Division of Gastrointestinal and Coagulation Drug Products: Medical Officer's Preliminary Efficacy Assessment for background packet for advisory committee review

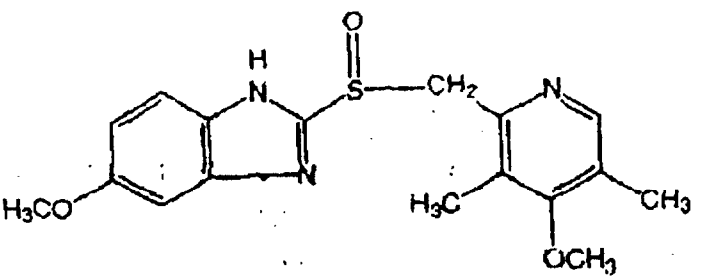
NDA # 21,229

Submission Date: January 27, 2000

Generic name: Omeprazole magnesium (OM)

Proposed trade name: Prilosec 1

Chemical name and structure: 5 methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl] 1H-benzimidazole



Sponsor: AstraZeneca LP
Agent: Procter & Gamble Co.

Pharmacologic category: Proton pump inhibitor gastric acid inhibitor

Proposed indications:
1. For relief of heartburn (HB), acid indigestion and sour stomach
2. For prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages or associated with events such as stress, hectic lifestyle, lying down, or exercise

Proposed directions:

For relief of symptoms: swallow 1 tablet with a glass of water
For prevention of symptoms for 24 hours: swallow 1 tablet with a glass of water anytime during the day, or if you prefer one hour before those events associated with occasional heartburn, such as consuming food and beverages, stress, hectic lifestyle, lying down or exercise
Do not take more than 1 tablet a day
Do not use for more than 10 days in a row unless directed by a physician
Dosage forms and route of administration: 20.6 mg capsule orally

Related drugs: Omeprazole delayed release capsules (10, 20 and 40 mg)

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6. Clinical background:

OM is a new formulation of omeprazole. It has been approved within the past two years in 25 countries and is marketed in 12 countries as of the submission date of January 27, 2000. Safety and efficacy of this formulation is the topic of the current NDA.

It is marketed as 10 and 20 delayed release capsules. Currently approved indications include the treatment of:

1. duodenal ulcer including eradication of H. pylori infection as part of combination therapy
2. gastric ulcer
3. Treatment of gastroesophageal reflux disease (GERD) including symptomatic GERD, erosive esophagitis, maintenance of healing of erosive esophagitis
4. Hypersecretory states

Heartburn is defined in Dorland's medical dictionary (26th edition) as, "an esophageal symptom consisting of a retrosternal sensation of warmth or burning occurring in waves and tending to rise upward towards the neck; it may be accompanied by a reflux of fluid into the mouth". While other descriptions may be applied, the concept of substernal chest pain usually of a burning nature is widely understood in the medical and lay populations While such symptoms may originate from cardiac or musculoskeletal etiologies it is accepted that the study of and clinical use of treatments of HB of esophageal origin can be successfully distinguished in the vast majority of cases from HB type symptoms of other etiologies.

In the majority of instances HB is associated with the upward movement of gastric acid into the esophagus (gastroesophageal reflux). Acid as well as other noxious agents such as bile or other dietary constituents may reflux. Although chemical agents are the direct trigger to most HB symptoms, the primary mechanism is felt to be a motility disorder allowing for gastric contents to reflux from the stomach into the esophagus. Thus, physiologically active compounds that lower the lower esophageal sphincter pressure as well as acid and acid stimulants are typical triggers of HB. Mechanical effects that increase reflux also can trigger HB. These include tight fitting clothes, horizontal position, and increased intra-abdominal pressure (due to large volume meals or obesity). Emotional triggers are also felt to induce HB although the mechanism is less well understood. Thus, the relationship between acid reflux and HB symptoms triggered by emotional triggers is less well understood. Response of emotion induced HB to acid reduction cannot be extrapolated from data on triggers that correlate more clearly to acid reflux.

Dietary and lifestyle changes are considered to be the initial preventive therapy for HB. Nonetheless, over the counter (OTC) treatments for HB are among the most widely used OTC medications. These include acid lowering agents, topical treatment to the esophagus and acid neutralizing compounds. There are currently four histamine-2 receptor antagonists (H2RA) approved for the treatment and prevention of heartburn. These drugs are felt to act by lowering the production of gastric acid. The doses approved for OTC use of the H2RA s is ½ the prescription dose approved for the treatment of pathology such as GERD and gastroduodenal ulcer disease. The degree of acid suppression by these compounds at the doses approved for OTC use is far below the physiologic acid suppressive effect of OM at the proposed dose. Furthermore, the duration of acid suppression is considered to be longer for proton pump inhibitors since they are permanently bound to the parietal cell membrane hydrogen/potassium ATPase enzyme system. Acid suppression is 50% even at 24 hours following a dose due to this permanent inhibition that requires new enzyme/receptor production by the cell to resume acid production. This unique mechanism of action and pharmacodynamic property mandate a thorough evaluation of the potential use and safety of OM in the OTC setting. Such evaluations are to be found in the safety reviews by Drs. Avigan and the reviews by the Division of OTC drugs. The present review is limited to the efficacy of the proposed dose and formulation in the treatment and prevention of HB.

HB is not always associated with particular food or beverages and not always temporally related to mealtime. Meal induced heartburn however, has been the most common study model used in the efficacy studies that have formed the basis for approval of the currently

marketed HB prevention medications. The prevention studies have been in the setting of meal induced HB and the instructions for use reflect this fact. Single episode prevention can only be accepted for meal induced episodes as no evidence has been presented that provides evidence of efficacy of single dose HB prevention for other settings of HB. The inherent differences between meal induced HB and other triggers such as supine position, emotions, and exercise prevents extrapolation of efficacy. The efficacy of currently approved drugs for HB has required enriching the study population with subjects that have previously responded to antacids or H2RA s. Furthermore, the treatment or challenge meal used to assess the ability to prevent meal induced HB have been highly exaggerated meals including very high fat and spicy meals with high caffeine beverages. Treatment study settings have primarily involved diary based home usage unrelated to HB precipitants. The label for OTC HB treatments therefore doses not specify the cause of the HB being treated. The currently proposed label for OTC omeprazole includes changes compared to the currently approved OTC HB medications. The proposed label indications include:

1. For relief of heartburn (HB), acid indigestion and sour stomach
2. For prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages or associated with events such as stress, hectic lifestyle, lying down, or exercise

Proposed directions:

For relief of symptoms: swallow 1 tablet with a glass of water
For prevention of symptoms for 24 hours: swallow 1 tablet with a glass of water anytime during the day, or if you prefer one hour before those events associated with occasional heartburn, such as consuming food and beverages, stress, hectic lifestyle, lying down or exercise

OTC H2RA indications:

Indications:

1. *For the relief of heartburn, acid indigestion and sour stomach*
2. *For the prevention of heartburn, acid indigestion and sour stomach brought on by consuming food and beverages*

Directions:

***For relief of symptoms:** take one tablet with water*
***For prevention of symptoms brought on by consuming food and beverages:** take one tablet with water (60, 30, 15 or 0 minutes; depending on the specific product)*

The addition of 24-hour prevention for up to 10 days continuously suggests that the target population for this product is **not** the episodic heartburn sufferer. **Daily, all day**

"prevention" of heartburn is the goal of treatment therapy for non erosive GERD.
The sponsor states in the summary volume of the submission:
" Episodic treatment of heartburn is different from the treatment of gastroesophageal reflux disease (GERD). GERD represents a distinct physician-diagnosed chronic disease characterized by acid reflux and attendant symptoms, usually heartburn or regurgitation with evidence of erosive esophagitis in 33% of patients and requires 4-8 weeks treatment with omeprazole. Although the symptom of heartburn is associated with GERD, it is not indicative of the disease. Many consumers have acute episodic heartburn." (page 40 of sponsor's summary volume)

The sponsor does not in the summary or elsewhere explain how the proposed indication is differentiated medically or symptomatically from GERD or how the study population in the submission was differentiated from GERD. Such an explanation is critical if the sponsor's position that GERD is a distinct physician diagnosed chronic disease is correct. The sponsor's direct to consumer advertisements reinforce this point. The following quote appeared in a full-page advertisement in the PARADE magazine of the Washington Post dated July 23, 2000:
"If you suffer from painful persistent heartburn two or more days a week, event though you've treated it with medicine or changed your diet, you may have acid reflux disease, a potentially serious condition. Ask your doctor if Prilosec is right for you."

A discussion of the optimal OTC dose of OM must be based on whether the OTC indication continues to be based on individual episodes, or whether all day prevention which is not by definition episode based, is to become an OTC use. The sponsor discusses the chose of dose in the context of maximal efficacy and acute adverse event profiles, without reference to past precedent.

An additional point:

The efficacy data in the current submission supporting episodic HB treatment and prevention is associated with a compound with a pharmacologic half-life much longer than the currently marketed HB medications. Thus carry over effects from prior doses of OM will need to be considered in evaluating the results of the submitted studies.

Reviewer's summary:

1. *The sponsor must clearly define the differences between nonerosive GERD and HB. The lack of physician diagnosis in the past is an artificial differentiation scientifically despite the practical value of using this as exclusion criteria for purposes of defining a study population.* ***If no differentiation is possible, approval of this product as proposed in the label will define GERD as an OTC condition. Such a change in status mandates thoughtful consideration by the Agency.***

2. *The sponsor must support new indications of HB "prevention caused by hectic lifestyle, stress, lying down or exercise" with clinical data. Extrapolation from meal induced HB data is inadequate.*
3. *Carryover effect may be a confounding effect in multidose trials of OM in view of the unique pharmacodynamic properties of this drug.*
4. *Optimal dose may differ depending on the approved indication.*

6.1 Foreign experience

Note Swedish experience

6.2 Human pharmacology, pharmacokinetics and pharmacodynamics

Discuss with Suleiman:

1. carry-over effects in PD study #129
2. intragastric pH results at 1 and 5 hours (table #10 section 7.4.1 of Biopharm submission
3. discuss lack of PD rationale for episodic use and compare to episodic PD data on H2RA s.
4. Protocol 131: lack of increase in intraesophageal pH over 5 hours **in HB subjects**

7. Description of clinical data sources

The current submission contains 6 controlled efficacy studies designed to support the proposed indications.

Heartburn prevention:

a. 005 and 006 were single dose meal induced HB prevention studies
b. 171 and 183 were 2-week multi-dose studies of HB prevention with the use daily dosing

Heartburn treatment:

c. 092 and 095 were 2-week multi-dose HB treatment studies with PRN at home use of OM limited to a single daily dose as needed with rescue medication allowed

8. Clinical Studies

Dose: The doses chosen were based on the efficacy of Omeprazole in previous studies. The sponsor stated that a 5-mg dose was considered but not included because it shows poor ability to inhibit gastric acid suppression. Two exploratory studies were done with

OM 20 mg (086, 087). The sponsor submitted several studies of the pharmacodynamic properties of OM 5, 10, and 20 mg.
Tables 1through 6 and figure 1 suggest that there is little difference between 5, 10, and 20 mg of omeprazole in the parameters studied. Table 5 displays the most clinically relevant pharmacodynamic measurement, percentage of time intra-esophageal pH< 4. The intrinsic pharmacodynamic property of relatively slow onset of action is of note when considering a drug intended for use in episodic symptoms.

Table 1

Intragastric pH at One Hour Post Dose
Descriptive statistics

	OME 20	OME 10	OME 5	Placebo
-- n	30	32	32	32
-- Mean	1.39	1.41	1.42	1.44
-- Standard Deviation	0.28	0.28	0.29	0.25
-- Median	1.42	1.42	1.45	1.40
-- Minimum	0.72	0.91	0.81	0.91
-- Maximum	2.00	2.40	2.10	2.09

Table 2

Intragastric pH at One Hour Post Dose
Least Squares Estimates and 95% Confidence Intervals for the Treatment Means

Treatment	Estimate	95% confidence interval	
		Lower Bound	Upper Bound
OME 20	1.38	1.28	1.47
OME 10	1.41	1.32	1.50
OME 5	1.42	1.33	1.51
Placebo	1.44	1.34	1.53

Table 3

Intragastric pH Over Five Hours Post Dose
Descriptive Statistics

	OME 20	OME 10	OME 5	Placebo
-- n	30	32	32	32
-- Mean	1.80	1.63	1.67	1.53
-- Standard Deviation	0.55	0.38	0.53	0.29
-- Median	1.73	1.65	1.61	1.56
-- Minimum	0.81	1.02	0.87	0.92
-- Maximum	3.71	2.65	4.16	2.12

Table 4

Intragastric pH Over Five Hours Post Dose
Least Squares Estimates and 95% Confidence Intervals for the Geometric Means by Treatment

Treatment	Estimate	95% confidence interval	
		Lower Bound	Upper Bound
OME 20	1.72	1.60	1.85
OME 10	1.61	1.50	1.72
OME 5	1.61	1.50	1.73
Placebo	1.49	1.39	1.59

Table 5

Percentage of Time Intra-esophageal pH < 4
Descriptive Statistics

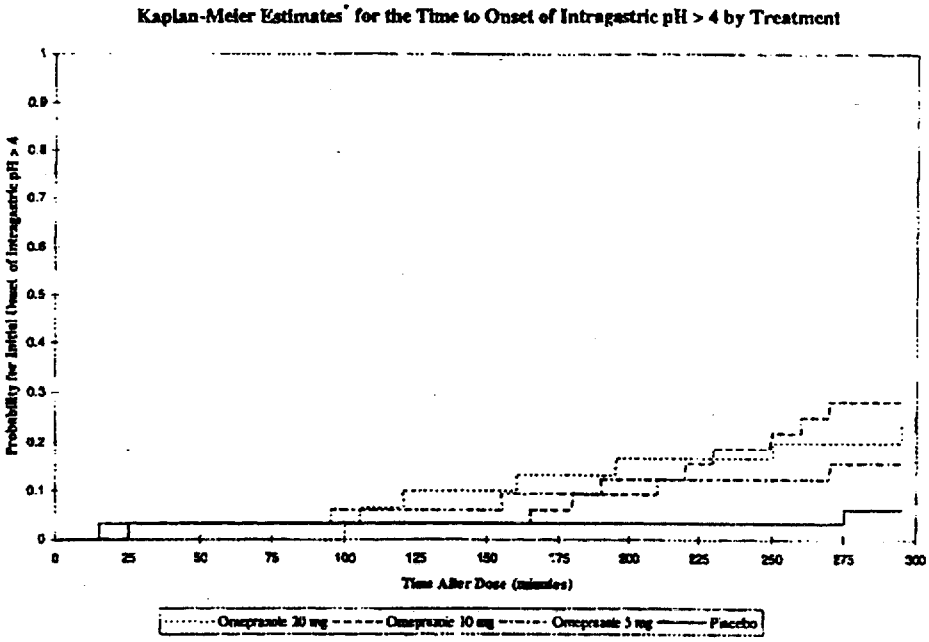
	OME 20	OME 10	OME 5	Placebo
-- n	30	32	32	32
-- Mean (%)	1.65	1.62	2.09	4.95
-- Standard Deviation (%)	1.93	2.16	2.39	15.95
-- Median (%)	0.88	0.61	1.27	1.30
-- Minimum (%)	0.00	0.00	0.00	0.00
-- Maximum (%)	5.73	8.91	10.43	90.85

Table 6

Percentage of Time Intra-esophageal pH < 4
Least Squares Estimates and 95% Confidence Intervals for the Geometric Means by Treatment

Treatment	Estimate	95% confidence interval	
		Lower Bound	Upper Bound
OME 20	0.043	0.007	0.277
OME 10	0.068	0.011	0.409
OME 5	0.036	0.006	0.214
Placebo	0.040	0.007	0.237

Figure 1



Reviewer's Comment: The pharmacodynamic data suggests that the three doses of OM may not significantly differ over the first 5 hours post-dose. This is a relevant treatment and episodic prevention interval. If the efficacy data in the current submission suggests an absence of a dose response relationship, this issue would need to be reassessed to ensure that excessive dose is not marketed.
Pharmacodynamic data suggests that OM may not be best suited for single dose use as needed for prevention or relief within the first hours post dose. Correlation between pharmacodynamic and clinical effects is the subject of the clinical studies. Unfortunately the sponsor did not study 5-mg

8.1 Indication : Heartburn treatment:

Studies 092 and 095 were identical in design and amendment. They were performed simultaneously: first subject enrolled February 17, 1998 and last subject's observation June 1998
In view of the identical study design these studies will be described together. Results will be shown side by side and conclusions will be integrated.

8.1.1 Trials 092, 095
8.1.1.1 Objective/Rationale

The primary objective of the study as described by the sponsor was to:
"Compare a single dose of OM 20.6 mg to placebo in providing sustained complete

relief of episodic heartburn for the first episode"
The secondary objective was to:
"Compare OM 10.3 mg to OM 20.6 mg and placebo for effectiveness in the treatment of episodic heartburn following repeated dosing (daily as needed) over a 2-week interval"

8.1.1.2 Design

Begin excerpt from sponsor's completed study report 092, 095

This study was a multi-center, single- and repeated-dose, randomized, double-blind, double-dummy, parallel, placebo-controlled study with a 7-day placebo run-in phase and a 14-day active treatment phase and a targeted study population of 1860 subjects.

To be eligible for the study, subjects must have experienced heartburn at least 2 days per week over the prior 30 days and must feel they get partial relief from antacids or OTC H_2RA treatments.

The purpose and procedures of the study were explained to potential subjects prior to enrollment. All subjects agreeing to participate were required to provide written informed consent and undergo eligibility screening, which included a physical exam, a medical/medication history, and a urine sample for a pregnancy test (if female subject of child-bearing potential).

Subjects went to the study center for 3 visits. At Visit 1 (Screening visit), the subject was given double-dummy placebo treatment and a Placebo Run-in Diary to record heartburn episodes, relief assessments, and backup medication (Gelusil®) use. The placebo was supplied in 2 bottles, each containing enough study medication for the placebo run-in phase. Subjects consumed 1 tablet with water from each bottle when they experienced heartburn symptoms they would normally treat. Subjects were also encouraged to treat the first heartburn episode of the day if it met the criteria for symptoms. Subjects were encouraged to refrain from food and beverage for the entire 3-hour evaluation period after dosing. Within 7 days (± 2) of completing Visit 1, subjects returned for Visit 2 (Baseline visit). Subjects who experienced heartburn on 2 or more days of the placebo run-in phase and satisfactorily completed at least 5 days of Placebo Run-in Diary pages were randomized to treatment.

Subjects were provided with a backup medication, Gelusil antacid, to be used if relief from study medication was insufficient. Subjects were instructed to wait at least 2 hours after dosing with the study medication before using the backup medication.

At Visit 2, subjects meeting the Continuance criteria were randomized to receive 1 of the following study treatments to be used over the next 14 days:

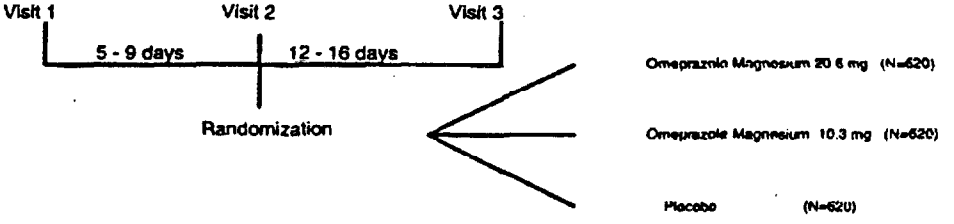
TREATMENT
Ome-Mg 20 (n = 620)
Ome-Mg 10 (n = 620)
Placebo (n = 620)

Subjects received 2 bottles of study medication, each containing enough medication for 16 days. Subjects were instructed to consume 1 tablet with water from each bottle when they experienced heartburn symptoms they would normally treat. Subjects were encouraged to treat the first heartburn episode of the day if it met the criteria for symptoms. Subjects were encouraged to refrain from food and beverage for the entire 3-hour evaluation period after dosing. Subjects then completed the Heartburn Symptom Diary questions evaluating the amount of relief they obtained.

