Gut 1983;24:270–276.

47. Lind T, Cederberg C, Ekenved G, *et al.* Inhibition of basal and betazole- and sham-feeding-induced acid secretion by omeprazole in man. Scand J Gastroenterol 1986;21:1004–1010.

48. Londong W, Londong V, Cederberg C, *et al.* Dose-response study of omeprazole on meal-stimulated gastric acid secretion and gastrin release. Gastroenterol 1983;85:1373–1378.

49. Lind T, Cederberg C, Axelson M, *et al.* Long-term acid inhibitory effect of different daily doses of omeprazole 24 hours after dosing. Scand J Gastroenterol 1986; (Suppl 118):137–138.

50. Lind T, Cederberg C, Forsell H, *et al.* Relationship between reduction of gastric acid secretion and plasma gastrin concentration during omeprazole treatment. Scand J Gastroenterol 1988;23:1259–1266.

51. Davis TC, Long SW, Jackson RH, *et al.* Rapid Estimate of Adult Literacy in Medicine: A Shortened Screening Instrument. Clinical Research and Methods. 1993;25:391–5.

52. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Arch Inter Med 1995;155:2165–73.

    DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 1999;94(6):1434–1442.

53. Chiba N, DeGara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II-IV gastroesophageal reflux disease: a meta-analysis. Gastroenterol 1997;112:1789–1810.

54. Castell DO, Richter JE, Robinson M *et al.* Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. Am J Gastro 1996;91(9):1749–1757.

55. Richter JE, Peura DA, Benjamin SB *et al*. Efficacy of omeprazole for the treatment of symptomatic acid reflux disease without esophagitis. Arch Int Med 2000;160:1810–1816.

56. Lind T, Havelund T, Carlsson R *et al.* Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. Scand J Gastroenterol 1997;32:974–979.

57. Bate CM, Griffin SM, Keeling PW *et al.* Reflux symptom relief with omeprazole in patients without unequivocal oesophagitis. Aliment Pharm Ther 1996;10:547–555.

58. Corinaldesi R, Valentine M, Belaiche J *et al*. Pantoprazole and omeprazole in the treatment of reflux oesophagitis: a European multicentre study. Aliment Pharm Ther 1995;9:667–671.

59. Mossner J, Holscher AH, Herz R, Schneiders A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. Aliment Pharm Ther 1995;9:321–326.

60. Hatleback JG, Hyggen A, Madsen PH *et al*. Heartburn treatment in primary care: randomised, double-blind study for 8 weeks. Br Med J 1999;319:550–553.

61. Richter JE, Kahrilas P, Johanson J *et al*. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomised controlled trial. Am J Gastro 2001;96:656–665.

62. Bardhan KD, Muller-Lissner SA, Bigard MA *et al*. Symptomatic gastro-oesophageal reflux disease: double-blind controlled study of intermittent treatment with omeprazole or ranitidine. Br Med J 1999;18:502–507.

63. Bardhan KD, Rensberg C. Comparable clinical efficacy and tolerability of 20 mg pantoprazole and 20 mg omeprazole in patients with grade I reflux oesophagitis. Aliment Pharm Ther 2001;15:1585–1591.

64. Katz PO. Treatment of gastro-esophageal reflux disease: use of algorithms to aid in management. Am J Gastro 1999;94(11):S3–S10.

65. Jones R, Bytzer P. Acid suppression in the management of gastro-oesophageal reflux disease – an appraisal of treatment options in primary care. Aliment Pharm Ther 2001;15:765–772

66. Fendrick MA. Management of patients with symptomatic gastroesophageal reflux disease" a primary care perspective. Am J Gastro 2001;96(8):S29–S33.

67. Moss SF, Arnold R, Tytgat GNJ *et al*. Consensus statement for management of gastroesophageal reflux disease. J Clin Gastro 1998;27(1):6–12.

68. Shaheen N, Ransohoff DF. Gastroesophageal reflux disease, Barrett's esophagus and esophageal cancer. JAMA 2002;287(15):1972–1986.

69. Fackler WK, Ours TM, Vacai MF, Richter JE. Long-term effect of H_2RA therapy on nocturnal gastric acid breakthrough. Gastroenterol 2002;122:625–632.

70. Tefera S, Hatlebakk JG, Berstad A. Stability of gastric secretory inhibition during 6-month treatment with omeprazole in patients with gastroesophageal reflux disease. AM J. Gastro 2001;96(4):969–974.

71. Sharma BK, Walt RP, Pounder RE, *et al*. Optimal dose of oral omeprazole for maximal 24 hour decrease of intrafastric acidity. Gut 1984;25:957–964.

72. Carlsson R, Dent J, Watts R, *et al.* Gastro-oesophageal reflux disease in primary care: an international study of different strategies with omeprazole. Eur J Gastro Hepato 1998;10:119–124.

73. Lind T, Havelund T, Carlsson R, *et al.* The effect of omeprazole 20 mg and 10 mg daily on heartburn in patients with endoscopy negative reflux disease treated on an on-demand basis. Gastroenterol 1996;110(4):A178.

74. Lind T, Havelund T, Lundell L, *et al.* On-demand therapy with omeprazole for the long-term management of patients with heartburn without esophagitis – a placebo controlled randomized trial. Aliment Phar Ther 1999;13:907–914.

75. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic GERD as a risk factor for esophageal adenocarcinoma. NEJM 1999;340:825-831.