Subjects were provided with a backup medication, Gelusil antacid, to be used if relief from study medication was insufficient. Subjects were strongly encouraged to wait at least 2 hours after dosing with the study medication before using the backup medication.

At Visit 3, subjects returned to the study center 14 days (± 2) after being randomized to treatment. At this final visit, subjects returned the study medication, Gelusil, and all diary pages.

Study medication safety was evaluated throughout the study and for 7 days following the last dose. Data was recorded on an Adverse Event (AE) Log case report form (CRF), which captured AEs experienced by the subject through the last visit or until the AEs were resolved, whichever was longer.



Study schedule of events

PROCEDURE	VISIT 1 (SCREENING/RUN-IN)	VISIT 2 (BASELINE)	VISIT 3 (COMPLETION)
Informed Consent	X		
Inclusion/Exclusion Review	X		
Demographics	X		
Medical History	X		
Medication History	X		
Physical Exam	X		
Urine Pregnancy Test*	X		
Diary Dispensed	X	X	
Placebo Run-In Medication Dispensed	X		
GELUSIL Dispensed	X	X	
Diaries Collected and Reviewed		X	X
Review of Concomitant Medications		X	X
Continuance Criteria		X	
Randomization		X	
Study Medication Dispensed		X	
Study Medication Accountability		X	X
Adverse Event Monitoring		X	X

* Female subjects of child-bearing potential only.

8.1.1.2.1 Inclusion and exclusion criteria

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

1. have a history of heartburn occurring at least 2 days per week over the prior 30 days,
2. have heartburn where they get partial relief from antacids or H_2-receptor antagonist treatments,
3. be male or non-pregnant, non-lactating female, in good general health, any race, and at least 18 years of age [women of child-bearing potential must be using an acceptable form of contraception (including abstinence) as determined by the Investigator and have a negative urine pregnancy test at Visit 1 (Screening)], and
4. be able to provide written informed consent and demonstrate an ability to understand and follow diary instructions.

To be considered eligible to continue participation at Visit 2 (Baseline Visit) and be randomized to treatment, subjects must continue to meet all specified Inclusion/Exclusion Criteria. Subjects must also have:

1. presence of heartburn on at least 2 days during the run-in phase, and
2. at least 5 out of 7 days with satisfactory entries in the run-in diary.

Subjects will be excluded from the study if they demonstrate:

1. a history (past or present) of erosive esophagitis verified by endoscopy,
2. a history (past or present) of GERD as diagnosed by a physician,
3. a history (past or present) of pathologic intraesophageal pH monitoring,
4. any medical condition or concomitant therapy which may interfere with the evaluation of heartburn treatment,
5. any chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) including Aspirin during the course of the study (low doses of Aspirin for cardiac conditions are acceptable),
6. the need for continuous treatment with ranitidine, famotidine, nizatidine, cimetidine, lanzoprazole, omeprazole magnesium, metoclopromide, misoprostol, or cisapride [the previous use of promotility agents, or misoprostol, is permitted as long as they are discontinued at least 24 hours prior to Visit 1(Screening Visit); the previous use of intermittent PPIs is permitted as long as they are discontinued at least 72 hours prior to Visit 1 (Screening Visit)],
7. the need for continuous treatment with phenytoin (Dilantin®), diazepam (Valium®), warfarin (Coumadin®), or the use of these agents at any time between Visit 1 (Screening Visit) and the final evaluation at Visit 3 (Completion Visit),
8. an unwillingness to participate in this study as demonstrated by taking any antacids or H_2 antagonists during the study, no matter what the indication for use, other than GELUSIL, if needed for heartburn,
9. participation in another investigational drug study within 30 days of Visit 1 (Screening Visit), or previous participation in this study,
10. known hypersensitivity to omeprazole magnesium or GELUSIL,
11. recent history (within the past 12 months) of alcoholism, illicit drug use, or abuse prior to Visit 1 (Screening Visit) or at any time during the study,
12. any other medical condition or situation which the investigator feels constitutes a safety concern (e.g., gastrointestinal bleeding, malignancy, etc.).

End of CSR excerpt

The intention to treat population was initially defined as all subjects who are randomized and for whom at least one efficacy evaluation is available following the first dose. In an amendment dated January 15, 1998 the sponsor added that no entry criteria be violated in the intention to treat population.

8.1.1.2.2 Endpoints

Begin excerpt from CSR 092, 095

Endpoint parameter definitions:

The subjects are only to evaluate at most one heartburn episode per day in their diary. Once a heartburn episode occurs which the subject would normally treat with medication, the subject will take one dose of study medication and record the time they take study medication. Then the subject will record their baseline severity:

None:	No heartburn is present.
Mild:	Heartburn is present but easily tolerated.
Moderate:	Heartburn is sufficient to cause interference with normal daily activities or sleep.
Severe:	Heartburn is incapacitating. Subject is unable to perform normal daily activities or sleep.

The subject will begin recording the following heartburn relief score every 10 minutes for the first hour and then hourly thereafter for a total of 3 hours.

- Complete relief ("no heartburn")
- Adequate relief ("satisfactory")
- Inadequate relief (including "no relief")

In this study heartburn is defined as an upward moving, uncomfortable sensation behind the breastbone, frequently accompanied by a burning or painful feeling.

The subject will also rate the overall assessment of the study medication at the end of the evaluation period or when back-up medication is taken by answering the following question:

"Overall, how would you rate the study medication?"

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

If back-up medication is taken, the subject will record the time back-up is taken and the number of tablets and will discontinue making evaluations for that episode.

In addition, safety will be assessed by the collection of volunteered AEs.

3.5.3 Primary Efficacy Variable

The primary efficacy variable is the occurrence of Sustained Complete Relief for the first-treated episode of heartburn. Sustained Complete Relief is defined as achieving complete relief within the first hour (inclusive), and sustaining the complete rating through (and including) the third hour after taking the study medication. Sustained relief (as defined here) is a variable which was evaluated in the Zantac 75 Summary Basis of Approval. However, since omeprazole magnesium's strength is expected to be in relieving symptoms completely, Sustained Complete Relief was utilized in a previous Astra Merck study using a similar protocol[9], and thus, is specified as primary in this study.

3.5.4 Secondary Efficacy Variables

The following secondary efficacy variables will be analyzed for the first-treated and the last-treated episodes of heartburn within the 2-week treatment period:

- the occurrence of complete relief (at least one complete relief evaluation within the first hour),
- the occurrence of sustained adequate relief (defined as achieving at least adequate relief within the first hour (inclusive) and sustaining the adequate rating through (and including) the third hour after taking the study medication),
- the occurrence of adequate relief (at least one adequate relief evaluation with the first hour),
- the occurrence of antacid (back-up medication) use (only for the treated heartburn episode),
- the time to onset of sustained complete relief,
- the time to onset of complete relief,
- the time to onset of sustained adequate relief,
- the time to onset of adequate relief,
- the time to antacid (back-up medication) use, and
- the overall assessment of the study medication.

In addition, the following five secondary efficacy variables will be analyzed:

- the occurrence of sustained complete relief for the last-treated episode of heartburn,
- the occurrence of sustained complete relief over all treated episodes of heartburn,
- the occurrence of complete relief over all treated episodes of heartburn,
- the occurrence of sustained adequate relief over all treated episodes of heartburn,
- the occurrence of adequate relief over all treated episodes of heartburn,
- the occurrence of antacid (back-up medication) use (over all treated episodes of heartburn), and
- the overall assessment of the study medication over all treated episodes of heartburn.

end of CSR excerpt

(note there were actually 7 additional secondary efficacy endpoints)

Reviewer's Comment:

Efficacy measurements: *The primary endpoint and the first 10 secondary endpoints relate to the first episode of HB. Endpoints #11 and 12 relate to the last treated and all treated episodes analysis. Previous medical reviews of OTC HB products have stressed the importance of first episode efficacy. The very concept of as needed dosing mandates that a single dose be effective. Current OTC HB labeling does not state that repeat doses are needed for efficacy. It is therefore imperative that truly episodic treatment provide efficacy if the current label is to be used. If the Agency were to change the expectation of an OTC HB treatment, then the label would need to be rewritten to accurately label a*

product requiring repeat dosing. This reviewer considers first episode efficacy to be necessary for approval of OTC HB treatment as currently labeled.

The sponsor cites the basis for approval of Zantac 75 (NDA 20,520) in 1995. While each submission must be judged within the context of the sponsor's defined development program and study results, some comparisons are valid. Such comparison however must be made with caution and awareness of the limitations of cross study comparisons. The sponsor of NDA 20,520 (Zantac OTC for HB treatment) showed the therapeutic gain displayed below for endpoints similar to the current sponsor displayed below. Tables 7and 8 are taken for the medical officer's review dated June 23, 1995. These results will need to be considered if precedent is to be invoked for approvability of the OM. If the therapeutic gain with OM is lower, not replicated and or not supported by other HB endpoints to the extent seen in the Zantac NDA, invoking precedent is of limited relevance. Furthermore, statistical penalties would be necessary if one of multiple secondary endpoints is to be considered the basis for establishing efficacy.

Table 7 (from NDA 20,520, Zantac)

ROC-300: Proportion of Successfully-Treated Episodes

	Placebo	Ran 25mg	Ran 75mg
First Episode proportion of successes (%) p-value vs. placebo	211/473 (44.6%)	253/485 (52.2%) (0.017)	284/481 (59.0%) (<0.001)
Last Episode proportion of successes (%) p-value vs. placebo	197/460 (42.8%)	231/471 (49.0%) (0.045)	258/474 (54.4%) (<0.001)
All Episodes (GEE approach) (%) proportion of successes (%) p-value vs. placebo	(42.4%)	(50.8%) (<0.001)	(56.6%) (<0.001)

TABLE 8

ROC-301: Proportion of Successfully-Treated Episodes

	Placebo	Ran 25mg	Ran 75mg
First Episode proportion of successes (%) p-value vs. placebo	231/510 (45.3%)	278/520 (53.5%) (0.010)	290/516 (56.2%) (<0.001)
Last Episode proportion of successes (%) p-value vs. placebo	196/501 (39.1%)	264/511 (51.7%) (<0.001)	272/512 (53.1%) (<0.001)
All Episodes (GEE approach) (%) proportion of successes (%) p-value vs. placebo	(41.9%)	(52.9%) (<0.001)	(52.7%) (<0.001)

In an amendment dated January 15, 1998 the sponsor deleted the following variables:

1. time to onset of complete relief
2. time to onset of sustained adequate relief
3. time to onset of adequate relief

Reviewer's Comment:
No explanation or justification was given for this deletion. Within the NDA 20,520 Zantac 75 showed statistically significantly higher rates of relief within 30 minutes of dosing.

3.1.1.1.1 Statistical considerations

The sponsor's statistical plan is not described in detail in the completed study report (CSR). The sponsor stated in the initial protocol that:
"A detailed statistical analysis plan will be completed prior to the treatment being unblinded."
Ultimately multiple different statistical tests were applied and will be addressed in the statistics review to ensure appropriate statistical tests were used.
The sponsor stated in the CSR that the intention to treat (ITT) population will be the basis of the primary efficacy evaluation and the per-protocol (PP) population will be the basis for the secondary analysis.

3.1.1.2 Results

Demographic and baseline data:

In studies 092 and 095 approximately 3% of screened subjects did not meet criteria to enter the placebo run-in phase of the study. Approximately 20 % of subjects enrolled in the run-in phase did not meet continuation criteria for multiple reasons. Discontinuation rates were under 4% on all groups. Between 2 to 6% of the ITT group were excluded from the PP analysis. The disposition of randomized subjects is listed in tables 11-14. There were no meaningful differences among the groups in demographic or baseline characteristics.
The demographic data revealed that:

1. The majority of subjects experienced HB of moderate intensity over 50% of days during the run-in period.
2. Essentially all subjects experienced meal induced HB. Lesser proportions of subjects had a history of other precipitants as well.

Table 9

8.7 Integrated Summary of Effectiveness

TABLE 34
DEMOGRAPHIC AND BASELINE CHARACTERISTICS

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS
(PAGE 1 OF 3)

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	092				095			
	Ome-Mg 20 (N = 621)	Ome-Mg 10 (N = 621)	PLACEBO (N = 627)	TOTAL (N=1869)	Ome-Mg 20 (N = 627)	Ome-Mg 10 (N = 623)	PLACEBO (N = 602)	TOTAL (N=1852)
Gender								
Female	49.3%	49.0%	47.0%	48.4%	52.5%	52.3%	56.0%	53.6%
Male	50.7%	51.0%	53.0%	51.6%	47.5%	47.7%	44.0%	46.4%
Race								
Caucasian	82.3%	82.8%	83.9%	83.0%	81.0%	84.9%	83.2%	83.0%
Black	13.0%	13.4%	12.0%	12.8%	16.3%	12.7%	14.8%	14.6%
Hispanic	2.6%	2.6%	2.9%	2.7%	2.1%	1.9%	1.0%	1.7%
Asian	1.6%	1.1%	0.8%	1.2%	0.3%	0.3%	0.3%	0.3%
American Indian	0.2%	0.0%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%
Multi-Racial/Other	0.3%	0.2%	0.3%	0.3%	0.3%	0.2%	0.7%	0.4%

Table 10

8.7 Integrated Summary of Effectiveness

TABLE 34 (CONTINUED)
DEMOGRAPHIC AND BASELINE CHARACTERISTICS

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS
(PAGE 2 OF 3)

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	092				095			
	Ome-Mg 20 (N = 621)	Ome-Mg 10 (N = 621)	PLACEBO (N = 627)	TOTAL (N=1869)	Ome-Mg 20 (N = 627)	Ome-Mg 10 (N = 623)	PLACEBO (N = 602)	TOTAL (N=1852)
Age (Years)								
Mean	44.8	43.9	44.7	44.5	44.6	44.4	43.2	44.1
Std. Deviation	13.66	13.53	13.41	13.54	12.69	12.69	12.60	12.67
Minimum–Maximum	18–87	18–89	18–89	18–89	18–81	18–77	18–82	18–82
< 65 Years	90.5%	92.1%	92.2%	91.6%	91.7%	92.8%	93.7%	92.7%
≥ 65 Years	9.5%	7.9%	7.8%	8.4%	8.3%	7.2%	6.3%	7.3%
Current Smoker								
Yes	26.7%	24.5%	31.1%	27.4%	31.1%	31.6%	26.7%	29.9%
No	73.3%	75.5%	68.9%	72.6%	68.9%	68.4%	73.3%	70.1%

Table 12

8.7 Integrated Summary of Effectiveness

TABLE 34 (CONTINUED)
DEMOGRAPHIC AND BASELINE CHARACTERISTICS

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS
(PAGE 3 OF 3)

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	092				095			
	Ome-Mg 20 (N = 621)	Ome-Mg 10 (N = 621)	PLACEBO (N = 627)	TOTAL (N=1869)	Ome-Mg 20 (N = 627)	Ome-Mg 10 (N = 623)	PLACEBO (N = 602)	TOTAL (N=1852)
Heartburn Frequency (% Of Days) During Run-In								
Mean	60.8	59.8	60.5	60.3	59.8	59.9	58.6	59.4
Std. Deviation	22.96	21.87	22.92	22.58	21.97	21.95	21.23	21.72
Minimum–Maximum	22.2–100	22.2–100	22.2–100	22.2–100	22.2–100	22.2–100	22.2–100	22.2–100
< 50%	39.5%	41.4%	43.2%	41.4%	41.9%	42.4%	43.5%	42.6%
≥ 50%	60.5%	58.6%	56.8%	58.6%	58.1%	57.6%	56.5%	57.4%
Average Heartburn Severity During Run-In								
Mean	1.8	1.9	1.9	1.9	1.8	1.8	1.8	1.8
Std. Deviation	0.45	0.45	0.47	0.46	0.46	0.46	0.48	0.47
Minimum–Maximum	1–3	1–3	1–3	1–3	1–3	1–3	1–3	1–3
Less than Moderate (<2)	48.8%	46.7%	47.0%	47.5%	49.9%	48.3%	51.7%	49.9%
Moderate to Severe (≥2)	51.2%	53.3%	53.0%	52.5%	50.1%	51.7%	48.3%	50.1%

Reviewer's Comment:

1. *Table 11 shows that at baseline the three groups had similar severity of HB in both studies. The majority of subjects had HB at least every other day on average and the majority experienced moderate to severe HB on average. Current medical practice warrants a medical evaluation in people who experience frequent severe HB. Appendix #1 includes a reprint of a fact sheet intended for the public that currently appears on the American College of Gastroenterology website. In addition the first page and relevant subsequent pages from other publications in the medical literature are reproduced. The commonality among these articles by academic leaders in gastroenterology is the acknowledgement that patients with severe and or chronic HB require medical evaluation for GERD. Practice guidelines published by the Practice Parameters Committee of the American College of Gastroenterology in 1999 State in the preamble that:*

"For the purpose of these guidelines GERD is defined as chronic symptoms or mucosal damage produced by abnormal reflux of gastric contents into the esophagus." 1

FIND MEAN DURATION OF SX IN THE DATABASE FOR ALL STUDIES

Opinion on the indications and the timing of endoscopy are not well defined. There is consensus however on the importance of assessing patient response to therapy as well as severity, duration and recurrence of symptoms. The baseline demographics of the current studies suggest that many may not be appropriate for empiric OTC therapy.

The OTC medical reviewer will address this issue in terms of safety. Critical to the efficacy review however is the therapeutic gain in subjects that are appropriate for OTC OM use. An analysis of response by severity will be reviewed in the efficacy results section.

2. The high frequency of HB suggests that daily Prilosec use may be expected by a large number of subjects in these studies. This may produce a confounding carry-over effect upon the results of treatment effect on days following the first HB episode in view of the long biologic ½ life of Omep. The effects of recent prior doses (doses within the prior 72 hours) on the results of current dose cannot be prevented or controlled. It will be important to sub-analyze the therapeutic effects on subjects stratifying for recent prior therapy. While statistical significance may be lost due to the smaller sample sizes, trends should be maintained if the results are to be interpreted as indicating a benefit for OM use that can truly be described as "episodic".

Table 13

8.7 Integrated Summary of Effectiveness

TABLE 35
SUMMARY OF FACTORS CONTRIBUTING TO HEARTBURN SYMPTOMS DURING 30-DAY PERIOD PRECEDING ENTRY INTO THE MULTIPLE-DOSE TREATMENT STUDIES
INTENT-TO-TREAT SUBJECTS

STUDY NUMBER	092	095
SAMPLE SIZE	1869	1852
Heartburn Symptom Factors[a]		
Food and/or Beverage	97.2%	97.5%
Stress and/or Anxiety	55.8%	59.3%
Lying Down	54.8%	54.8%
Hectic Lifestyle	26.4%	30.0%
Physical Activity	19.6%	19.5%
Medication	4.8%	5.3%

a Subject could select more than one heartburn symptom factor to describe typical cause over the past month.

3.1.1.2.1 Efficacy Results:

First Treated Episode Results

Table 14

8.7 Integrated Summary of Effectiveness

TABLE 36
ANALYSIS OF PRIMARY EFFICACY VARIABLE — SUSTAINED COMPLETE RELIEF
FIRST-TREATED EPISODE OF HEARTBURN

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS

STUDY 092	Ome-Mg 20	Ome-Mg 10	PLACEBO
Sustained Complete Relief (%)	30.2% (187/620)	31.5% (195/620)	29.5% (185/627)
COMPARISON	P-VALUE[a]	ODDS RATIO (95% C.I.)[b]	DIFF IN PROP (95% C.I.)[c]
Ome-Mg 20 vs. Placebo	0.822	1.03 (0.80, 1.31)	0.7% (-4.6%, 5.9%)
Ome-Mg 10 vs. Placebo	0.503	1.09 (0.86, 1.39)	1.9% (-3.3%, 7.2%)
Ome-Mg 20 vs. Ome-Mg 10	0.593	0.94 (0.74, 1.20)	-1.3% (-6.6%, 4.0%)

STUDY 095	Ome-Mg 20	Ome-Mg 10	PLACEBO
Sustained Complete Relief (%)	29.2% (183/627)	29.9% (186/623)	29.4% (177/602)
COMPARISON	P-VALUE[a]	ODDS RATIO (95% CI)[b]	DIFF IN PROP (95% CI)[c]
Ome-Mg 20 vs. Placebo	0.934	0.99 (0.77, 1.27)	-0.2% (-5.5%, 5.0%)
Ome-Mg 10 vs. Placebo	0.810	1.02 (0.80, 1.31)	0.5% (-4.8%, 5.7%)
Ome-Mg 20 vs. Ome-Mg 10	0.819	0.97 (0.76, 1.23)	-0.7% (-5.9%, 4.6%)

[a] *P*-values for treatment comparisons obtained from Cochran-Mantel-Haenszel chi-square test with investigator as a stratification variable.

[b] Estimated odds ratios and 95% confidence intervals (CI) from logistic regression analysis with Treatment and (pooled) Investigator as categorical variable.

[c] Estimated differences in proportions (expressed as a percent) and their 95% confidence intervals using a normal approximation.

Reviewer's comment:

The primary endpoint is stringent and has not been required of past sponsors for the approval of heartburn treatment. It is the most valuable and clinically relevant to the patient. The lack of even a trend in favor of the Omep group in either study is therefore important.

Prior review summary:
Axid won on complete relief of all and of first 4 episodes in 1996) Tagamet won on first episode (onset and duration of relief- not complete relief 1993f) and the all episodes analysis isn't considered!!! KRS

Adequate relief within 1 hour that was sustained for three hours was primary efficacy for Zantac (45% versus 59 and 56%- replicated and robust and consistent across secondary endpoints as well) (proportion of successfully treated patients over study period 61 vs 45%)(all episodes GEE approach was 42 vs 53%

Pepcid –first episode was primary endpoint- global assessment over study was primary endpoint- Excellent, good fair poor and none: good or excellent 62 vs 74 %

The first episode COMPLETE relief within 60 minutes analysis was requested by the FDA and showed 28 vs 39% NS but trend in small n of 100: this is more robust than OM

Bottom line : FIRST EPISODE RELIEF DATA WAS replicated and MORE ROBUST FOR OTHER PRODUCTS THAN OM ALTHOUGH COMPLETE RELIEF WAS NOT USED IN ANALYSIS OF ALL. Tagamet had first episode success

Table 15

8.7 Integrated Summary of Effectiveness

TABLE 37
ANALYSIS OF SECONDARY EFFICACY VARIABLES
PERCENTAGE OF SUBJECTS WITH INDICATED OUTCOME
FIRST-TREATED EPISODE OF HEARTBURN

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	PLACEBO
Complete Relief within 1 Hour[a]			
Study 092	32.7%	34.2%	32.5%
Study 095	31.9%	33.7%	31.6%
Sustained Adequate Relief[a]			
Study 092	65.2%	66.8%	62.2%
Study 095	**69.7%[A,B]**	64.2%	61.8%
Adequate Relief within 1 Hour[a]			
Study 092	72.3%	75.3%	71.0%
Study 095	**76.6%[A]**	72.7%	69.6%
Backup Medication Use[a]			
Study 092	6.9%	7.2%	9.6%
Study 095	**5.9%[A]**	8.2%	9.1%
Overall Assessment of Study Medication[b]			
Study 092	54.7%	56.3%	50.8%
Study 095	**57.3%[A]**	**56.4%[A]**	47.4%

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

[b] Percentage of subjects with Good, Very Good, and Excellent ratings on Overall Assessment of Study Medication. All levels of this variable were utilized for test for treatment difference using Extended-Mantel-Haenszel chi-square test with investigator as a stratification variable.

[A] Significantly different from Placebo ($p \leq 0.05$); values are bolded in table.

[B] Ome-Mg 20 significantly different from Ome-Mg 10 ($p \leq 0.05$); values are bolded in table.

Reviewer's Comments:

1. *There was no meaningful dose trend in either primary or secondary endpoints for the first treated endpoint. In the review of Tagamet for OTC treatment of HB; the first approved OTC H2RA, the medical reviewer, Dr. Kathy Robie-Suh stated that only first episode data is not confounded by prior treatment. Therefore, subsequent episode data cannot provide adequate support for efficacy of treatment for episodic HB. This reviewer concurs with this stated view. Pharmacodynamics of OM suggest that carry over effects may more profoundly influence subsequent episode results in OM studies than short acting OTC products.*
2. *Table fifteen reveals that study 092 failed at the secondary endpoints displayed. Study 095 showed statistically significant differences between the proposed dose of 20-mg OM and placebo in four of the five parameters studied. The sponsor notes that previously accepted applications for products to treat HB (notable Zantac75) have been approved on the basis of overall assessment of medication. This was an important part of the analysis that was the basis for approval of Zantac 75 for heartburn treatment (NDA 20,520 review date June 23, 1995). However, it was not the only evidentiary basis for approval. Furthermore, the results were replicated and the therapeutic gain was greater in the case of the Zantac submission. The results of studies presented in NDA 20,520 referenced by the current sponsor were more robust than the unreplicated secondary endpoints proposed by the current sponsor in support of their claim of efficacy of OM for first episode treatment of heartburn.*

Last Treated Episode Efficacy

Table 16

8.7 Integrated Summary of Effectiveness

TABLE 38
ANALYSIS OF PRIMARY EFFICACY VARIABLE — SUSTAINED COMPLETE RELIEF
LAST-TREATED EPISODE OF HEARTBURN

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS

STUDY 092	Ome-Mg 20	Ome-Mg 10	PLACEBO
Sustained Complete Relief (%)	34.2%	33.8%	28.6%
COMPARISON	P-VALUE[a]	ODDS RATIO (95% CI)[b]	DIFF IN PROP (95% CI)[c]
Ome-Mg 20 vs. Placebo	0.035	1.30 (1.02, 1.66)	5.6% (0.2%, 10.9%)
Ome-Mg 10 vs. Placebo	0.054	1.28 (1.00, 1.63)	5.2% (-0.2%, 10.5%)
Ome-Mg 20 vs. Ome-Mg 10	0.886	1.02 (0.80, 1.29)	0.4% (-5.1%, 5.9%)

STUDY 095	Ome-Mg 20	Ome-Mg 10	PLACEBO
Sustained Complete Relief (%)	35.5%	30.8%	26.1%
COMPARISON	P-VALUE[a]	ODDS RATIO (95% CI)[b]	DIFF IN PROP (95% CI)[c]
Ome-Mg 20 vs. Placebo	0.001	1.56 (1.22, 1.99)	9.4% (4.0%, 14.7%)
Ome-Mg 10 vs. Placebo	0.068	1.26 (0.98, 1.62)	4.7% (-0.6%, 9.9%)
Ome-Mg 20 vs. Ome-Mg 10	0.060	1.23 (0.97, 1.57)	4.7% (-0.7%, 10.1%)

[a] P-values for treatment comparisons obtained from Cochran-Mantel-Haenszel chi-square test with investigator as a stratification variable.

[b] Estimated odds ratios and their 95% confidence intervals (CI) from logistic regression analysis with Treatment and (pooled) Investigator as categorical variables.

[c] Estimated differences in proportions (expressed as a percent) and their 95% confidence intervals using a normal approximation.

Table 17 reveals a 6-10% therapeutic gain that is statistically significant for the complete sustained relief within one hour for the last treated episode.

Table 17

8.7 Integrated Summary of Effectiveness

TABLE 39
ANALYSIS OF SECONDARY EFFICACY VARIABLES
PERCENTAGE OF SUBJECTS WITH INDICATED OUTCOME
LAST-TREATED EPISODE OF HEARTBURN

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	PLACEBO
Complete Relief within 1 Hour[a]			
Study 092	**35.6%[A]**	**35.9%[A]**	29.7%
Study 095	**37.3%[A]**	32.9%	28.1%
Sustained Adequate Relief[a]			
Study 092	66.3%	67.4%	62.4%
Study 095	**71.9%[A,B]**	**66.6%[A]**	59.8%
Adequate Relief within 1 Hour[a]			
Study 092	73.8%	73.7%	70.4%
Study 095	**77.6%[A]**	**73.6%[A]**	67.2%
Backup Medication Use[a]			
Study 092	9.7%	**7.1%[A]**	11.6%
Study 095	**6.0%[A]**	8.2%	9.0%
Overall Assessment of Study Medication[b]			
Study 092	**57.7%[A]**	**62.4%[A]**	52.9%
Study 095	**63.7%[A]**	**60.3%[A]**	49.2%

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

[b] Percentage of subjects with Good, Very Good, and Excellent ratings on overall assessment of study medication. However, all levels of this variable were utilized for test for treatment difference using Extended-Mantel-Haenszel chi-square test with investigator as a stratification variable.

[A] Significantly different from Placebo ($p \leq 0.05$); values are bolded in table.

[B] Ome-Mg 20 significantly different from Ome-Mg 10 ($p \leq 0.05$); values are bolded in table.

All Treated Episode Results

Table 18

8.7 Integrated Summary of Effectiveness

TABLE 40
ANALYSIS OF PRIMARY EFFICACY VARIABLE USING GEE
TREATMENT COMPARISON BASED ON ALL TREATED EPISODES
DURING THE ACTIVE TREATMENT PHASE

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS

STUDY 092	Ome-Mg 20	Ome-Mg 10	PLACEBO
Sustained Complete Relief (%)[a]	31.7%	30.7%	27.5%
COMPARISON	P-VALUE[b]	ODDS RATIO[c]	95% C.I.[c]
Ome-Mg 20 vs. Placebo	0.032	1.23	(1.02, 1.49)
Ome-Mg 10 vs. Placebo	0.102	1.17	(0.97, 1.42)
Ome-Mg 20 vs. Ome-Mg 10	0.593	1.05	(0.87, 1.27)

STUDY 095	Ome-Mg 20	Ome-Mg 10	PLACEBO
Sustained Complete Relief (%)[a]	32.3%	29.8%	26.3%
COMPARISON	P-VALUE[b]	ODDS RATIO[c]	95% CI[c]
Ome-Mg 20 vs. Placebo	0.002	1.34	(1.11, 1.62)
Ome-Mg 10 vs. Placebo	0.069	1.19	(0.99, 1.45)
Ome-Mg 20 vs. Ome-Mg 10	0.217	1.12	(0.93, 1.35)

[a] Predicted probabilities from generalized estimating equations analyses using Treatment as categorical variable in the model.

[b] *P*-values for treatment comparisons from Wald chi-square test.

[c] Estimated odds ratio and confidence interval (CI) obtained from GEE model with Treatment, Investigator, and Episode as categorical explanatory variables (exchangeable correlation assumed). Robust variance estimate used. The odds ratio is the ratio for the estimated odds of having the indicated outcome in the first group relative to the second group shown. See Section 8.7.3.8.3 for a discussion of interactions between Treatment and Episode, which are not reflected in the models above.

Table 19

8.7 Integrated Summary of Effectiveness

TABLE 41
ANALYSIS OF EFFICACY VARIABLES USING GEE
TREATMENT COMPARISONS BASED ON ALL TREATED EPISODES
DURING THE ACTIVE TREATMENT PHASE

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS
(PAGE 1 OF 2)

	Ome-Mg 20 vs. Placebo			Ome-Mg 10 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]	Odds Ratio[a]	95% CI[a]	P-value[b]
Complete Relief within 1 Hour									
Study 092	1.19	(0.99, 1.44)	0.064	1.17	(0.97, 1.41)	0.106	1.02	(0.85, 1.23)	0.803
Study 095	1.35	(1.12, 1.62)	0.002	1.24	(1.02, 1.50)	0.029	1.09	(0.90, 1.31)	0.370
Sustained Adequate Relief									
Study 092	1.25	(1.05, 1.49)	0.014	1.21	(1.02, 1.44)	0.031	1.03	(0.86, 1.23)	0.732
Study 095	1.58	(1.32, 1.88)	<0.001	1.27	(1.07, 1.51)	0.006	1.24	(1.04, 1.48)	0.017
Adequate Relief within 1 Hour									
Study 092	1.19	(0.98, 1.44)	0.073	1.16	(0.96, 1.40)	0.122	1.03	(0.84, 1.25)	0.792
Study 095	1.54	(1.27, 1.87)	<0.001	1.28	(1.06, 1.54)	0.009	1.20	(0.99, 1.46)	0.065

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

[b] P-values for treatment comparisons using Wald chi-square test.

Note: See Tables 8.2.20, 8.2.24, and 8.2.25 in Clinical Study Reports 1997092 and 1997095 for the table results.

8.7 Integrated Summary of Effectiveness

TABLE 41 (CONTINUED)
ANALYSIS OF EFFICACY VARIABLES USING GEE
TREATMENT COMPARISONS BASED ON ALL TREATED EPISODES
DURING THE ACTIVE TREATMENT PHASE

MULTIPLE DOSE TREATMENT STUDIES: HEARTBURN OF UNSPECIFIED CAUSE
INTENT-TO-TREAT SUBJECTS
(PAGE 2 OF 2)

	Ome-Mg 20 vs. Placebo			Ome-Mg 10 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]	Odds Ratio[a]	95% CI[a]	P-value[b]
Backup Medication Use									
Study 092	0.74	(0.57, 0.97)	0.030	0.84	(0.49, 0.83)	0.001	1.17	(0.88, 1.55)	0.279
Study 095	0.71	(0.53, 0.94)	0.018	0.90	(0.69, 1.17)	0.443	0.79	(0.59, 1.04)	0.095
Overall Assessment of Study Medication									
Study 092	1.38	(1.15, 1.66)	<0.001	1.38	(1.15, 1.65)	<0.001	1.00	(0.83, 1.20)	0.982
Study 095	1.65	(1.37, 1.98)	<0.001	1.42	(1.18, 1.70)	<0.001	1.16	(0.97, 1.39)	0.108

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

[b] P-values for treatment comparisons using Wald chi-square test.

Note: See Tables 8.2.20, 8.2.24, and 8.2.25 in Clinical Study Reports 1997092 and 1997095 for the table results.

Reviewer's Comment:

1. *Tables 18 and 19 shows a small therapeutic gain of 4-6% in the two studies in the composite endpoint of sustained complete relief over the entire two week study period using a generalized estimating equation (GEE) model. The data on treatment usage over the two-week treatment period appear in tables 19 and 20. The average treatment frequency is 7 out of 14 days. The pharmacodynamic profile of OM suggests that a substantial carry-over effect from previous doses impacted on efficacy after the first episode of HB treatment. In effect, the results of the "all treated"*

analyses offer more support for prevention of subsequent episodes rather than treatment of an occasional episode.

2. *Tables 20 and 21 display the usage pattern in studies 092 and 095. The mean usage was 7/14 study days. Pharmacodynamics of OM suggest that the study results for episodes beyond the first episode reflects "management of subacute/ chronic symptoms (GERD) rather than "occasional" HB.*

Table 20 (exposure in study 092)

Study No. 1997092

TABLE 8.3.1
SUMMARY OF EXTENT OF EXPOSURE
BY TOTAL NUMBER OF DAYS STUDY MEDICATION TAKEN
ACTIVE TREATMENT PHASE[a,b]

TOTAL NUMBER OF DAYS STUDY MEDICATION TAKEN	Ome-Mg 20 (N = 622)[c]	Ome-Mg 10 (N = 624)[c]	PLACEBO (N = 627)[c]	OVERALL (N = 1873)[c]
Mean	6.8	7.2	7.5	7.2
Std. Deviation	3.37	3.33	3.48	3.40
Minimum–Maximum	1–16	1–16	1–16	1–16
By Number of Days Study Medication Taken[d]				
1	11	4	7	22
2	24	22	17	63
3	49	41	40	130
4	99	79	66	244
5	79	79	82	240
6	65	87	85	237
7	70	76	57	203
8	54	36	59	149
9	38	55	41	134
10	35	34	36	105
11	28	28	34	90
12	15	20	24	59
13	18	26	28	72
14	26	27	41	94
15	9	6	7	22
16	2	4	3	9

[a] See Appendix 2.6.2.2 for complete data listings.

[b] See Appendices 1.9.3.29 and 1.9.4.17 for full statistical analyses and documentation.

[c] Number of subjects who took at least 1 dose of study medication in the active treatment phase in each treatment group and overall.

[d] Number of subjects included in each treatment group and overall by number of days of study medication taken.

Source: Tt9961/ home1/ts6801/1997092/saspgm/extexp.sas
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Table 21 (Exposure in study 095)

Study No. 1997095

TABLE 8.3.1
SUMMARY OF EXTENT OF EXPOSURE
BY TOTAL NUMBER OF DAYS STUDY MEDICATION TAKEN
ACTIVE TREATMENT PHASE[a,b]

TOTAL NUMBER OF DAYS STUDY MEDICATION TAKEN	Ome-Mg 20 (N = 629)[c]	Ome-Mg 10 (N = 627)[c]	PLACEBO (N = 606)[c]	OVERALL (N = 1862)[c]
Mean	7.0	7.0	7.3	7.1
Std. Deviation	3.12	3.09	3.14	3.12
Minimum–Maximum	1–16	1–16	1–16	1–16
By Number of Days Study Medication Taken[d]				
1	10	11	5	26
2	20	15	16	51
3	33	37	27	97
4	70	74	56	200
5	86	96	87	269
6	113	81	88	282
7	81	76	76	233
8	45	69	53	167
9	44	46	58	148
10	33	32	34	99
11	25	28	32	85
12	20	16	25	61
13	25	23	20	68
14	18	17	20	55
15	2	4	5	11
16	4	2	4	10

[a] See Appendix 2.6.2.2 for complete data listings.

[b] See Appendices 1.9.3.29 and 1.9.4.17 for full statistical analyses and documentation.

[c] Number of subjects who took at least one dose of study medication in the active treatment phase in each treatment group and overall.

[d] Number of subjects included in each treatment group and overall by number of days of study medication taken.

Source: TT9981/homa1/ts6801/1997095/saspgm/extexp.sas
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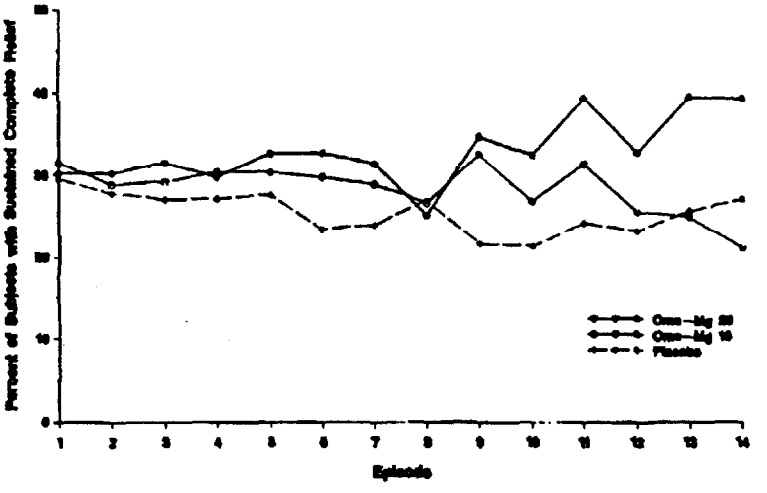
Figure 2

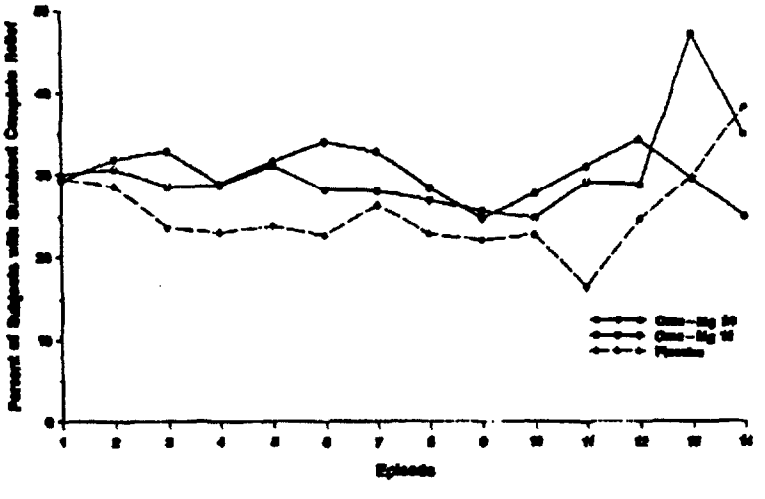
FIGURE 6
TREATMENT OF HEARTBURN SYMPTOM STUDIES
PERCENTAGE OF SUBJECTS WITH SUSTAINED COMPLETE RELIEF BY EPISODE
INTENT-TO-TREAT SUBJECTS

STUDY 1997092



EPISODE:	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N:	1867	1847	1775	1647	1407	1165	925	720	569	433	328	240	187	114

STUDY 1997095



EPISODE:	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N:	1852	1824	1774	1674	1473	1203	919	674	516	368	279	195	129	66

Reviewer's Comment:

Figures 2 and 3 provide a visual image of the efficacy of OM compared to placebo over time/episodes. As time passes for those subjects that ultimately require more than several doses, there may be separation of the response curves among the groups. However, the results from study 095 are not consistent over time. Furthermore, the results of the 2 studies plotted over cumulative episodes appear to have different patterns. The inconsistency in these data create a problem when trying to use a model rather than interpreting raw data that has readily interpretable value.
There was a statistically significant treatment by episode interaction in both studies. This finding is consistent with the carry over effect anticipated with the use of multiple doses of OM. If carries over effects are needed to obtain efficacy for the treatment of HB, labeling use for occasional HB is not supported.
The label must inform consumers that the drug is only effective for multidose use in recurrent HB. Such a label is not consistent with current OTC indications for HB management and in effect would establish OTC treatment for GERD.

Conclusions from studies 092 and 095: HB relief

<u>First HB episode</u>

The sponsor has failed to show a statistically significant difference or trend in favor of active treatment (OM 10 or 20 mg) for the primary efficacy endpoint: sustained complete relief of HB for the first episode. This was true for both studies 092 and 095.

Results of secondary efficacy endpoints were inconsistent. Table 15 summarizes these results:

1. *Complete relief : No trend in either study*
2. *Results of study 092 showed no meaningful or statistically differences between the three arms in the secondary endpoints of :*

A. sustained adequate relief

B. adequate relief within 1 hour

C. backup medication use

D. overall assessment of study medication

Results of study 095 showed numerically small but statistically significant benefit for OM 20 mg over placebo for the following endpoints for the first episode of HB:

A. sustained adequate relief

B. adequate relief within 1 hour

C. backup medication use

D. Overall assessment of study medication

?? discuss multiplicity corrections with statisticians

The failure to show a trend in favor of OM for the primary endpoint combined with the inconsistent results for secondary endpoints precludes approval of OM for the treatment of occasional HB.

REVIEW IR SUBMISSION FOR EPISODIC RX with statistician

The last-treated HB episode

There was a consistent modest benefit of OM 10 mg over placebo in the primary endpoint of sustained complete relief for the last episode. This effect approaches statistical significance. There was a statistically significant modest benefit to OM 20 mg over placebo for this endpoint. These data are displayed in table 16.

Study 095 shows consistent statistically significant benefit to OM 20- mg over placebo. The OM 10-mg dose was less consistent. Interestingly, the most robust and consistent benefit over placebo was seen for both doses in both studies in the overall assessment of medication endpoint. This endpoint represents a global assessment that may be reflective of the cumulative treatment effect over 2 weeks. This highlights the possibility of a carry-over effect from prior doses.

All treated episodes

1. *There appears to be marginal to absent benefit for doses 1-5 in study 092 and inconsistent benefit over time in study 095 as reflected in figure 2.*

2. *The two studies suggest different phenomena are occurring during the last 5 episodes. Study 092 suggests a clearer separation of results over time. OM 20mg is consistently better than placebo during the second week of treatment. Study 095 suggest that over the last three episodes placebo response rates increase and in fact surpass OM at both doses for the last episode.*

These results highlight the lack of consistent benefit of treatment with OM even beyond the first episode data. When one acknowledges the carryover effect of

therapy with repeated episodes, the value of true "episodic" treatment is further diminished.

The results of the secondary endpoints for "all treated episodes" reveal that only OM 20 mg shows consistent statistically significant benefit over placebo only in study 095. Small clinically and statistically insignificant trends are seen in study 092. One would expect more robust secondary endpoint efficacy data to consider approval of a treatment when the primary endpoints are not successfully reached and when the most important, first episode is not treated successfully.

As noted, the "all episode" composite and "last treated" episode data inherently include some carry-over effect from prior doses and do not represent true episodic treatment. Such a carry-over effect must be well characterized before last dose or overall benefit can be interpreted. If the modest efficacy suggested at some endpoints in these studies only extends to subjects that require daily or every other day treatment the product may be misbranded for treating the general population of occasional heartburn sufferers. The population with more frequent/ daily HB suffers that may benefit from OM treatment clearly overlap with GERD and may require medical assessment for Barrett's esophagus or erosive/ulcerative GERD before beginning therapy. Furthermore, continuous usage represents another concern when assessing the appropriateness of OTC treatment for HB.

Ultimately, last treated episode does not reflect a relevant endpoint for the current OTC indication of occasional HB. The frequent use in these studies represents subacute/chronic management.

In summary: Adequate and well controlled studies have failed to show efficacy for OM 10 or 20 mg for complete relief of single episodes of HB. Very modest benefit for secondary endpoints of adequate relief, backup medication use and overall assessment seen in study 095 were not reproduced in study 092.

The benefit of OM in the treatment of last episode and all episode HB treatment was modest and cofounded by carry-over effects from prior treatment. These last and all treated episode results are not relevant for consideration of OTC treatment of occasional HB.

Awaiting IR responses for analysis of truly episodic HB events and efficacy by severity. Discuss these results even if supportive of OTC approval

OTC appropriateness:

Finally, the issue of safety for OTC must consider the issue of missed diagnosis and delay of medical evaluation/treatment. As noted in the background section, severe frequent heartburn is considered to be a high risk for Barrett's esophagus and possibly esophageal cancer. If efficacy is limited to or primarily found in subjects with severe and frequent HB, the subpopulation least appropriate for OTC usage may be the population most likely to respond symptomatically. This effect may result in inappropriate use in subjects that should have sought medical evaluation and lack of efficacy in the population that is most appropriate for OTC treatment of HB. Adjust conclusions based on IR data submission for interaction between severity and efficacy.

Table 22

Study No. 1997095

TABLE 8.2.27 (CONTINUED)
PERCENT OF SUBJECTS WITH SUSTAINED COMPLETE RELIEF FOR THE FIRST-TREATED EPISODE OF HEARTBURN BY DEMOGRAPHIC[a] AND BASELINE CHARACTERISTICS
INTENT-TO-TREAT SUBJECTS[b,c]

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	Ome-Mg 20 (N = 627)[d]			Ome-Mg 10 (N = 623)[d]			PLACEBO (N = 602)[d]	
	n / m[e]	%[f]	Diff[g]	n / m[e]	%[f]	Diff[g]	n / m[e]	%[f]
Heartburn Frequency (% of days) During Run-In								
< 50 %	88/263	33.5%	2.9%	88/264	33.3%	2.8%	80/262	30.5%
≥ 50 %	95/364	26.1%	-2.4%	98/359	27.3%	-1.2%	97/340	28.5%
Average Heartburn Severity During Run-In								
< 2 (less than Moderate)	98/313	31.3%	-3.7%	93/301	30.9%	-4.2%	109/311	35.0%
≥ 2 (Moderate to Severe)	85/314	27.1%	3.7%	93/322	28.9%	5.5%	68/291	23.4%
Food Consumption During the 3-Hour Evaluation Period								
Yes	7/28	25.0%	-16%	12/32	37.5%	-3.9%	12/29	41.4%
No	176/595	29.6%	0.7%	174/591	29.4%	0.6%	165/572	28.8%

[a] Demographic characteristics at Screening (Visit 1).
[b] See Appendix 2.6.1.1 for complete data listings.
[c] See Appendices 1.9.3.26 and 1.9.4.14 for full statistical analyses and documentation.
[d] Number of subjects in each treatment group.
[e] Number of subjects with Sustained Complete Relief / number of subjects with non-missing values.
[f] Percentage of subjects with Sustained Complete Relief.
[g] Difference between treatment percentage and placebo percentage.

Table 23

Study No. 1997082

TABLE 8.2.27 (CONTINUED)
PERCENT OF SUBJECTS WITH SUSTAINED COMPLETE RELIEF FOR THE FIRST-TREATED EPISODE OF HEARTBURN BY DEMOGRAPHIC[a] AND BASELINE CHARACTERISTICS
INTENT-TO-TREAT SUBJECTS[b,c]

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	Ome-Mg 20 (N = 621)[d]			Ome-Mg 10 (N = 621)[d]			PLACEBO (N = 627)[d]	
	n / m[e]	%[f]	Diff[g]	n / m[e]	%[f]	Diff[g]	n / m[e]	%[f]
Heartburn Frequency (% of days) During Placebo Run-In Phase								
< 50 %	82/244	33.6%	3.7%	88/256	34.4%	4.5%	81/271	29.9%
≥ 50 %	105/376	27.9%	-1.3%	107/364	29.4%	0.2%	104/356	29.2%
Average Heartburn Severity During Placebo Run-In Phase								
< 2 (less than Moderate)	86/303	28.4%	-1.8%	84/290	29.0%	-1.2%	89/295	30.2%
≥ 2 (Moderate to Severe)	101/317	31.9%	2.9%	111/330	33.6%	4.7%	96/332	28.9%
Food Consumption During the 3-Hour Evaluation Period								
Yes	13/42	31.0%	6.0%	14/37	37.8%	12.8%	11/44	25.0%
No	174/578	30.1%	0.2%	180/581	31.0%	1.0%	174/581	29.9%

[a] Demographic characteristics at Screening visit (Visit 1).
[b] See Appendix 2.6.1.1 for complete data listings.
[c] See Appendices 1.9.3.26 and 1.9.4.14 for full statistical analyses and documentation.
[d] Number of subjects in each treatment group.
[e] Number of subjects with Sustained Complete Relief / Number of subjects with non-missing values.
[f] Percentage of subjects with Sustained Complete Relief.
[g] Difference between treatment percentage and placebo percentage.

Tables 22 and 23 indicate that in subjects with mild HB, OM trended worse than placebo. This represents the most appropriate population for OTC HB treatment.

GET Analysis of only severe suffers and daily sufferers.

8.2 Indication #2

Prevention of Meal induced HB

8.2.1 Studies 005 and 006: Multi-center, double-blind, randomized, single dose, placebo-controlled studies to investigate the efficacy of 10.3 and 20.6 mg Omeprazole Magnesium in preventing meal-induced heartburn symptoms following a provocative meal.

Studies 005 and 006 were identical in design. They were both conducted over the summer of 1998 by the same clinical research organization
In view of the replicative nature of the studies, they will be reviewed together.

Objective:
The primary objective of these studies was to assess the efficacy of pre-prandial dosing with OM 20.6 mg versus placebo in preventing the occurrence of heartburn over a 4-hour

period following a provocative meal. Secondary objectives included the comparison of OM 10.3 mg versus OM 20.6 mg and placebo for effectiveness in preventing the occurrence of HB over a 4-hour period following a provocative meal.

Study design:

Begin excerpt from CSR 005, 006

This study was a multi-center, double-blind, randomized, single-dose, placebo-controlled, double-dummy, parallel study with an initial target population of approximately 1242 completed subjects. The study consisted of four visits: two visits during the Screening period, a Baseline meal visit, and a Randomization meal visit. To be eligible for randomization to treatment, subjects must have experienced Moderate to Severe heartburn following the Baseline meal.

The purpose and procedures of the study were explained to potential subjects prior to enrollment. All subjects agreeing to participate were required to provide written informed consent and undergo eligibility screening, which included a physical exam and a medical/medication history.

Subjects who met all Continuance criteria were randomly assigned (in a 1:1:1 ratio) to one of the following treatment groups:

TREATMENT
Ome-Mg 20
Ome-Mg 10
Placebo

At the Randomization meal, subjects received two bottles of study medication, each containing one tablet. In the presence of study staff, subjects consumed both of their allocated tablets. Subjects consumed the tablets with water 1-hour prior to the Randomization meal. Subjects remained at the study center to evaluate their heartburn for 4 hours after the Randomization meal commenced (for study schematic, please consult Figure 1). Subjects who required relief from heartburn symptoms were strongly encouraged to wait until they experienced Moderate to Severe heartburn. They were to wait at least 2 hours after start of the Randomization meal before dosing with one or two tablets of a standard OTC antacid, Gelusil®, as backup medication.

Subjects were discharged from the study following the completion of all required Randomization visit procedures.

Study medication safety was evaluated from the self-reported adverse events (AEs) experienced by subjects after dosing and through the 4-hour evaluation period and from self-reported AEs experienced by subjects for the 48 hours following the Randomization meal. All AEs were tracked until resolution or until it was determined by a study physician that an ongoing AE was stable.

Study Scheme

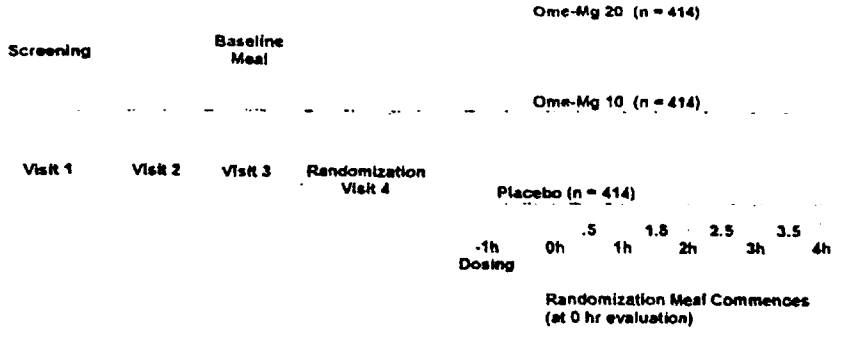


Table 24

Table A displays study-specific procedures performed at each visit:

Study No. 1998006

TABLE A
SCHEDULE OF EVENTS

PROCEDURE	VISIT 1	VISIT 2	VISIT 3 (BASELINE MEAL)	VISIT 4 (RANDOMIZATION MEAL)
Subject Number Assigned	X			
Informed Consent	X			
Inclusion/Exclusion Review	X			
Demographic Information Obtained	X			
Heartburn Symptom Screening Diary Dispensed	X			
Review of Prohibited Medications and Activities for Visit 2	X			
Heartburn Symptom Screening Diary Returned and Reviewed		X		
Medical History		X		
Medication History		X		

* female subjects of child-bearing potential only

TABLE 24 (CONTINUED)

Study No. 1998006

TABLE A (CONTINUED)
SCHEDULE OF EVENTS

PROCEDURE	VISIT 1	VISIT 2	VISIT 3 (BASELINE MEAL)	VISIT 4 (RANDOMIZATION MEAL)
Physical Exam		X		
Continuance Criteria Review for Visit 2		X		
Baseline Meal Visit Scheduling		X		
Before Meal Continuance Criteria			X	
Baseline Meal Diary Dispensed			X	
Administration of Baseline Meal			X	
After Meal Continuance Criteria			X	
Continuance Criteria Review for Randomization Visit				X
Urine Pregnancy Test*				X
Adverse Event Monitoring				X
Randomization Meal Diary Dispensed				X
Randomization to Study Medication				X
Study Medication Dosing				X
Administration of 30-minute Randomization Meal			X	X
Symptom Severity Assessment			X	X
Rescue Available as Backup Medication			X	X
Study Medication Accountability				X

* female subjects of child-bearing potential only

SYMPTOM SEVERITY ASSESSMENTS

At 30-minute intervals for the 4 hours following the beginning of the 30-minute provocative meal (as depicted in Table B), subjects evaluated their heartburn symptoms using the following categorical scale:

None (0): No heartburn is present.

Mild (1): Heartburn is present but easily tolerated.

Moderate (2): Heartburn is sufficient to cause interference with normal daily activities or sleep.

Severe (3): Heartburn is incapacitating. Subject is unable to perform normal daily activities or sleep.

Subjects recorded their evaluations directly onto the appropriate source diary. To ensure that subjects used identical terms to describe their heartburn, each subject was provided with uniform definitions of heartburn and heartburn severity (see Section 3.5.1). The table monitor supervised the subjects' recording of symptom severity and clock time of the evaluation on an appropriate source diary.

Inclusion Criteria

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

1. had provided written informed consent;
2. had a history of developing at least Moderate heartburn within 1-hour after provocative meals and the ability to identify foods/beverages that produced these heartburn symptoms;
3. had a history of developing heartburn which responds, to some degree, to antacids or OTC H_2RA treatments;
4. were male or non-pregnant, non-lactating female (women of child-bearing potential must have used an acceptable form of contraception [including abstinence] as determined by the Investigator), in good general health, any race, and at least 18 years of age; and
5. were willing to fast for the 4 hours preceding a scheduled provocative meal, to consume no H_2RAs or PPIs within 72 hours of the scheduled provocative meals, to consume no antacids or promotility agents within 24 hours of the scheduled provocative meals, and to abstain from sleeping or smoking during the scheduled provocative meal evaluation periods.

Continuance criteria at visit 2

To be considered eligible to continue participation in the Baseline meal, subjects:

1. continued to meet all specified Inclusion and Exclusion criteria;
2. returned a Heartburn Symptom Screening Diary indicating Moderate to Severe heartburn episodes occurring on at least 2 of the 7 days, with at least one of those episodes related to the ingestion of food; and
3. used NO phenytoin (Dilantin®), diazepam (Valium®), or warfarin (Coumadin®) since Visit 1.

Continuance criteria Visit 3

BEFORE MEAL CONTINUANCE CRITERIA

To be considered eligible to continue participation in the Baseline meal, subjects:

1. continued to meet all specified Inclusion and Exclusion criteria;
2. fasted for the 4 hours preceding the Baseline meal;
3. experienced no symptoms suggestive of heartburn during the 4 hours preceding the Baseline meal;
4. consumed no H_2RAs or PPIs within 72 hours of the Baseline meal;
5. consumed no antacids or promotility agents, for any reason, within 24 hours of the Baseline meal; and
6. used NO phenytoin (Dilantin), diazepam (Valium), or warfarin (Coumadin) since Visit 1.

AFTER MEAL CONTINUANCE CRITERIA

To be considered eligible to continue participation after the Baseline meal, subjects:

7. attained a peak heartburn severity of Moderate to Severe at some point during the evaluation period of the Baseline meal, and
8. experienced no vomiting at any time during the Baseline meal or during the subsequent 4-hour evaluation period.

Continuance criteria Visit 4

To be considered eligible to continue participation at Randomization visit, subjects:

1. continued to meet all specified Inclusion and Exclusion criteria;
2. had a negative urine pregnancy test at Visit 4, if female, prior to dosing with study medication, or documentation that she was not of childbearing potential;
3. fasted for the 4 hours preceding the Randomization meal;

Efficacy Measurements

Efficacy measurements were collected from subjects at the beginning of the provocative meals and every 30 minutes for 4 hours after the beginning of the provocative meals. To ensure that subjects used identical terms to describe their heartburn, each subject was instructed to use the following definitions throughout the study:

HEARTBURN DEFINITIONS
Heartburn is defined as an upward moving, uncomfortable sensation behind the breastbone, frequently accompanied by a burning or painful feeling.

SEVERITY SCALE DEFINITIONS:

None (0):	No heartburn is present.
Mild (1):	Heartburn is present but easily tolerated.
Moderate (2):	Heartburn is sufficient to cause interference with normal daily activities or sleep.
Severe (3):	Heartburn is incapacitating. Subject is unable to perform normal daily activities or sleep.

Subjects also provided an Overall Assessment of the study medication at the 4-hour evaluation or when dosing with backup medication by answering the following question:

"Overall, how would you rate the study medication?"

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

If backup medication was taken, the time was recorded. The subject then continued to record evaluations for the entire 4-hour period so they would not disrupt the study conduct.

In addition, safety was assessed by the collection of voluntary AEs after dosing with study medication at Visit 4.

Choice of parameter

The categorical severity score measured at each time point following the provocative meal is a common measure which has been used to assess heartburn symptoms. This 4-point scale has been used in previous studies evaluating heartburn prevention and should be capable of discriminating between the efficacy of omeprazole from placebo.[7]

The overall rating of study medication was used in several H_2RA (Rx-to-OTC switch) Summary Basis for Approvals. The 5-point scale has also been used in other OTC therapeutic areas which measure relief, such as analgesics.[9]

Primary efficacy variable

The primary efficacy variable is the percentage of subjects Heartburn-Free over the entire 4-hour period after the Randomization meal (i.e., severity score is 0 at all times).

Secondary efficacy variables

The following secondary efficacy variables were analyzed for the comparison of treatment effects:

1. the Overall Assessment of the study medication at the end of the 4-hour measurement period,
2. the Average Symptom Severity Score across the 4-hour measurement period,
3. the Maximum Symptom Severity Score over the 4-hour measurement period,
4. the Reduction of Maximum Symptom Severity Score of the Randomization meal from the Maximum Symptom Severity Score of the Baseline meal, and
5. the percentage of subjects who took backup medication (Backup Medication Use).
6. the Time to Backup Medication Use.

end of CSR excerpt

Study meal:

The study meal consisted of a McDonald's sausage biscuit and egg, one slice of cheese, 30 grams of raw onions and 8 ounces of Borden's chocolate milk. The sponsor chose this meal after preliminary studies showed a high post-meal HB incidence of 99% in a sample population of frequent HB sufferers.

Results:

Demographics: Tables 25-30 display the disposition and demographics of the three groups in both studies.

Table 25

8.7 Integrated Summary of Effectiveness

TABLE 6
SUBJECT DISPOSITION

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL

	005				006			
	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL
Randomized to Treatment	433	430	424	1287	394	387	390	1171
Completed 4-hour treatment phase[a]	428 (98.8%)	422 (98.1%)	421 (99.3%)	1271 (98.8%)	392 (99.5%)	386 (99.7%)	386 (99.0%)	1164 (99.4%)
Discontinued during treatment phase	5	8	3	16	2	1	4	7
Reasons For Discontinuation								
Did not meet Inclusion/Exclusion criteria	0	0	0	0	0	0	0	0
Did not meet Continuance criteria	0	2	0	2	0	0	0	0
Adverse Event	3	3	1	7	1	0	0	1
Subject reconsidered/withdrew consent	2	2	1	5	1	1	3	5
Lack of Efficacy	0	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0	0
Investigator/Sponsor decision	0	1	1	2	0	0	1	1

[a] Subjects who dosed with study medication and recorded severity ratings up to the 4-hour evaluation period.

There were no significant differences among the groups in discontinuations or reasons for discontinuation.

Table 26

8.7 Integrated Summary of Effectiveness

TABLE 8
DEMOGRAPHIC AND BASELINE CHARACTERISTICS

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL
INTENT-TO-TREAT SUBJECTS
(PAGE 1 OF 3)

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	005				006			
	Ome-Mg 20 (N = 433)	Ome-Mg 10 (N = 428)	PLACEBO (N = 423)	TOTAL (N = 1284)	Ome-Mg 20 (N = 393)	Ome-Mg 10 (N = 387)	PLACEBO (N = 390)	TOTAL (N = 1170)
Gender								
Female	63.0%	66.1%	61.5%	63.6%	59.3%	58.4%	59.2%	59.0%
Male	37.0%	33.9%	38.5%	36.4%	40.7%	41.6%	40.8%	41.0%
Race								
Caucasian	77.8%	76.3%	76.1%	77.4%	83.0%	89.1%	85.9%	86.0%
Black	17.3%	16.1%	17.7%	17.1%	13.5%	7.0%	11.3%	10.6%
Hispanic	3.2%	3.9%	4.0%	3.5%	3.1%	1.3%	2.6%	2.3%
Asian	0.5%	0.2%	0.7%	0.5%	0.0%	0.8%	0.0%	0.3%
American Indian	0.7%	0.5%	0.7%	0.6%	0.0%	0.3%	0.3%	0.2%
Multi-Racial/Other	0.5%	1.6%	0.7%	0.9%	0.5%	1.8%	0.0%	0.7%

Note: See Table 8.1.7 in Clinical Study Reports 1998005 and 1998006 and Appendix 1.1.8 in Section 8.7 for the table results.

Reviewer's Comment:

In study 006 there was an imbalance between groups in race. In some HB trials Black subjects have tended to have lower response rates than Caucasians. The relatively small differences in the primary efficacy results for OM 20 mg between Caucasian and Black subjects and the relatively small number of Blacks in the study make it very unlikely that

the results are biased by this asymmetry. If the OM 10-mg dose were to be considered for approval, the issue may need to be addressed.

Table 27

8.7 Integrated Summary of Effectiveness

TABLE 7
DATA SETS ANALYZED[a]

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL

	005				006			
	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL
Analysis Sets								
Intent-to-Treat	433 (100.0%)	428 (99.5%)	423 (99.8%)	1284 (99.8%)	393 (99.7%)	387 (100.0%)	390 (100.0%)	1170 (99.9%)
Per-Protocol	406 (93.8%)	396 (92.6%)	400 (94.3%)	1204 (93.6%)	389 (98.7%)	380 (98.2%)	380 (97.4%)	1149 (98.1%)

[a] Figures indicate number of subjects eligible for analyses. In some analyses, the numbers may be less due to missing data.

Note: See Table 8.1.5 in Clinical Study Reports 1998005 and 1998006 for the table results.

Table 28

8.7 Integrated Summary of Effectiveness

TABLE 8 (CONTINUED)
DEMOGRAPHIC AND BASELINE CHARACTERISTICS

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL
INTENT-TO-TREAT SUBJECTS
(PAGE 2 OF 3)

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	005				006			
	Ome-Mg 20 (N = 433)	Ome-Mg 10 (N = 428)	PLACEBO (N = 423)	TOTAL (N = 1284)	Ome-Mg 20 (N = 393)	Ome-Mg 10 (N = 387)	PLACEBO (N = 390)	TOTAL (N = 1170)
Age (Years)								
Mean	42.8	42.7	42.7	42.7	42.2	44.6	43.4	43.4
Std. Deviation	12.75	12.92	13.27	12.97	12.83	13.34	13.56	13.30
Minimum–Maximum	18–78	18–86	18–81	18–86	18–83	19–80	18–81	18–83
< 65 Years	94.5%	93.2%	94.3%	94.0%	94.4%	91.7%	91.3%	92.5%
≥ 65 Years	5.5%	6.8%	5.7%	6.0%	5.6%	8.3%	8.7%	7.5%
Current Smoker								
Yes	29.1%	27.8%	27.9%	28.3%	30.0%	33.9%	29.0%	30.9%
No	70.9%	72.2%	72.1%	71.7%	70.0%	66.1%	71.0%	69.1%

Note: See Table 8.1.7 in Clinical Study Reports 1998005 and 1998006 and Appendix 1.1.8 in Section 8.7 for the table results.

The age and smoking status were well distributed between groups. Not displayed are the demographics on the most frequent concomitant medications. The subjects were well distributed among groups in both studies in this regard as well.

Table 29

8.7 Integrated Summary of Effectiveness

TABLE 8 (CONTINUED)
DEMOGRAPHIC AND BASELINE CHARACTERISTICS

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL
INTENT-TO-TREAT SUBJECTS
(PAGE 3 OF 3)

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	005				006			
	Ome-Mg 20 (N = 433)	Ome-Mg 10 (N = 428)	PLACEBO (N = 423)	TOTAL (N = 1284)	Ome-Mg 20 (N = 393)	Ome-Mg 10 (N = 387)	PLACEBO (N = 390)	TOTAL (N = 1170)
Average Heartburn Severity Following Baseline Meal								
Mean	1.4	1.3	1.4	1.3	1.4	1.4	1.4	1.4
Std. Deviation	0.43	0.43	0.40	0.42	0.43	0.42	0.44	0.43
Minimum–Maximum	0.2–2.7	0.4–2.7	0.4–2.7	0.2–2.7	0.3–2.7	0.3–2.7	0.3–2.7	0.3–2.7
Less than Moderate (<2)	91.0%	90.4%	91.1%	90.8%	88.0%	90.4%	89.7%	89.4%
Moderate to Severe (≥2)	9.0%	9.6%	8.9%	9.2%	12.0%	9.6%	10.3%	10.6%
Maximum Heartburn Severity Following Baseline Meal								
N/A	5.3%	4.9%	4.7%	5.0%	0.0%	0.3%	0.0%	0.1%
Mild	0.0%	0.7%	0.0%	0.2%	0.0%	1.0%	1.0%	0.7%
Moderate	65.1%	69.6%	67.1%	67.3%	66.2%	66.7%	67.2%	66.7%
Severe	29.6%	24.8%	28.1%	27.5%	33.8%	32.0%	31.8%	32.6%

Note: See Table 8.1.7 in Clinical Study Reports 1998005 and 1998006 and Appendix 1.1.8 in Section 8.7 for the table results.

Heartburn severity was well distributed among groups at baseline.

Table 30

8.7 Integrated Summary of Effectiveness

TABLE 9
SUMMARY OF FACTORS CONTRIBUTING TO HEARTBURN SYMPTOMS
DURING 30-DAY PERIOD PRECEDING ENTRY
INTO THE PRE-PRANDIAL STUDIES
INTENT-TO-TREAT SUBJECTS

STUDY NUMBER	005	006
SAMPLE SIZE	1284	1170
Heartburn Symptom Factors[a]		
Food and/or Beverage	99.8%	99.8%
Stress and/or Anxiety	63.1%	60.3%
Lying Down	53.0%	51.4%
Hectic Lifestyle	37.5%	37.6%
Physical Activity	22.6%	23.2%
Medication	6.7%	8.4%

[a] Subject could select more than one heartburn symptom factor to describe typical cause over the past month.
Note: Information in this table is extracted from Table 8.1.9 in Clinical Study Reports 005 and 006.

Reviewer's Comment:
The sponsor's proposed label includes the indication: "prevention of HB symptoms due to a multitude of causes". The activities above are considered to exacerbate or trigger HB. Essentially 100% of subjects have food/beverage induced HB. Without a validated methodology to specifically study activity induced HB (similar to the provocative meal

model), it is impossible to assess the efficacy of OM on HB other than meal induced HB in the provocative meal setting and overall HB in the 2-week prevention model.

Efficacy results:

Table 31

6.7 Integrated Summary of Effectiveness

TABLE 10
ANALYSIS OF PRIMARY EFFICACY VARIABLE
HEARTBURN-FREE THROUGH 4 HOURS

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL
INTENT-TO-TREAT SUBJECTS

STUDY 005	Ome-Mg 20	Ome-Mg 10	PLACEBO
Heartburn-Free (%)	25.4% (110/433)	24.3%(104/428)	20.1% (85/423)
COMPARISONS	P-VALUE[a]	ODDS RATIO (95% CI)[b]	DIFF IN PROP (95% CI)[c]
Ome-Mg 20 vs. Placebo	0.057	1.38 (0.99,1.92)	5.3%(-0.5%,11.1%)
Ome-Mg 10 vs. Placebo	0.139	1.29 (0.92,1.79)	4.2% (-1.6%,10.0%)
Ome-Mg 20 vs. Ome-Mg 10	0.675	1.07 (0.78,1.47)	1.1% (-4.9%,7.1%)

STUDY 006	Ome-Mg 20	Ome-Mg 10	PLACEBO
Heartburn-Free (%)	25.7% (101/393)	25.3% (98/387)	17.2% (67/390)
COMPARISON	P-VALUE[a]	ODDS RATIO (95% CI)[b]	DIFF IN PROP (95% CI)[c]
Ome-Mg 20 vs. Placebo	0.004	1.70 (1.19,2.43)	8.5% (2.5%,14.5%)
Ome-Mg 10 vs. Placebo	0.005	1.67 (1.17,2.38)	8.1% (2.2%,14.1%)
Ome-Mg 20 vs. Ome-Mg 10	0.854	1.03 (0.74,1.44)	0.3% (-6.0%,6.8%)

[a] P-values for treatment comparisons obtained from Cochran-Mantel-Haenszel chi-square test with investigator as a stratification variable.

[b] Estimated odds ratios and 95% confidence intervals (CI) from logistic regression analysis with Treatment and Investigator (pooled) as categorical variables.

[c] Estimated difference in proportion (expressed as a percent) with 95% confidence interval using a normal approximation.

Note: See Tables 6.2.1, 6.2.2, 6.2.3, and 6.2.16 in Clinical Study Reports 1998005 and 1998006 for the table results. See Appendix 1.1.2 of Section 6.7 for documentation of these table results.

Reviewer's Comment:

Results of studies 005 and 006 are displayed in table 34. These data reflect modest benefit for OM 10 or 20mg for total prevention of HB in study 006 and a trend of smaller numeric benefit in study 005. Results of study 005 were supportive in trend but not statistically significant. Efficacy at HB prevention could not be confidently claimed if this endpoint was the only clinically relevant endpoint studied. In view of the multiple other meaningful endpoints, the issue of efficacy at preventing meal induced HB will need to be considered in light of the entire efficacy database. The lack of meaningful differentiation between doses is of note and unless other efficacy results are compelling in support of OM 20 mg, the proposed dose will need to be seriously reconsidered.

Table 32

8.7 Integrated Summary of Effectiveness

TABLE 16
ANALYSIS OF PRIMARY EFFICACY VARIABLE
HEARTBURN-FREE THROUGH 4 HOURS
(COMBINED DATA FROM STUDIES 005 & 006)

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	PLACEBO
Heartburn-Free (%)	25.5% (211/826)	24.8% (202/815)	18.7% (152/813)

COMPARISONS	ODDS RATIO (95% CI)[a]	DIFF IN PROPORTIONS (95% CI)[b]
Ome-Mg 20 vs. Placebo	1.49 (1.18,1.89)	6.8% (2.7%,11.0%)
Ome-Mg 10 vs. Placebo	1.43 (1.13,1.82)	6.1% (2.0%,10.2%)
Ome-Mg 20 vs. Ome-Mg 10	1.04 (0.83,1.30)	0.8% (-3.6%,5.1%)

[a] Estimated odds ratios and 95% confidence intervals (CI) from logistic regression analysis with Treatment and Study as categorical factors. The Study-by-Treatment interaction was not significant ($p = 0.565$).

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

Note: See Appendix 1.1.6 in Section 8.7 for documentation of table results.
Source: TT9961 /home3/tj4346/ise056/saspgm/logist.sas, mergecmh.sas, hb_free.sas
H:\data\wfw\hc39\ise\005006\tables\isetab.doc

Discuss with statistics....

Odds ratios are of great value in assessing clinical benefit when the clinical endpoints are mortality or a seriously morbid condition. The therapeutic gain or difference in proportions may be more appropriate for providing a meaningful measure to a patient in this setting than the odds ratio. The combined analysis in table 35 highlights the comparability of 10 and 20 mg OM.

Secondary efficacy endpoints

Table 33

8.7 Integrated Summary of Effectiveness

TABLE 11
ANALYSIS OF SECONDARY EFFICACY VARIABLES

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	PLACEBO
Overall Assessment[a]			
Study 005	**77.3%[A]**	70.6%	69.2%
Study 006	**81.1%[A]**	**76.7%[A]**	71.8%
Maximum Severity Score[b]			
Study 005	**75.3%[A]**	**72.0%[A]**	66.2%
Study 006	**76.6%[A]**	**73.1%[A]**	63.1%
Backup Medication Use (within 4 Hours)[c]			
Study 005	**4.4%[A]**	7.0%	8.3%
Study 006	**1.8%[A]**	**3.6%[A]**	6.4%
Average Symptom Severity[d]			
Study 005	**0.49[A]**	0.50	0.58
Study 006	**0.44[A]**	**0.47[A]**	0.60
Reduction of Maximum Severity Scores[d]			
Study 005	**-1.31[A]**	-1.20	-1.10
Study 006	**-1.35[A]**	**-1.25[A]**	-1.06

[a] Percentage of subjects with Good, Very Good, and Excellent ratings on overall assessment of study medication. All levels of this variable were utilized for testing for treatment differences using Extended-Mantel-Haenszel chi-square test with investigator as a stratification variable.

[b] Percentage of subjects with None or Mild scores on maximum severity. All levels of this variable were utilized for testing for treatment differences using Extended-Mantel-Haenszel chi-square test with investigator as a stratification variable.

[c] Percentage of subjects who took backup medication, treatment difference was tested using Cochran-Mantel-Haenszel chi-square test with investigator as a stratification variable.

[d] Least-square means from ANOVA with Treatment and Investigator as factors.

[A] Significantly different from Placebo ($p \leq 0.05$); values are bolded in table.

Note, no differences between Ome-Mg 20 and Ome-Mg 10 were statistically significant ($p > 0.05$).

Note: See Tables 8.2.1, 8.2.2, 8.2.4, and 8.2.5 in Clinical Study Reports 1998005 and 1998006 for the table results.

Reviewer's Comment's:

The consistent statistically significant therapeutic gain associated with OM 20 mg in 5 secondary endpoints in both studies is convincing that there is a measurable preventive effect of OM 20-mg in the setting of a single provocative meal. These results are displayed in table 33. The issue of dose is raised again in this analysis. Although the efficacy of 10-mg OM only reached statistical significance at all secondary endpoints displayed in table 33 for study 006, the trend was maintained in study 005. There were no statistically significant differences between OM 10 and 20 mg and the numeric differences were modest to marginal.

Stratification by baseline history of factors contributing to HB

Table 34 displays the efficacy results for the primary endpoint of total HB prevention over the 4-hour observation period post meal **based on the 30-day run-in diary of "typical" HB precipitants.**

Table 34

8.7 Integrated Summary of Effectiveness

TABLE 14
PERCENTAGE OF SUBJECTS HEARTBURN-FREE THROUGH 4 HOURS
BY FACTOR CONTRIBUTING TO HEARTBURN DURING THE 30-DAY PERIOD PRECEDING THE STUDY[a]
(COMBINED DATA FROM STUDIES 005 & 006)

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20 (N = 826)[b]			Ome-Mg 10 (N = 815)[b]			Placebo (N = 813)[b]	
FACTOR	n / m[c]	%[d]	Diff[e]	n / m[c]	%[d]	Diff[e]	n / m[c]	%[d]
Hectic Lifestyle								
Yes	74/313	23.6%	6.2%	72/315	22.9%	5.5%	51/293	17.4%
No	137/513	26.7%	7.3%	130/500	26.0%	6.6%	101/520	19.4%
Stress and/or Anxiety								
Yes	126/503	25.0%	6.4%	133/517	25.7%	9.1%	82/495	16.6%
No	85/323	26.3%	4.3%	69/298	23.2%	1.2%	70/318	22.0%
Food and/or Beverage								
Yes	211/826	25.5%	6.9%	202/812	24.9%	6.3%	151/812	18.6%
No	0/0	N/A	N/A	0/3	0.0%	-100.0%	1/1	100.0%
Physical Activity								
Yes	49/192	25.5%	8.2%	47/191	24.6%	7.3%	31/179	17.3%
No	162/634	25.6%	6.5%	155/624	24.8%	5.7%	121/634	19.1%
Medication								
Yes	11/59	18.6%	5.0%	18/66	27.3%	13.7%	8/59	13.6%
No	200/767	26.1%	7.0%	184/749	24.6%	5.5%	144/754	19.1%
Lying Down								
Yes	109/412	26.5%	7.2%	113/469	24.1%	4.8%	77/400	19.3%
No	102/414	24.6%	6.4%	89/346	25.7%	7.5%	75/413	18.2%

[a] Subjects may indicate more than one factor contributing to heartburn.
[b] Number of Intent-to-Treat subjects in each treatment group.
[c] Number of subjects heartburn free / Number of subjects with non-missing values.
[d] Percentage of subjects heartburn-free.
[e] Difference between treatment percentage and placebo percentage.

Note: See Appendix 1.1.5 of Section 8.7 for supporting documentation.
Source: TT9981 /home3/l/l4346/lse056/sasppm/demogra3.sas
H:\data\w\w\hc39\lse\005006\tables\lsetab.doc

Reviewer's Comment:
No conclusions can be drawn about the efficacy of OM in preventing HB caused by the various specific factors listed. The efficacy results from the present studies can only be applied to the study model; meal induced HB. One may be tempted to over interpret the results on the "stress and or anxiety" subgroup. This category is not well defined and is not easily distinguished from "hectic lifestyle". The sponsor provided no evidence to

validate the instrument used to ascertain these demographic data and no evidence to support a relationship between the various historically reported HB precipitants and the efficacy data (except for meal induced HB model that was used).

Subgroup analysis

Table 35

8.7 Integrated Summary of Effectiveness

TABLE 12
PERCENTAGE OF SUBJECTS HEARTBURN-FREE THROUGH 4 HOURS
BY DEMOGRAPHIC[a] AND BASELINE CHARACTERISTICS
(COMBINED DATA FROM STUDIES 005 & 006)

SINGLE DOSE PREVENTION STUDIES: HEARTBURN ASSOCIATED WITH A PROVOCATIVE MEAL
INTENT-TO-TREAT SUBJECTS

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	Ome-Mg 20 (N = 826)[b]			Ome-Mg 10 (N = 815)[b]			PLACEBO (N = 813)[b]	
	n / m[c]	%[d]	Diff[e]	n / m[c]	%[d]	Diff[e]	n / m[c]	%[d]
Gender								
Female	111/506	21.9%	5.4%	118/509	23.2%	6.7%	81/491	16.5%
Male	100/320	31.3%	9.3%	84/306	27.5%	5.5%	71/322	22%
Race								
Caucasian	169/663	25.5%	7.1%	175/680	25.7%	7.3%	121/657	18.4%
Non-Caucasian	42/163	25.8%	5.9%	27/135	20.0%	0.1%	31/156	19.9%
Age (Years)								
< 65	202/780	25.9%	7.2%	187/754	24.8%	6.1%	141/755	18.7%
≥ 65	9/46	19.6%	0.6%	15/61	24.6%	5.6%	11/58	19%
Current Smoker								
Yes	71/244	29.1%	11.5%	57/238	23.9%	6.3%	42/239	17.6%
No	140/582	24.1%	4.9%	145/577	25.1%	5.9%	110/574	19.2%
Average Heartburn Severity Following Baseline Meal[f]								
Less than Moderate (< 2)	197/719	27.4%	7.3%	192/717	26.8%	6.7%	144/717	20.1%
Moderate to Severe (≥ 2)	9/84	10.7%	4.1%	6/76	7.9%	1.3%	5/76	6.6%
Overall								
	211/826	25.5%	6.8%	202/815	24.8%	6.1%	152/813	18.7%

[a] Demographic characteristics collected at Screening visit (Visit 1).
[b] Number of Intent-to-Treat subjects in each treatment group.
[c] Number of subjects heartburn free / Number of subjects with non-missing values.
[d] Percentage of subjects heartburn-free.
[e] Difference between treatment percentage and placebo percentage.
[f] Scores are 1 = Mild, 2 = Moderate, and 3 = Severe.

Note: See Appendix 1.1.3 of Section 8.7 for supporting documentation.
Source: TT9981 /home3/lj4348/lee056/saspgm/demogra3.sas
H:\data\wfwhc39\lee\005006\tables\lastab.doc

The data in table 35 do not allow for any conclusions to be drawn regarding efficacy in the various subgroups when both doses are considered. Non-Caucasian participants and those ≥65 years of age had less robust data but at least one dose displayed a positive trend for these subgroups.

The issue of efficacy based on severity of HB is important in view of the concern in the medical literature over the proper evaluation of severe HB suffers. Unfortunately, when used in the medical literature, there is no consensus on the optimal definition of "severe

heartburn" despite frequent references to the importance of this subgroup. ***For this reason, the sponsor has been asked to subanalyze the efficacy of OM in all pivotal trials stratified by >50% of days with HB and severity average over 2.5 (out of a three-point scale). If the efficacy is limited to this group, the appropriateness of OM for the OTC market will need to be reassessed.***

Conclusions:

1. *The sponsor has not provided replicated evidence of a statistically significant benefit of OM at 10 or 20 mg over placebo for the complete prevention of meal induced HB. The evidence for the claim of HB prevention however may be considered adequate based on:*
   a. *small p- value of 0.005 in study 006, a large multicenter study with over 1200 subjects*
   b. *supportive trends for both 10 and 20 mg OM (p= 0.057, 0.139) in study 005*
   c. *supportive secondary endpoints that measured other parameters related to efficacy of OM at lessening the severity of HB. These endpoints include:*
      i. *overall assessment of study drug*
      ii. *maximum HB severity*
      iii. *backup medication use*
      iv. *average symptom severity*
      v. *reduction of maximum severity score*

2. The optimal dose for OTC approval may be 10 mg. This issue should be addressed in the context of all indications, meal induced HB, 24 hour prevention, and treatment of HB. The indication of meal induced HB appears to be comparably prevented with both doses. Optimal dose involves safety as well as efficacy issues and is a subject for discussion with the division of OTC medication.

8.3 Indication #3

"Subacute heartburn prevention": Studies 171, 183

The sponsor has conducted two identical studies to provide evidence that OM at 10 and 20-mg **prevents HB over a 24 hour period.** The protocol provided for a 2-week daily

usage with secondary analyses including prolonged prevention off therapy. These studies were submitted to support the following portion of the label.

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

Directions:
"For prevention of symptoms for 24 hours: swallow 1 tablet with a glass of water, anytime during the day, or if you prefer, one hour before those events associated with occasional heartburn, such as consuming food and beverages, stress, hectic lifestyle, lying down, or exercise"
excerpt from summary volume page 29

Reviewer's Comment:
The proposed label includes HB prevention not related to a specific meal. This label and the supporting studies 171 and 183 introduce a new indication for OTC treatment of HB. The currently approved OTC medications for HB are labeled for prevention of meal induced HB and treatment of specific episodes of HB. The intended usage is for occasion sufferers of HB and usage beyond 10 days is not indicated without the direction of a physician. The current H2RA OTC template label is intended to discourage chronic therapy for chronic HB. In fact there is a very thin line between HB and GERD. HB is the most prominent symptomatic manifestation of GERD. The more severe and chronic the HB symptoms, the more likely one is in effect dealing with GERD. Daily usage of any medication for HB is indistinguishable from GERD treatment. OTC treatment of GERD is not currently approved. Efficacy at preventing HB for 24 hours a day for 10 days in an undiagnosed population is not the only issue in considering OTC usage. OTC use for daily 24 hour prevention for 10 days is a new indication. This issue that should be addressed independent of efficacy within the context of a clinical trial.
Nonetheless, the efficacy of OM in this setting will be reviewed.

8.3.1 Studies 171, 183:

Identical multicenter, double blind, randomized, placebo controlled studies to investigate the safety and efficacy of omeprazole, 10 and 20 mg qd in preventing heartburn

Both studies were conducted between January and July of 1998 in the United States. Both studies had 25 study centers.

Beginning excerpt from CSR:

The primary objective of this study was to demonstrate that a single dose of omeprazole

magnesium is effective in completely preventing the occurrence of heartburn over a full day.
Secondary objectives included:

1. The comparison of treatment groups with regard to the maximum severity of heartburn and the occurrence of nocturnal heartburn after a single dose,
2. The comparison of treatment groups with regard to the complete prevention of heartburn over a full day, the maximum severity of heartburn and the occurrence of nocturnal heartburn over repeated daily doses,
3. The description of incidence of heartburn for each treatment group during the follow-ups phase,
4. The demonstration that omeprazole magnesium is safe and well tolerated when used to prevent heartburn

Study design:

This study was a multicenter, double-blind, randomized, parallel, placebo-controlled study to investigate the safety and efficacy of omeprazole magnesium, 10 mg qd and 20 mg qd, in preventing heartburn. The five week study had the following three phases:

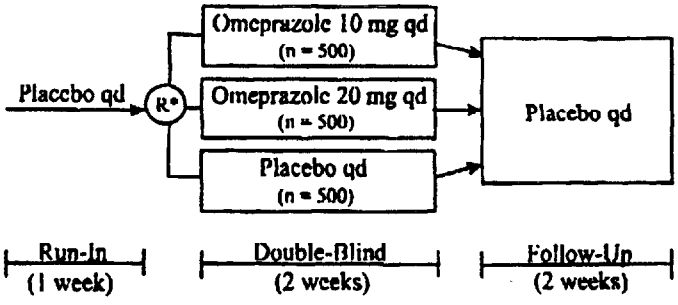
- Single-Blind placebo Run-In (one week),
- Double-Blind randomized treatment (two weeks), and
- Single-Blind placebo Follow-Up (two weeks).

For all phases of the study, subjects were given a diary with instructions to complete it on a daily basis. The diary was designed to collect information on maximum heartburn severity, nocturnal heartburn, and antacid consumption for the previous 24 hours. In addition, the date and time of study medication consumption was recorded. Subjects were provided with uniform definitions of heartburn and heartburn severity.

During each study phase the blinded nature of the study was preserved using double dummy packaging. The subject was always dispensed two bottles of medication: Bottle A contained active or placebo Ome-Mg 10, Bottle B contained active or placebo Ome-Mg 20. Both bottles contained placebo for the placebo arm of the treatment phase and during the Run-In and Follow-Up phases.

Subjects were dispensed GELUSIL® at every visit but encouraged not to use it unless absolutely necessary for the relief of heartburn. Subjects were instructed to take one tablet for the relief of heartburn, but no more than six tablets per day.

The following schematic illustrates the design of the study.



* Randomization

Visit 1 (Screening)
Consented subjects who satisfied entrance criteria received a sequential enrollment number. The first subject enrolled by each investigator was identified as 001. This report and appendices identify each subject with the investigator number as a preface (eg. 012001: investigator 012, subject 001). The enrollment number did not change when subjects were randomized.

At Visit 1, informed consent was obtained, a complete medical history was obtained, physical exam performed, and routine laboratory samples collected. These included SGOT, SGPT, serum creatinine, serum magnesium, hemoglobin, platelets, and WBC counts as well as a serum pregnancy test for women of childbearing potential. Subjects were questioned regarding factors that they felt contributed to their heartburn over the past month. Properly consented subjects who satisfied enrollment criteria were entered into the Run-In phase and dispensed single-blind placebo kits and heartburn diaries. GELUSIL® tablets were also supplied to the subjects to use throughout the study, if necessary.

Visit 2 (Baseline/Randomization)
At Visit 2, seven to nine days following Visit 1, the Run-In phase diaries were reviewed to determine if subjects satisfied the following criteria for randomization:

- at least two days with heartburn,
- no more than two days with missed doses, and
- no more than two days with incomplete or inconsistent diary entries.

Compliance with study medication and safety were also monitored at this visit. Approximately 1500 eligible subjects were to be randomized and dispensed diaries to record heartburn symptomatology and the date and time of study medication consumption. They were to receive one of the following medications:

• Ome-Mg 20, qd	500 subjects
• Ome-Mg 10, qd	500 subjects
• placebo qd	500 subjects

GELUSIL® tablets were also supplied to the subjects to use throughout the study, if necessary.

One week following Visit 2 subjects were contacted by telephone to monitor safety, encourage diary and medication compliance and confirm the date of Visit 3.

Visit 3 (Week 2)
At Visit 3, 14 days (± 2 days) following randomization, the diaries from the Double-Blind phase were collected and reviewed. Subjects were evaluated for adverse events and blood specimens were drawn at this visit for laboratory analysis. Subjects were dispensed a diary and single-blind placebo to be used over the next 14 days. A new supply of GELUSIL® was also supplied.

One week following Visit 3 subjects were contacted by telephone to monitor safety, encourage diary and medication compliance and confirm the date of Visit 4.

Visit 4 (Week 4)
At Visit 4, 15 days (± 2 days) following Visit 3, subjects returned for their final visit where Visit 3 diaries were reviewed and adverse events were recorded.

Table A displays the procedures that were to be performed and target dates for each of the office visits.

STUDY NO. 171

TABLE A
STUDY FLOW CHART

PROCEDURES	VISIT 1 SCREENING	VISIT 2† BASELINE	WEEK 1	VISIT 3 WEEK 2	WEEK 3	VISIT 4 WEEK 4
Study Day	-7	0	7	14	21	29
Informed Consent	X					
Medical History	X					
Physical Exam[1]	X					
Laboratory Analysis[1]	X			X		
Diary Dispensed	X	X		X		
Diary Collected and Reviewed		X		X		X
Study medication, GELUSIL® Dispensed	X	X		X		
Study medication, GELUSIL® Accountability		X		X		X
Prior/Concomitant Medications	X	X		X		X
Adverse Event Monitoring		X	X	X	X	X
Telephone Contact			X		X	

† Randomization occurs.

[1] To be repeated during the study if deemed necessary by the investigator due to an adverse event.

Inclusion Criteria:

Subjects who met the following symptoms and criteria were eligible for enrollment:

- Heartburn on at least two days per week over the past month.
- Heartburn which responds, to some degree, to antacids or OTC H_2-receptor antagonist treatment.
- Male or non-pregnant, non-lactating female ≥18 years. Women of childbearing potential must maintain effective contraception during the study and must have a negative serum pregnancy test at screening.
- An ability to provide written informed consent and to demonstrate an ability to understand and follow diary instructions.

Continuance Criteria:

Subjects must have met the following criteria to be eligible for randomization:

- Presence of heartburn on at least two days during the Run-In phase.
- No more than two days with missed doses or with incomplete or inconsistent entries in the Run-In diary.

Exclusion Criteria:

Subjects were excluded from the study if they demonstrated:

- History of erosive esophagitis verified by endoscopy.
- History of gastroesophageal reflux disease (GERD) diagnosed by a physician.
- History of pathologic intraesophageal pH monitoring.
- Any underlying medical condition or necessary concomitant medication which may interfere with the evaluation of heartburn treatment.
- Clinically significant and/or unstable renal or hepatic disease as demonstrated via medical history or screening laboratory analyses.
- The need for continuous treatment with ranitidine, famotidine, nizatidine, cimetidine, lansoprazole, omeprazole, metoclopramide, or cisapride. The previous use of intermittent antisecretory or promotility agents is permitted as long as they are discontinued at least 3 days prior to the Run-In phase.
- The need for continuous treatment with diazepam, phenytoin or warfarin.
- An unwillingness to participate in this study by taking something other than GELUSIL®, if needed, for heartburn.
- The use of any antacids for other indications (eg., dyspepsia, diarrhea, calcium supplement) throughout the study.
- Known hypersensitivity to any component of omeprazole or GELUSIL®.
- Participation in an Ome-Mg study since January 1, 1998.
- Participation in another investigational drug study within 30 days of the Run-In phase.
- Known history (within the past 12 months) of alcoholism or illicit drug use or abuse, or any condition associated with poor compliance.
- Any other medical condition or situation that the investigator feels constitutes a safety concern (eg., gastrointestinal bleeding, malignancy, etc.).

Dose selection:

The doses selected in this study, omeprazole 10 mg and omeprazole 20 mg, have been previously evaluated in patients with reflux symptoms associated with GERD as well as in erosive esophagitis. [1,2] Therefore, we investigated the efficacy and safety of Ome-Mg 10 and Ome-Mg 20 in this study to determine the optimal effective OTC dose for prevention of occasional episodic heartburn.

end of CSR excerpt

Reviewer's Comments:

1. *Inclusion/Exclusion Criteria: Excluding subjects that have not responded to OTC HB treatments enriches the response rate of the study population. If efficacy were to be limited to subjects who have benefited from antacids or H2RA s, such information would be very important for labeling purposes. The presence of a proton pump inhibitor OTC will be assumed by many to be better than other OTC treatments and OM may be used by subjects refractory to other OTC medications. It would be very valuable for consumers to know if OM was not effective in those refractory to the currently available medications. Unfortunately, the sponsor has conducted a study with the opposite design.*
2. *In view of the presumed difference between episodic HB and GERD, a lower dose of OM should have been considered. The sponsor was advised by the Division to study lower doses of OM such as 5 mg prior to conducting the submitted studies. Such dose ranging would have been appropriate given the profound effects on gastric acid production of both 10 and 20 mg of OM.*
3. *The study design excluded occasional HB sufferers with less than 2 episodes per week. The demographic results displayed in table 40 reveal that the mean frequency of HB during the run-in phase for these studies was over 70% of days and the mean severity was between "easily tolerated" and "interfering with normal daily activities or sleep". The inclusion criteria yielded a study population of HB sufferers that would likely fall into a clinical category suggesting GERD.*
4. *The continuance criteria excluded individuals that may not be compliant with dosing instructions. This enhances the likelihood of finding a difference between groups but overestimates what can be expected in OTC use setting.*

Timing of dose:

Begin CSR excerpt

Subjects were instructed to begin taking their first dose of the newly dispensed study medication the morning following each visit. Subjects were instructed to take their study medication every morning when they woke up and to record the date and time of dosing in their new diary. Study medication was requested to be taken before breakfast, if possible, and before noon in all cases.

GELUSIL® tablets were supplied to the subjects for use throughout the study. Subjects were encouraged not to use the GELUSIL® unless absolutely necessary for the relief of heartburn. Subjects were instructed to take one tablet for the relief of heartburn, but no more than six tablets per day.

Reviewer's Comment:
The instructions were to take the study medication on awakening. The proposed label directs the consumer to 'Swallow 1 tablet with a glass of water anytime during the day". The study design does not support the proposed label for instructions.

Prior and concomitant medications:

GELUSIL® was available at all times although the subject was required to carefully document its use in the heartburn evaluation diary. Concomitant use of other antacids, pro-motility agents, proton pump inhibitors and H_2-RAs was prohibited. Subjects requiring routine treatment with diazepam, phenytoin or warfarin were excluded.

Primary efficacy variable:

The primary efficacy variable was no heartburn over 24 hours (i.e., complete prevention of heartburn) and the primary evaluation was the period between the first and second daily dose following randomization (Day 1).

Secondary efficacy variables:

The following efficacy variables were to be evaluated on Day 1:
- the complete prevention of nocturnal heartburn (no nocturnal heartburn)
- the occurrence of no more than mild heartburn (no more than mild heartburn over 24 hours)

Over the two-week double-blind phase, the following variables were also to be evaluated:
- the percentage of days with the outcome of no heartburn over 24 hours
- the percentage of days with the outcome of no nocturnal heartburn
- the percentage of days with the outcome of no more than mild heartburn over 24 hours

The occurrence of heartburn during the single-blind placebo Follow-Up phase was also of interest in this study.

Ascertainment tools:

All measures of efficacy were derived from data recorded in the subject diaries after daily self-assessment. Prevention of heartburn after the first dose was of principal interest, although the overall benefit of subsequent doses was evaluated.

In order to prevent subjects from using different terms to describe their heartburn, each subject was instructed to use the following uniform definitions throughout the study.

Heartburn is defined as an upward moving, uncomfortable sensation behind the breastbone, frequently accompanied by a burning or painful feeling.

To classify heartburn severity, subjects were instructed to use the most intense episode of the 24 hour period.

Intensity Scale Definitions:

No heartburn:	No heartburn is present
Mild:	Heartburn is present but easily tolerated
Moderate:	Heartburn is sufficient to cause interference with normal daily activities or sleep
Severe:	Heartburn is incapacitating. Subject is unable to perform normal daily activities or sleep

Every morning during the five week study, each subject completed his or her diary by answering the following questions:

Over the last 24 hours (yesterday and last night), what was the severity of your most intense episode of heartburn? (No Heartburn, Mild, Moderate, Severe)

Did you experience heartburn during the night (from going to bed last night to getting out of bed this morning)? (Yes, No)

Over the last 24 hours, how many GELUSIL® tablets did you take?

Subjects were instructed to complete their diary and take their dose of study medication each morning prior to breakfast. After recording information for the previous 24 hour period, subjects took that day's dose of study medication, ensuring the date and time were recorded in their diary.

End excerpt from CSR

Results:

Due to the identical design of studies 171 and 183, the results will be presented and discussed together.

Subject disposition:

Table 36

8.7 Integrated Summary of Effectiveness

TABLE 17
SUBJECT DISPOSITION

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
(PAGE 1 OF 2)

	STUDY 171				STUDY 183			
	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL
Randomized to Treatment	529	527	526	1582	526	527	527	1580
Entered the Placebo Follow-Up Phase*	506 (95.7%)	513 (97.3%)	501 (95.2%)	1520 (96.1%)	512 (97.3%)	513 (97.3%)	506 (96.0%)	1531 (96.9%)
Did Not Enter the Placebo Follow-Up Phase	23	14	24	61	14	14	21	49
Reason for Discontinuation								
Did not meet Enrollment criteria	0	0	0	0	1	0	0	1
Did not meet Randomization criteria	0	0	0	0	1	0	0	1
Adverse Event	4	2	4	10	3	3	6	12
Consent withdrawn	11	3	7	21	5	3	7	15
Lack of therapeutic response	0	0	4	4	0	0	2	2
Lost to follow-up	4	6	4	14	2	4	2	8
Sponsor/Investigator decision	4	3	5	12	2	4	4	10

* One subject (020060), randomized to placebo in Study 171, did not take placebo in the follow-up phase and is not included in the total.

Note: Information in this table is extracted from Tables 8.1.2 and 8.1.3 in the Clinical Study Reports 171 and 183. See Tables 4A and 4B in Section 8.4.1.2.3 for a subject listing.

8.7 Integrated Summary of Effectiveness

TABLE 17 (CONTINUED)
SUBJECT DISPOSITION

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
(PAGE 2 OF 2)

	Study 171				STUDY 183			
	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL
Randomized to Treatment	529	527	526	1582	526	527	527	1580
Completed the Study (Double-Blind and Follow-Up Phases)	496 (93.8%)	508 (96.4%)	498 (94.7%)	1502 (94.9%)	509 (96.8%)	508 (96.4%)	504 (95.6%)	1521 (96.2%)
Entered the Follow-Up Phase But Did Not Complete the Study	10	5	4	19	3	5	2	10
Reason for Discontinuation								
Did not meet Enrollment criteria	0	0	0	0	0	0	0	0
Did not meet Randomization criteria	0	0	0	0	0	0	0	0
Adverse Event	5	0	0	5	1	2	1	4
Consent withdrawn	0	2	2	4	1	1	0	2
Lack of therapeutic response	3	0	1	4	0	0	0	0
Lost to follow-up	1	3	0	4	1	1	0	2
Sponsor/Investigator decision	1	0	1	2	0	1	1	2

Note: Information in this table is extracted from Tables 8.1.2 and 8.1.3 in the Clinical Study Reports 171 and 183. See Tables 4A and 4B in Section 8.4.1.2.3 for a subject listing.

Table 37

8.7 Integrated Summary of Effectiveness

TABLE 18
DATA SETS ANALYZED[a]

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY

	STUDY 171				STUDY 183			
	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL	Ome-Mg 20	Ome-Mg 10	PLACEBO	TOTAL
Analysis Sets								
Intent-To-Treat	523 (98.9%)	518 (98.3%)	519 (98.7%)	1560 (98.6%)	524 (99.6%)	520 (98.7%)	520 (98.7%)	1564 (99.0%)
Per-Protocol	519 (98.1%)	514 (97.5%)	515 (97.9%)	1548 (97.9%)	514 (97.7%)	515 (97.7%)	511 (97.0%)	1540 (97.5%)

[a] Figures indicate the number of subjects eligible for analysis. In some analyses, the numbers may be lower due to missing data.

Note: Information in this table is extracted from Table 8.1.6 in the Clinical Study Reports 171 and 183.

Table 38

8.7 Integrated Summary of Effectiveness

TABLE 19
DEMOGRAPHIC AND BASELINE CHARACTERISTICS

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS
(PAGE 1 OF 3)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS	STUDY 171				STUDY 183			
	Ome-Mg 20 (N = 523)	Ome-Mg 10 (N = 518)	PLACEBO (N = 519)	TOTAL (N = 1560)	Ome-Mg 20 (N = 524)	Ome-Mg 10 (N = 520)	PLACEBO (N = 520)	TOTAL (N = 1564)
Gender								
Female	56.8%	54.8%	55.3%	55.6%	54.0%	55.2%	56.3%	55.2%
Male	43.2%	45.2%	44.7%	44.4%	46.0%	44.8%	43.7%	44.8%
Race								
Caucasian	76.7%	79.0%	76.9%	77.5%	84.5%	86.5%	85.6%	85.5%
Black	12.0%	10.6%	11.0%	11.2%	6.1%	6.0%	6.3%	6.1%
Hispanic	9.2%	7.9%	9.8%	9.0%	6.9%	5.6%	6.3%	6.3%
Asian	0.8%	1.4%	1.3%	1.2%	0.2%	0.4%	0.8%	0.4%
American Indian	0.2%	0.4%	0.2%	0.3%	0.8%	0.2%	0.2%	0.4%
Multi-Racial/Other	1.1%	0.8%	0.8%	0.9%	1.5%	1.3%	0.8%	1.2%

Note: Information in this table is extracted from Table 8.1.11 in the Clinical Study Reports 171 and 183.

8.7 Integrated Summary of Effectiveness

TABLE 19 (CONTINUED)
DEMOGRAPHIC AND BASELINE CHARACTERISTICS
MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS
(PAGE 2 OF 3)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS	STUDY 171				STUDY 183			
	Ome-Mg 20 (N = 523)	Ome-Mg 10 (N = 518)	PLACEBO (N = 519)	TOTAL (N = 1560)	Ome-Mg 20 (N = 524)	Ome-Mg 10 (N = 520)	PLACEBO (N = 520)	TOTAL (N = 1564)
Age (Years)								
Mean	44.5	44.1	43.7	44.1	46.7	47.3	46.0	46.7
Std. Deviation	12.8	13.0	13.2	13.0	14.2	14.7	14.1	14.4
Minimum–Maximum	18–86	18–86	18–79	18–86	20–84	18–84	18–79	18–84
< 65 Years	90.6%	91.7%	91.5%	91.3%	85.5%	85.4%	86.3%	85.7%
≥ 65 Years	9.4%	8.3%	8.5%	8.7%	14.5%	14.6%	13.7%	14.3%
Current Smoker								
Yes	22.9%	24.3%	26.2%	24.5%	25.4%	19.4%	22.3%	22.4%
No	77.1%	75.7%	73.8%	75.5%	74.6%	80.6%	77.7%	77.6%
Heartburn Frequency (% of Days) During the Run-In								
Mean	74.3	73.7	75.2	74.4	74.2	74.3	74.2	74.3
Std. Deviation	24.39	24.14	24.18	24.23	23.57	24.57	24.19	24.10
Minimum–Maximum	25.0–100.0	22.2–100.0	20.0–100.0	20.0–100.0	25.0–100.0	14.3–100.0	22.0–100.0	14.3–100.0
< 50%	18.9%	18.1%	18.7%	18.6%	18.7%	20.4%	19.6%	19.6%
≥ 50%	80.1%	81.9%	81.3%	81.1%	81.3%	79.6%	80.2%	80.4%

Note: Information in this table is extracted from Table 8.1.11 in the Clinical Study Reports 171 and 183.

Reviewers Comment:

The baseline HB frequency data indicates that the study population experienced HB substantially more frequently than the minimum requirement of 2/7 days. Subjects who suffer HB 75% of days may be more accurately described as GERD sufferers rather than occasion HB suffers. The lack of medical diagnosis required at the time of inclusion does not mean that these subjects do not have GERD. The frequency of symptoms may be adequate to define this population as GERD sufferers. What is not well defined is whether these subjects have nonerosive, erosive, or ulcerative GERD.
This reviewer has concerns over the generalizability of this study to the occasional HB population that represents the OTC target.

Table 39

8.7 Integrated Summary of Effectiveness

TABLE 19 (CONTINUED)
DEMOGRAPHIC AND BASELINE CHARACTERISTICS
MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS
(PAGE 3 OF 3)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS	STUDY 171				STUDY 183			
	Ome-Mg 20 (N = 523)	Ome-Mg 10 (N = 518)	PLACEBO (N = 519)	TOTAL (N = 1560)	Ome-Mg 20 (N = 524)	Ome-Mg 10 (N = 520)	PLACEBO (N = 520)	TOTAL (N = 1564)
Average Heartburn Severity During the Run-In								
Mean	1.5	1.5	1.5	1.5	1.6	1.5	1.5	1.5
Std. Deviation	0.42	0.41	0.42	0.42	0.43	0.41	0.39	0.41
Minimum–Maximum	1.0–3.0	1.0–3.0	1.0–2.9	1.0–3.0	1.0–3.0	1.0–2.7	1.0–3.0	1.0–3.0
Less than Moderate (<2)	80.7%	81.5%	81.3%	81.2%	77.7%	81.7%	83.1%	80.8%
Moderate to Severe (≥ 2)	19.3%	18.5%	18.7%	18.8%	22.3%	18.3%	16.9%	19.2%

Note: Information in this table is extracted from Table 8.1.11 in the Clinical Study Reports 171 and 183.

Table 40

8.7 Integrated Summary of Effectiveness

TABLE 20
SUMMARY OF FACTORS CONTRIBUTING TO HEARTBURN SYMPTOMS DURING 30-DAY PERIOD PRECEDING ENTRY INTO THE 24-HOUR PREVENTION STUDIES
INTENT-TO-TREAT SUBJECTS

STUDY NUMBER	171	183
SAMPLE SIZE	1560	1564
Heartburn Symptom Factors[a]		
Food and/or Beverage	96.5%	97.3%
Stress and/or Anxiety	69.0%	66.5%
Lying Down	58.8%	66.4%
Hectic Lifestyle	44.2%	44.8%
Physical Activity	27.2%	30.5%
Medication	11.9%	10.2%

[a] Subject could select more than one heartburn symptom factor to describe typical cause over the past month.
Note: Information in this table is extracted from Table 8.1.15 in Clinical Study Reports 171 and 183.

Efficacy Results:

Primary endpoint: Total HB prevention over 24 hours following the first dose

Table 41

8.7 Integrated Summary of Effectiveness

TABLE 21
ANALYSIS OF PRIMARY EFFICACY VARIABLE
NO HEARTBURN OVER 24 HOURS ON DAY 1

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

STUDY 171	Ome-Mg 20	Ome-Mg 10	PLACEBO
Heartburn-Free (%)	49.7% (260/523)	41.5% (215/518)	32.6% (169/519)
COMPARISON	P-VALUE[a]	ODDS RATIO (95% CI)[b]	DIFF IN PROP. (95% CI)[c]
Ome-Mg 20 vs. Placebo	<0.001	2.08 (1.61, 2.68)	17.2% (11.3, 23.0)
Ome-Mg 10 vs. Placebo	0.003	1.48 (1.15, 1.91)	8.9% (3.1, 14.8)
Ome-Mg 20 vs. Ome-Mg 10	0.006	1.40 (1.09, 1.79)	8.2% (2.2, 14.2)

STUDY 183	Ome-Mg 20	Ome-Mg 10	PLACEBO
Heartburn-Free (%)	46.6% (245/524)	45.2% (235/520)	32.1% (167/520)
COMPARISON	P-VALUE[a]	ODDS RATIO (95% CI)[b]	DIFF IN PROP. (95% CI)[c]
Ome-Mg 20 vs. Placebo	<0.001	1.90 (1.47, 2.45)	14.6% (8.8, 20.5)
Ome-Mg 10 vs. Placebo	<0.001	1.77 (1.37, 2.28)	13.1% (7.2, 18.9)
Ome-Mg 20 vs. Ome-Mg 10	0.572	1.07 (0.84, 1.37)	1.6% (-4.5, 7.6)

[a] P-values for treatment comparisons obtained from Cochran-Mantel-Haenszel chi-square test with investigator as a stratification variable.

[b] Estimated odds ratios and 95% confidence intervals (CI) from logistic regression analysis with Treatment and Center (pooled investigators) as categorical variables.

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

Note: Information in this table is extracted from Tables 8.2.1, 8.2.2, 8.2.3, and 1.9.5.4 (Appendix 1.9.5) in the Clinical Study Reports 171 and 183.

Table 42

8.7 Integrated Summary of Effectiveness

TABLE 22
ANALYSIS OF SECONDARY EFFICACY VARIABLES
PERCENTAGE OF SUBJECTS WITH NO NOCTURNAL AND NO MORE THAN MILD HEARTBURN ON DAY 1

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	PLACEBO
No Nocturnal Heartburn[a]			
Study 171	**78.4%[A]**	**79.1%[A]**	70.4%
Study 183	77.7%	75.6%	73.9%
No More Than Mild Heartburn Over 24 Hours[a]			
Study 171	**81.0%[A]**	**79.0%[A]**	71.6%
Study 183	**81.8%[A]**	**78.0%[A]**	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.

[A] Significantly different from Placebo ($p \leq 0.05$); values are bolded in table.

Note, no differences between Ome-Mg 20 and Ome-Mg 10 were statistically significant ($p > 0.05$).

Note: Information in this table is extracted from Tables 8.2.1 and 8.2.2 in the Clinical Study Reports 171 and 183.

Reviewer's Comment:

Tables 41 and 42 display the first day HB prevention data. There is replicated robust differentiation between both doses of OM and placebo at the rigorous endpoint of complete HB prevention. The difference between OM and placebo at preventing nocturnal HB is statistically significant in study 171 for both doses. There is a trend in favor of both doses of OM in study 183. The lack of replication or robust therapeutic gain at this clinically important endpoint is of note. The evidence is not adequate to consider a specific claim for prevention of nocturnal HB although the results are supportive of overall HB prevention. The endpoint of "no more than mild HB over 24 hours" is less meaningful that the other two endpoints displayed and may not independently support a HB prevention claim. Similar to nocturnal HB however, the results are meaningfully supportive of HB prevention efficacy.

Table 43

8.7 Integrated Summary of Effectiveness

TABLE 23
ANALYSIS OF EFFICACY VARIABLES ON DAY 14[a]
PERCENTAGE OF SUBJECTS WITH NO HEARTBURN OVER 24 HRS, NO NOCTURNAL HEARTBURN, AND NO MORE THAN MILD HEARTBURN OVER 24 HRS

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	PLACEBO
No Heartburn over 24 Hours[b]			
Study 171	**69.7%[A]**	**71.7%[A]**	42.7%
Study 183	**73.0%[A,B]**	**66.4%[A]**	43.0%
No Nocturnal Heartburn[b]			
Study 171	**86.5%[A]**	**87.7%[A]**	75.9%
Study 183	**88.8%[A,B]**	83.5%	80.0%
No More Than Mild Heartburn Over 24 Hours[b]			
Study 171	**89.8%[A]**	**92.2%[A]**	79.6%
Study 183	**92.2%[A]**	**89.3%[A]**	77.0%

[a] Last evaluation of double-blind medication within the interval Day 14 ± 2.

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

[A] Significantly different from Placebo ($p \leq 0.05$); values are bolded in table.

[B] Ome-Mg 20 significantly different from Ome-Mg 10 ($p \leq 0.05$); values are bolded in table.

Note: Information in this table is extracted from Tables 1.9.5.1 and 1.9.5.2 (Appendix 1.9.5) in the Clinical Study Reports 171 and 183.

Table 44

8.7 Integrated Summary of Effectiveness

TABLE 24
MEAN PERCENTAGE OF DAYS (ADJUSTED) WITH INDICATED OUTCOME OVER 14 DAYS OF DOUBLE-BLIND PHASE[a]

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

	Ome-Mg 20	Ome-Mg 10	PLACEBO
No Heartburn over 24 Hours[b]			
Study 171	**64.4%[A]**	**60.8%[A]**	39.4%
Study 183	**67.8%[A,B]**	**61.4%[A]**	37.9%
No Nocturnal Heartburn[b]			
Study 171	**84.7%[A]**	**83.5%[A]**	74.5%
Study 183	**86.1%[A,B]**	**82.5%[A]**	75.4%
No More Than Mild Heartburn Over 24 Hours[b]			
Study 171	**88.6%[A]**	**86.8%[A]**	75.9%
Study 183	**88.6%[A]**	**86.1%[A]**	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.

[A] Significantly different from Placebo ($p \leq 0.05$); values are bolded in table.

[B] Ome-Mg 20 significantly different from Ome-Mg 10 ($p \leq 0.05$); values are bolded in table.

Note: Information in this table is extracted from Tables 8.2.5 and 8.2.6 in the Clinical Study Reports 171 and 183.

Reviewer's Comment's:

The results of HB prevention over 14 days and on day 14 of daily dosing strongly support the efficacy of OM at both doses for symptomatic GERD management. What remains unanswered is whether this indication is appropriate for OTC use before medical evaluation.

Two important findings bear mentioning.

1. *The therapeutic gain associated with the use of OM at both doses rises dramatically from day one to day 14 of prevention therapy. The therapeutic gain of OM compared to placebo on day one for complete prevention over 24 hours is in the range of 9-17%. By day 14 of continuous therapy the therapeutic gain is in the range of 23 – 30%. These data suggest that there is some therapeutic effect extending beyond an episode of symptomatic relief. Mucosal healing may be occurring to a limited extent in those subjects that have undiagnosed erosive or ulcerative GERD. The pharmacodynamic effects of OM increase with repeat dosing and the esophageal exposure to acid is likely to be progressively decrease with the longer duration of therapy. This product is optimal for repeat dosing rather than episodic dosing.*
2. *The rising therapeutic gain with time underscores the fact that a more chronic condition is likely being treated in these trials, GERD. The selected population had frequent HB (on average 3 out of 4 days) and benefited maximally from daily treatment. An accurate statement of the most relevant finding of this study is:*

*OM at 10 or 20 mg/d taken every morning for 2 weeks successfully prevents the HB symptoms of **unselected** patients with GERD. The relevant question is whether OTC treatment of unselected GERD patients is appropriate. This study cannot answer that question. Review of current clinical practice and optimal recommendations for management of GERD is necessary to answer this question. This discussion is beyond the scope of this review of "efficacy".*

Time to recurrence:

Table 45

8.7 Integrated Summary of Effectiveness

TABLE 31
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
Ome-Mg 10	2	3	4	5
Placebo	1	1	3	3

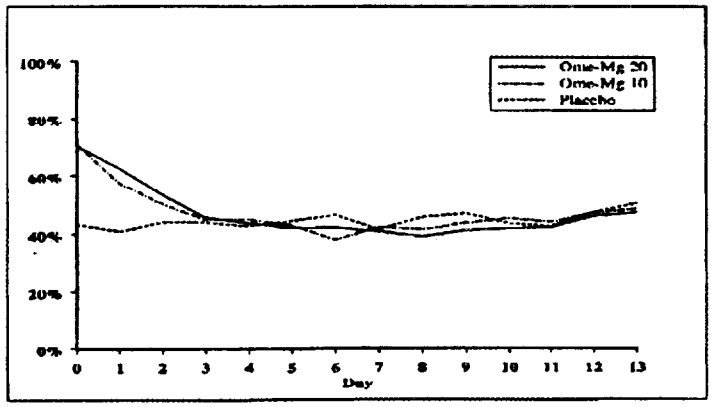
[a] Estimated using Kaplan-Meier method.

Note: Information in this table is extracted from Table 8.2.16 in the Clinical Study Reports 171 and 183.

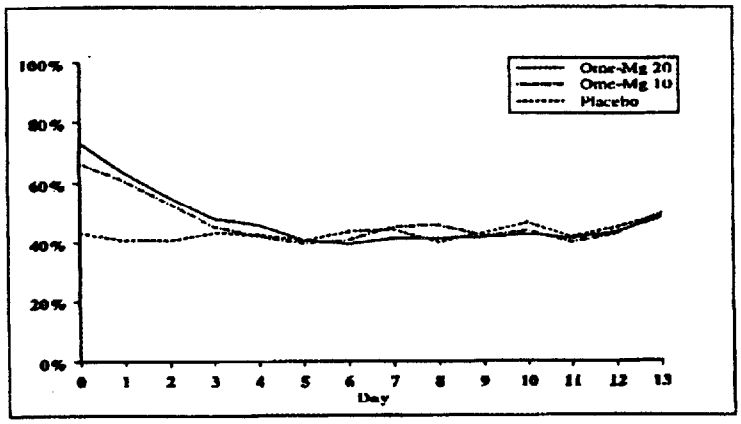
Figure 3

Figure 4
Percentage of Subjects with No Heartburn over 24 Hours by Day[a] after end of Double-Blind Phase
Per Protocol Subjects who enter Follow-Up Phase

Study 171



Study 183



[a] Note: Day 0 is last evaluation of double-blind medication.

Table 45 and figure 3 indicate that HB symptoms recur within several days in most subjects. This is not unexpected based on the known chronicity of GERD and the chosen patient population in the trials. Inclusion criteria required frequent HB for enrollment.

Reviewer's Comment:

HB as a symptom of GERD is chronic and recurrent in most patients. This fact creates a dilemma in considering how to instruct an OTC patient on usage. The proposed label advises use for no longer than 10 days in a row unless directed by a doctor. If a

two-week course of daily OM were to prevent recurrence for a meaningful period of time then it may obviate the need for evaluation by a physician. If symptoms return promptly, the proposed OTC label allows for indefinite repeat courses of therapy separated by as little as one day drug holiday. The data indicate that rapid recurrence of symptoms will logically result in chronic therapy without every warning subjects of the need for medical evaluation. Suggesting that the proposed label addresses a truly episodic symptomatic condition is not consistent with the common medical understanding of heartburn chronicity, the pharmacodynamics of OM, the demographic composition of the study population, the results from the treatment period and the rapid recurrence of symptoms in the study population.

If continuous use beyond 10 days without a medical evaluation is not appropriate, the proposed label does not address the true target population of currently approved indications for OTC HB treatment.

A potential concern with the use of potent acid suppressive agents is rebound hypersecretion. The lack of a more rapid return of symptoms in the OM groups may be interpreted as indicating an absence of rebound hypersecretion. It is possible however that there was mucosal healing in subjects with undiagnosed esophagitis which delayed symptomatic recurrence despite or regardless of any rebound hypersecretory effect. The time to recurrence dose not suggest that rebound acid hypersecretion would be a clinically relevant problem following two weeks of therapy. It would be of value to assess the severity of recurring symptoms as well as the results following a longer treatment duration which is likely to occur in the majority of consumers who would use OM OTC based on the chronicity and recurrence of HB in the vast majority of HB sufferers and the usage studies to be reviewed by the OTC division reviewer's.

Subgroup Analysis:

Table 46

8.7 Integrated Summary of Effectiveness

TABLE 26A
PERCENTAGE OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS ON DAY 1
BY DEMOGRAPHIC[a] AND BASELINE CHARACTERISTICS
(COMBINED DATA FROM STUDIES 171 AND 183)

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS
(PAGE 1 OF 2)

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	Ome-Mg 20 (N = 1047)[b]			Ome-Mg 10 (N = 1038)[b]			PLACEBO (N = 1039)[b]	
	n / m[c]	%[d]	Diff[e]	n / m[c]	%[d]	Diff[e]	n / m[c]	%[d]
Gender								
Female	281/580	48.4	14.8	248/571	43.4	9.8	195/580	33.6
Male	224/467	48.0	17.2	202/467	43.3	12.5	141/459	30.7
Race								
Caucasian	420/844	49.8	18.5	379/859	44.1	12.8	264/844	31.3
Non-Caucasian	85/203	41.9	4.9	71/179	39.7	2.7	72/195	36.9
Age (Years)								
< 65	441/922	47.8	14.6	395/919	43.0	9.8	307/924	33.2
≥ 65	64/125	51.2	26.0	55/119	46.2	21.0	29/115	25.2
Current Smoker								
Yes	109/253	43.1	12.1	88/227	38.8	7.8	78/252	31.0
No	396/794	49.9	17.1	362/811	44.6	11.9	258/787	32.8
Heartburn Frequency (% of days) During Run-in								
< 50 %	140/202	69.3	3.8	134/200	67.0	1.5	131/200	65.5
≥ 50 %	365/845	43.2	18.8	316/838	37.7	13.3	205/839	24.4

[a] Demographic characteristics collected at Screening visit (Visit 1).
[b] Number of Intent-to-Treat subjects in each treatment group.
[c] Number of subjects with no heartburn over 24 hours / Number of Intent-to-Treat subjects represented in subgroup. Note: In this analysis, subjects with missing data are assumed to have heartburn.
[d] Percentage of subjects with no heartburn over 24 hours.
[e] Difference between treatment percentage and placebo percentage.
[f] Scores are 1 = Mild, 2 = Moderate, 3 = Severe. The average score is based only on days with heartburn.

Note: See Appendix 2.1.2 of Section 8.7 for supporting documentation.

8.7 Integrated Summary of Effectiveness

TABLE 26A (CONTINUED)
PERCENTAGE OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS ON DAY 1
BY DEMOGRAPHIC[a] AND BASELINE CHARACTERISTICS
(COMBINED DATA FROM STUDIES 171 AND 183)

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS
(PAGE 2 OF 2)

DEMOGRAPHIC AND BASELINE CHARACTERISTIC	Ome-Mg 20 (N = 1047)[b]			Ome-Mg 10 (N = 1038)[b]			PLACEBO (N = 1039)[b]	
	n / m[c]	%[d]	Diff[e]	n / m[c]	%[d]	Diff[e]	n / m[c]	%[d]
AVERAGE HEARTBURN SEVERITY SCORE[f] DURING RUN-IN								
Less than Moderate (< 2)	422/829	50.9	15.9	400/847	47.2	12.2	299/854	35.0
Moderate to Severe (≥ 2)	83/218	38.1	18.1	50/191	26.2	6.2	37/185	20.0
OVERALL								
	505/1047	48.2	15.9	450//1038	43.4	11.0	336/1039	32.3

[a] Demographic characteristics collected at Screening visit (Visit 1).
[b] Number of Intent-to-Treat subjects in each treatment group.
[c] Number of subjects with no heartburn over 24 hours / Number of Intent-to-Treat subjects represented in subgroup. Note: In this analysis, subjects with missing data are assumed to have heartburn.
[d] Percentage of subjects with no heartburn over 24 hours.
[e] Difference between treatment percentage and placebo percentage.
[f] Scores are 1 = Mild, 2 = Moderate, 3 = Severe. The average score is based only on days with heartburn.

Note: See Appendix 2.1.2 of Section 8.7 for supporting documentation.

Table 47

8.7 Integrated Summary of Effectiveness

TABLE 26B
PERCENTAGE OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS ON DAY 1 BY HEARTBURN FREQUENCY (% OF DAYS) DURING RUN-IN
(COMBINED DATA FROM STUDIES 171 AND 183)

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS

Frequency (% of Days)	Ome-Mg 20			Ome-Mg10			Placebo	
	n/m[a]	%[b]	Diff[c]	n/m[a]	%[b]	Diff[c]	n/m[a]	%[b]
<50%	140/202	69.3	3.8	134/200	67.0	1.5	131/200	65.5
50%-74%	173/302	57.3	15.4	166/298	55.7	13.8	124/296	41.9
75%-99%	97/200	48.5	22.4	75/197	38.1	12.0	47/180	26.1
100%	95/343	27.7	18.3	75/343	21.9	12.5	34/363	9.4

[a] Number of subjects with no heartburn over 24 hours/Number of Intent-to-Treat subjects represented in subgroup. Note: In this analysis, subjects with missing data are assumed to have heartburn.
[b] Percentage of subjects with no heartburn over 24 hours.
[c] Difference between treatment percent and placebo percent.
Note: See Appendix 2.1.5 of Section 8.7 for supporting documentation.

Table 48

8.7 Integrated Summary of Effectiveness

TABLE 28
PERCENTAGE OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS ON DAY 1 BY FACTOR CONTRIBUTING TO HEARTBURN AT SCREENING VISIT[a]
(COMBINED DATA FROM STUDIES 171 AND 183)

MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY
INTENT-TO-TREAT SUBJECTS[b]

FACTOR	Ome-Mg 20 (N = 1047)[b]			Ome-Mg 10 (N = 1038)[b]			PLACEBO (N = 1039)[b]	
	n/m[c]	%[d]	Diff[e]	n/m[c]	%[d]	Diff[e]	n/m[c]	%[d]
Hectic Lifestyle								
Yes	227/490	46.3	13.8	171/464	37.7	6.2	145/446	32.5
No	278/557	49.9	17.7	279/584	47.8	15.6	191/583	32.2
Stress and/or Anxiety								
Yes	335/713	47.0	13.7	264/699	40.6	7.3	235/705	33.3
No	170/334	50.9	20.7	186/339	49.0	16.7	101/334	30.2
Food and/or Beverage								
Yes	488/1016	48.1	16.0	437/1008	43.4	11.2	322/1002	32.1
No	16/31	51.6	13.8	13/30	43.3	5.5	14/37	37.8
Physical Activity								
Yes	142/298	48.0	20.7	114/290	39.3	12.0	86/315	27.3
No	363/751	48.3	13.8	336/748	44.9	10.4	250/724	34.5
Medication								
Yes	53/106	50.0	20.3	58/111	52.3	22.6	36/128	29.7
No	452/941	48.0	16.3	392/927	42.3	9.6	299/911	32.7
Lying Down								
Yes	311/658	47.3	16.7	264/649	40.7	10.1	196/648	30.6
No	194/389	49.9	14.6	186/389	47.8	12.5	138/391	35.3

[a] Subject may indicate that more than one factor contributes to their heartburn.
[b] Number of Intent-to-Treat subjects in each treatment group.
[c] Number of subjects with no heartburn over 24 hours / Number of Intent-to-Treat subjects represented in subgroup. Note: In this analysis, subjects with missing data are assumed to have heartburn.
[d] Percentage of subjects with no heartburn over 24 hours.
[e] Difference between treatment percentage and placebo percentage.
Note: See Appendix 2.1.4 of Section 8.7 for supporting documentation.

Reviewer's comments:

1. Subgroup analysis as displayed in table 46 reveals some variations in strength of trend but no reverse trends.
Interestingly, similar to the results of studies 005 and 006 (table 35; meal provoked HB prevention) non-Caucasian subjects had a much smaller magnitude of therapeutic benefit that Caucasians for the 24 hour prevention on day one in studies 171 and 183. Racial differences in response rate may be meaningful if consistently seen across submissions related to omeprazole. A review of databases should be requested of the sponsor to address this finding.

2. *As displayed in table 46, HB sufferers with $\geq$ 50 % of days with HB had a much larger therapeutic gain than those with less frequent HB. This finding suggests that efficacy may not be present for the target population of occasional HB sufferers. If the Divisions were to consider approval for this product, it would be important to have the sponsor address this finding in a prospective way pre-approval.*
3. *Table 47 displays the efficacy results stratified by baseline "factor contributing to heartburn". Ascertainment of this baseline data does not indicate that efficacy related to any one of them is demonstrated based on a composite efficacy of HB prevention. The overriding food/beverage related HB frequency precludes any extrapolation to other contributing factors. The relative frequency of HB triggered by any one of these factors is critical to considering extrapolation. It is unknown how often subjects suffer from any of the contributing factors and whether during the study, subjects noted any response in HB typically attributed to the specific factor. Contributing factor specific labeling cannot be extrapolated as suggested by the sponsor's proposed label. Study design of HB prevention therapy to support such labeling has not been validated and would be problematic. Such studies would require discussion between the Division and the sponsor.*

Conclusions of studies 171 AND 183 for 24 hours HB prevention.

1. **This indication is not currently within any OTC label for HB management. There are broad implications to labeling an OTC product for 24-hour prevention for up to 10 days. Such labeling more clearly includes GERD than a single episode related prevention claim.**
2. **Table 48 concisely displays the results for the primary endpoint of "no HB for 24 hours". The first dose efficacy is demonstrated and replicated for both 10 and 20 mg doses of OM. The endpoint of "no more than mild HB" is supportive of the heartburn prevention claim. The nocturnal HB endpoint result offers support to the overall claim. Efficacy at this endpoint is not replicated. Such replication is necessary to consider labeling efficacy for this clinically important endpoint.**
3. **Last dose or overall efficacy during a two week daily dosing study represents study of a more chronic process than occasional or episodic HB and is not appropriate to support labeling for an "as needed" episodic condition.**
4.

Table 48

8.7 Integrated Summary of Effectiveness

TABLE 29
SUMMARY OF TREATMENT DIFFERENCES FOR 24-HOUR HEARTBURN PREVENTION STUDIES
INTENT-TO-TREAT SUBJECTS

		First Dose			Repeated Dose		
Primary Endpoints	Study Number	Ome-Mg 20 vs. Placebo	Ome-Mg 10 vs. Placebo	Ome-Mg 20 vs. Ome-Mg 10	Ome-Mg 20 vs. Placebo	Ome-Mg 10 vs. Placebo	Ome-Mg 20 vs. Ome Mg 10
HBF-24[a,b]	171	17.2*	8.9*	8.2*	25.0*	21.4*	3.6
	183	14.6*	13.1*	1.6	29.8*	23.5*	6.4*
NOC-HB[a,b]	171	8.0*	8.6*	-0.7	10.2*	9.0*	1.1
	183	3.8	1.7	2.1	10.7*	7.1*	3.6*
NMMH[a,b]	171	9.5*	7.4*	2.1	12.7*	10.9*	1.8
	183	11.0*	7.3*	3.7	14.9*	12.4*	2.5

[a] For first dose, cell entry is estimated difference in proportions between treatment groups. Treatment difference was tested using Cochran-Mantel-Haenszel chi-square test with Investigator as a stratification variable.

[b] For repeated dose, cell entry is estimated difference in mean percentage of days with outcome between treatment groups. Difference in LSMEANS tested with t-test using Treatment and Investigator as factors in the ANOVA model.

PREVENTION ENDPOINT: HBF-24 = Heartburn Free for 24 hours; NOC-HB = No Nocturnal Heartburn; NMMH = No More than Mild Heartburn.

* Statistically significant ($p \leq 0.05$).

Note: Information in this table is extracted from Table 21 (Section 8.7) and Tables 8.2.1, 8.2.2 and 8.2.6 (*Study Reports*) for Studies 171 and 183.

9 Overview of Efficacy

Treatment of HB

The sponsor has failed to show efficacy for either 10 or 20 mg OM for the treatment of episodic HB in studies 092 and 095. Data on last treated episode and across all treated episodes cannot be considered adequate evidence of efficacy for episodic HB. Labeling OM for episodic HB without information on the need for repeat dosing and lack of efficacy for the first episode would in fact be mislabeling.

Prevention of meal induced episodic HB

a. Support for the claim of prevention of episodic meal induced HB with OM 20 mg rests on the following data:

i. a single study (006) demonstrating a statistically significant therapeutic gain of 8.5% in the proportion of subjects HB free for the 4-hour post-meal study period

ii. a trend (therapeutic gain of 5.3%, p=0.057) in favor of OM 20 mg versus placebo in the same endpoint in study 005

iii. statistically significant superiority of OM 20 mg versus placebo in <u>both studies</u> for the five endpoints: overall assessment, maximum severity score, backup medication use within 4 hours, average symptom score and reduction of maximum severity score

b. Support for a claim of prevention of episodic HB with OM 10 mg rests on the following data:

i. statistically significant therapeutic gain of 8.1% in the proportion of subjects HB free for the 4-hour post meal study period for OM 10 mg versus placebo in study 006

ii. a trend at the same endpoint in study 005 (therapeutic gain of 4.2%, p=0.139)

iv. statistically significant superiority to placebo in both studies for the endpoint of maximum severity score

v. statistically significant superiority to placebo in study 006 for the endpoints; overall assessment, backup medication use, average symptom score and reduction of maximum severity score

vi. trends in favor of OM 10 mg in study 005 for overall assessment, backup medication use, average symptom score and reduction of maximum severity score.

If one were to accept the efficacy of OM for the prevention of HB when taken 1-hour before a meal, the next question is whether it is appropriate to label an OTC product for "management" of HB when a currently required element, treatment, does not exist. There is a major change in clinical paradigm when disconnecting the efficacy of a product with only 1-hour pre-meal prevention from treatment of an existing episode. In the OTC arena efficacy of both these two temporally defined events should be present.
These data require review in the context of the current OTC label for other HB remedies, the proposed OTC label for OM and discussion of any future changes by the Agency on the role of acid reducing agents in the OTC market.

24 hour prevention of heartburn for up to 10 days

Efficacy of OM 20 mg for the prevention of HB over a 24-hour period has been demonstrated based on:

a. statistically significant therapeutic gain over placebo in studies 171 and 183 for the endpoints

i. HB free over 24 hours (therapeutic gain 17%, 15%)
ii. No more than mild HB over 24 hours (therapeutic gain 9%, 11%)
b. statistically significant gain over placebo for the endpoint of "no nocturnal HB" in study 171 (therapeutic gain 8%)
c. trend over placebo for the endpoint of "no nocturnal HB" in study 183 (therapeutic gain 8%)

A specific claim related to prevention of nocturnal HB is not recommended.

Efficacy of OM 10 mg for the prevention of HB over a 24-hour period has been demonstrated based on:

a. statistically significant therapeutic gain over placebo in studies 171 and 183 for the endpoints:
i. "HB free for 24 hours" (therapeutic gain 9%, 13%)
iii. "no more than mild HB over 24 hours" (therapeutic gain 7%, 7%)

b. statistically significant therapeutic gain over placebo in study 171 for the endpoint "no nocturnal HB" (therapeutic gain 9%)
c. trend over placebo for the endpoint : no nocturnal HB" in study 183 (therapeutic gain 2.5%)

The significant increase in efficacy seen with repeated daily dosing is noted. This reviewer considers the indication of "HB prevention over 24 hours for up to 10 days" to be an indication for the treatment of GERD, not occasional/ episodic HB. This necessitates a thorough discussion within the Agency of the differentiation of "occasional/episodic HB" from GERD and the role of OTC therapy in the treatment of GERD.
If OTC use of OM for the management of GERD over 24 hours a day for up to 10 days were to be considered by the Agency, this reviewer recommends approval of the 10 mg dose.

The sponsor has not presented evidence to support the proposed label for dosing of OM anytime of day. If approved, directions for 24-hour prevention should be limited to dosing in the morning as noted in the study protocol. Physiological determinants of HB and pharmacokinetic data on OM do not suggest that study results can be extrapolated as proposed in the label.

Other conclusions:

1. **Trends towards lesser efficacy for non-Caucasians seen in the prevention studies 005, 006, 171, 183 should be further explored by the sponsor. Review of data from databases from GERD studies should be performed and submitted by the sponsor with recommendations for labeling changes or further prospective study.**
2. **Labeling for OTC management of HB based on specific contributing factors cannot be based on simple demographic data without supportive evidence for efficacy.**
3. **It should be noted that all pivotal studies in this submission contained entry criteria that limited enrollment to subjects with a history of antacid or H2RA responsive HB. This enriches the study population significantly with subjects that will more likely respond to therapy than the naïve subject. Thus the efficacy seen in these studies may not be generalizable to subjects who have taken antacids or H2RA s previously <u>without</u> success and to those who have never used OTC HB products.**
4. **The disparity seen in the efficacy in OM in frequent (50% of days) versus less frequent HB sufferers suggests that efficacy may not be generalizable to the current OTC target population of episodic or occasional HB sufferers.**

7/13/00 September 19, 2000

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Medical Team Leader

Appendix 1